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REVIEW

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Sensitivity and specificity of prostate-specific antigen and its surrogates towards the detection of prostate cancer in sub-Saharan Africa: a systematic review with meta-analysis

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Abstract

Background Racial disparities associated with pathogenesis and progression of prostate cancer makes a global diagnostic prostate-specific antigen (PSA) cut-off value inappropriate. Our review aimed to evaluate the pooled sensitivity and specificity of PSA and its surrogates, and to systematically synthesize the optimum thresholds for the detection of prostate cancer in sub-Saharan Africa.

Methods This was a systematic review of 6861 peer-reviewed literature from five databases: MEDLINE, PubMed, CINAHL, African Journal Online and Academic Search Complete, last search was in September 2022. Studies reporting the diagnostic accuracy of PSA and/or its surrogates towards the detection of prostate cancer in patients, using histology of prostate biopsy as the reference test for cancer diagnosis, were included. Studies that did not report sensitivity and/or specificity, or histology diagnosis of prostate cancer were excluded. Risk of bias assessment was conducted using quality assessment of diagnostic accuracy studies (QUADAS) by two independent investigators. Random effect model of meta-analysis was performed using Comprehensive Meta-Analysis version 3.

Results Thirteen (13) studies of males diagnosed with prostate cancer were included—10 studies reported PSA sensitivity/specificity/both; 4 reported on PSA surrogates (3 reported %freePSA, and 1 reported PSA density). We conducted 2 meta-analyses to pool the diagnostic accuracy of PSA and %freePSA. The sensitivity of PSA ($n=10$) at the cut-off values of < 4 ng/ml, 4–10 ng/ml, > 10 ng/ml were 86.8%, 93.1%, and 76.0% respectively; while specificity ($n=8$) were 42.3%, 29.3%, and 28.8% respectively. The PSA cut-off of 4–10 ng/ml possessed the highest diagnostic accuracy (55.7%). The specificity (91.5%) and diagnostic accuracy (84%) of %freePSA ($n=3$) was best at cut-off value ≤ 10%.

Conclusion Having the highest diagnostic accuracy individually, a combination of PSA 4–10 ng/ml and %freePSA ≤ 10% may be a more appropriate criteria for deciding eligibility for prostate biopsy among males in sub-Saharan Africa.

Keywords Prostate cancer, Diagnostic accuracy, Prostate specific antigen, PSA surrogates, Sub-Saharan Africa

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1 Background

Prostate cancer (PCa) is the main malignancy in terms of incidence and death in males of African descent [1]. In comparison to males from other regions of the world, men of sub-Sahara African heritage tend to be more affected by PCa [2]. It is a growing problem in Africa, with approximately 28,006 deaths from the disease in 2010 [3], and a 104% increase in the prevalence of PCa is predicted by 2030 [3], as life expectancy, access to healthcare, and screening facilities improve in African countries. Although high-income countries have a higher incidence rate of PCa [1], the rate of PCa mortality is higher in low- and middle-income countries, especially sub-Saharan Africa [1]. The disparities in prostate cancer incidence and death reported between locations are partly due to the availability of effective screening and improved treatment methods, both of which are directly linked to resources [4]. Notwithstanding the severe impact of PCa in sub-Saharan Africa, there are no proven primary prevention methods for PCa and no cures for tumours that have advanced beyond the early stages. Consequently, cancer care has focused on employing screening tests to detect early-stage PCa and then treating it aggressively with surgery or radiation [5].

The prostate-specific antigen (PSA) assay is arguably the most efficient cancer screening test for PCa, especially when performed in conjunction with a digital rectal examination (DRE) [6]. However, it is not exclusive to PCa since it is also increased after prostate gland manipulation, urinary tract infection, and benign prostate illnesses such as benign prostatic hypertrophy and prostatitis. Despite its shortcomings, PSA testing has increased over time, but routine PCa screening has been hampered by ambiguity regarding the efficacy of PSA-based screening and treatment for prostate-related morbidity and mortality [7]. For example, the American College of Physicians [8] and the United States Preventive Services Task Force [9] both reported inconclusive evidence regarding the diagnostic accuracy of PSA in detecting PCa, whereas Schröder et al. [7] and Tsodikov et al. [10] both reported conclusive evidence, casting doubt on PSA's diagnostic performance. One critical problem with PSA testing is overt sensitivity and low specificity leading to overdiagnosis and treatment of latent cancer that would not have shown clinically [11]. The weakness of PSA i.e. total PSA (tPSA) has paved the way for PSA surrogates such as percent free PSA (%fPSA), PSA density, PSA velocity, and PSA slope as they reportedly increase the specificity of PSA in the diagnosis of PCa [12–14]. Notwithstanding, their diagnostic accuracy is hitherto not well established. Because of the global disagreement about PSA's diagnostic accuracy, different medical societies have different guidelines for prostate cancer screening using PSA [15, 16]. This may be due to racial and ethnic differences in PCa aetiology, especially as blacks secrete more PSA per unit tissue than Caucasians [17], hence PSA may be less sensitive and specific for PCa across racial lines.

Therefore, it is critical to analyze and establish the diagnostic performance of PSA and its surrogates across racial lines. The diagnostic accuracy of PSA has been reported with conflicts in sub-Saharan Africa. For example, PSA sensitivity and specificity of 96.3% and 18.2% respectively were reported in Nigeria [18], whereas the sensitivity of 53.3% and specificity of 37.1% were recorded in South Africa [19]. The unpredictability of the PSA test's diagnostic accuracy lies at the heart of this argument. Thus, we aimed to synthesize the pooled sensitivity and specificity of PSA and its surrogates for the detection of PCa in Sub-Saharan Africa in a systematic way. Our specific objectives were:

1. To synthesize the pooled sensitivity of PSA and its surrogate for PCa
2. To synthesize the pooled specificity of PSA and its surrogate for PCa
3. To ascertain the optimum cut-off values of PSA and its surrogate for PCa

2 Main text

2.1 Design

This was a systematic review of observational studies. We structured the protocol following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline [20]. The protocol was registered with PROSPERO (CRD4202233690).

2.2 Eligibility criteria

2.2.1 Study characteristics

In this review, we included peer-reviewed literature written in English language. Studies in which sensitivity and specificity of PSA were measured for screening of symptomatic or asymptomatic cases of PCa were included. We were not restricted to sample size, tumour stage, and test statistics. Diagnosis of PCa was verified with a reference test (histology of prostate biopsy). We excluded studies if sensitivity and/or specificity were not reported or when it was not possible to extract data for a complete two-by-two table for the target condition.

2.2.2 Participants

In this review, we considered studies that involved males of sub-Saharan origin with PCa who had no prior history of the disease. Participants' age was not a limiting factor in this review.

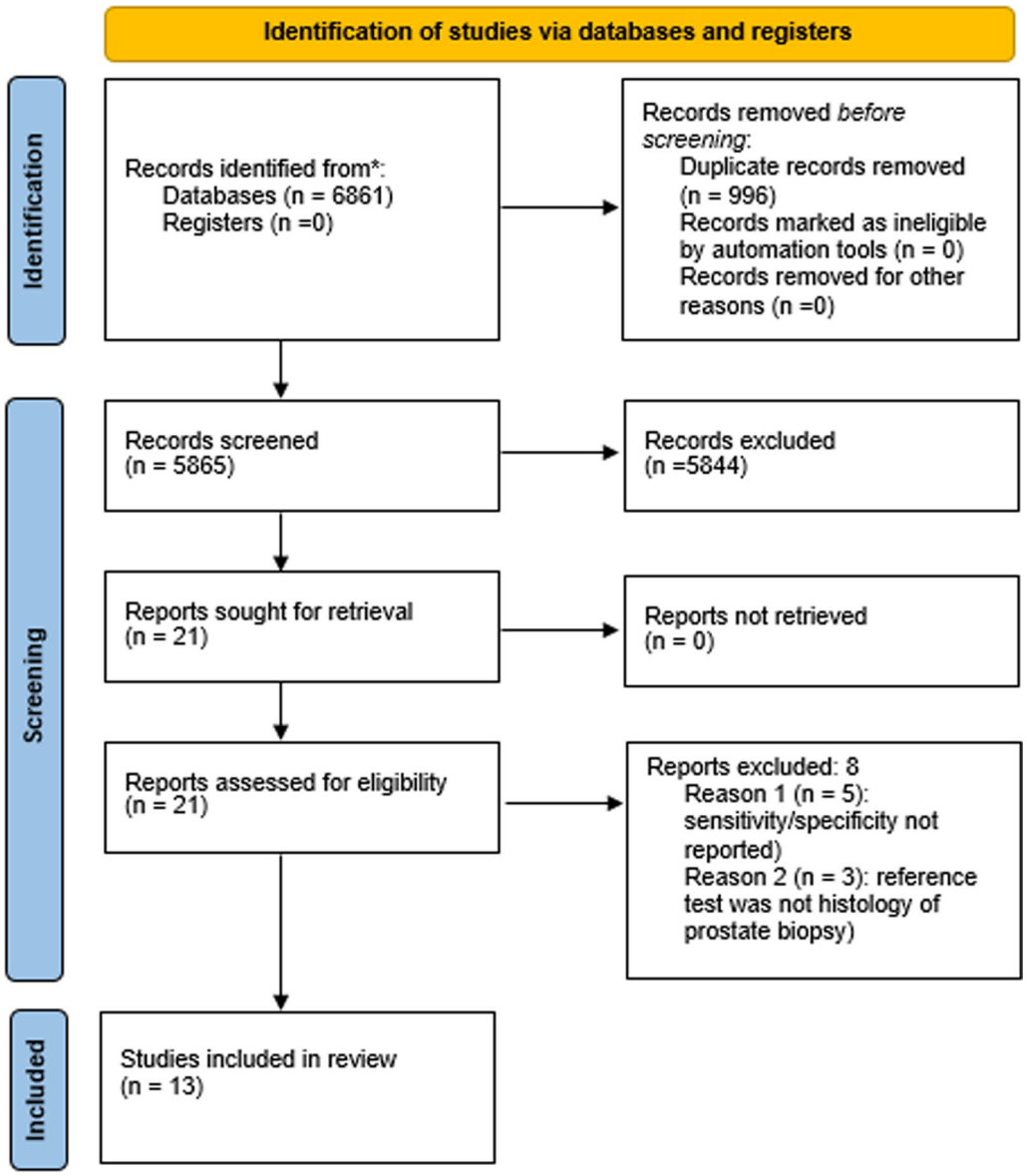


Fig. 1 PRISMA flow diagram of the systematic review of the sensitivity and specificity od prostate-specific antigen and its surrogates towards the detection of prostate cancer in sub-Saharan Africa (2001–2018)

2.2.3 Index test

The index test in this review was PSA measured in nanograms per millilitre (ng/mL) in a peripheral blood sample. There were no pre-determined PSA levels; rather, the PSA thresholds utilized in each research were recorded during data extraction.

2.2.4 Target condition

Prostate cancer was the target condition in this review. No limitation based on Gleason grade or tumour stage was imposed.

2.2.5 Reference test

The reference test was histology of prostate biopsy. We included studies regardless of the prostate biopsy method used.

2.3 Information sources and search strategy

Using Medical Subject Headings (MeSH), searches were conducted in five databases: PubMed, MEDLINE, CINAHL, African Journal Online and Academic Search Complete and keywords were found in the title, abstract, and/or text of the publications. The search strategy was piloted in PubMed. MeSH terms

Table 1 Characteristics of studies examining the sensitivity and specificity of PSA in sub-Saharan Africa

Authors	Age*	Sensitivity < 4	4–10	> 10	Specificity < 4	4–10	> 10	Country	Patient symptoms/conditions	Event/Sample size	Design
Abdrabo et al. 2011[31]	70.0 (6.75)	Na	91.6	Na	Na	24.00	Na	Sudan	Lower urinary tract symptoms	36/118	Pros
Amayo and Obara, 2004 [29]	Nr	89.8	83.7	Na	37.00	66.00	Na	Kenya	Pre-surgery patients	49/100	Retro
Heyns et al. 2001 [27]	78.85 (9.32)	Na	96.0	Na	Na	25.50	Na	South Africa	Patients referred to tertiary hospital	../3837	Retro
Manyahi et al. 2009 [32]	73.00 (-)	Na	Na	100.0	Na	Na	Nr	Tanzania	Prostatism	24/94	Pros
Mbaeri et al. 2018 [23]	70.99 (9.1)	Na	99.13	86.97	Na	2.15	25.84	Nigeria	DRE suspicious of PCa	../208	Pros
Niang et al. 2011 [30]	65.50 (13.7)	95.5	Na	Nr	4.50	Na	36.36	Senegal	Population screening	22/72	Pros
Nnabugwu et al. 2014 [18]	Na	Na	96.3	85.2	Na	18.20	33.30	Nigeria	Symptomatic prostate enlargement	26/117	Retro
Ojewola et al. 2013 [24]	67.9 (7.5)	Na	91.9	75.7	Na	18.1	53.2	Nigeria	Clinic evaluation for prostatic dx	74/168	Pros
Oranusi et al. 2011 [25]	70.00 (10.1)	nr	99.2	Na	nr	nr	nr	Nigeria	Patients diagnosed with PCa	133/133	Retro
Tijani et al. 2017 [26]	64.05 (6.75)	Na	21.9	Na	Na	78.10	Na	Nigeria	Abnormal DRE suggestive of PCa	37/167	Pros

* Mean (standard deviation) age; na: not applicable; nr: not reported; Pros – prospective study; Retro – retrospective study

Table 2 Characteristics of studies examining the sensitivity and specificity of PSA

Authors	Age Mean (SD)	%fPSA Cut-off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Prevalence (%)	Country	PCa Event/ Sample size	Design
Ezenwa et al. 2012 [12]	64.4 (6.6)	< 10	7.14	100	100	Nr	13.3	Nigeria	14/105	Prosp.
		< 15	35.7	100	100					
		< 20	57.1	98.9	88.9					
		< 25	78.6	97.8	84.6					
		< 30	85.7	96.7	80.0					
Tijani et al. 2017 [26]	64.05 (6.75)	≤ 10	43.2	92	62	85	21.9	Nigeria	37/167	Prosp.
		≤ 15	76	76	47	92				
		≤ 20	100	45	34	100				
		≤ 25	100	27	28	100				
		≤ 30	100	16	25	100				
Phiri-Ramongane & Khine, 2018 [28]	65.9 (7.3)	10	26	81	24	82	21.4	South Africa	28/122	Retros p
		15	52	61	24	84				
		20	69	42	22	85				
		25	86	27	21	90				
		30	95	15	21	93				
Authors	**Age Mean (SD)**	**PSAD Cut-off# (ng/ml/cm^3)**	**Sensitivity**	**Specificity**	**PPV (%)**	**NPV (%)**	**Prevalence(%)**	**Country**	**PCa Event/ Sample size**	**Design**
Ude et al	66.4 (15.3)	0.15	33.3	85.7	38.2	82.8	38.2	Nigeria	97/254	Prosp.
2016 [13]		0.04	86.7	20.0	22.4	84.9				

Surrogates: %free PSA and PSA density in sub-Saharan Africa

PSA- Prostate specific antigen; %fPSA- % free PSA; PSAD- prostate specific antigen density; PCa- prostate cancer; SD- standard deviation; PPV- positive predictive value; NPV- negative predictive value; nr – not reported; #-for PSA 4-10 ng/ml (grey zone); Prosp – Prospective study; Retrosp – Retrospective study

Table 3 Study characteristics of studies examining the sensitivity and specificity of PSA combined with the digital rectal examination in sub-Saharan Africa

Authors	Sensitivity per cut-off			Specificity per cut-off		
	< 4 ng/ml (%)	4–10 ng/ml (%)	> 10 ng/ml (%)	< 4 ng/ml (%)	4–10 ng/ml (%)	> 10 ng/ml (%)
Abdrabo et al. 2011 [31]	91.60	Na	Na	Na	24	Na
Manyahi et al. 2009 [32]	na	na	100	Na	na	Na
Mbaeri et al. 2018 [23]	na	100	89.69	Na	0	30.88
Ojewola et al. 2013 [24]	Na	70.3	Na	Na	64.9	Na
Oranusi et al. 2011 [25]	Na	100	Na	Na	nr	Na

na: not applicable; nr: not reported

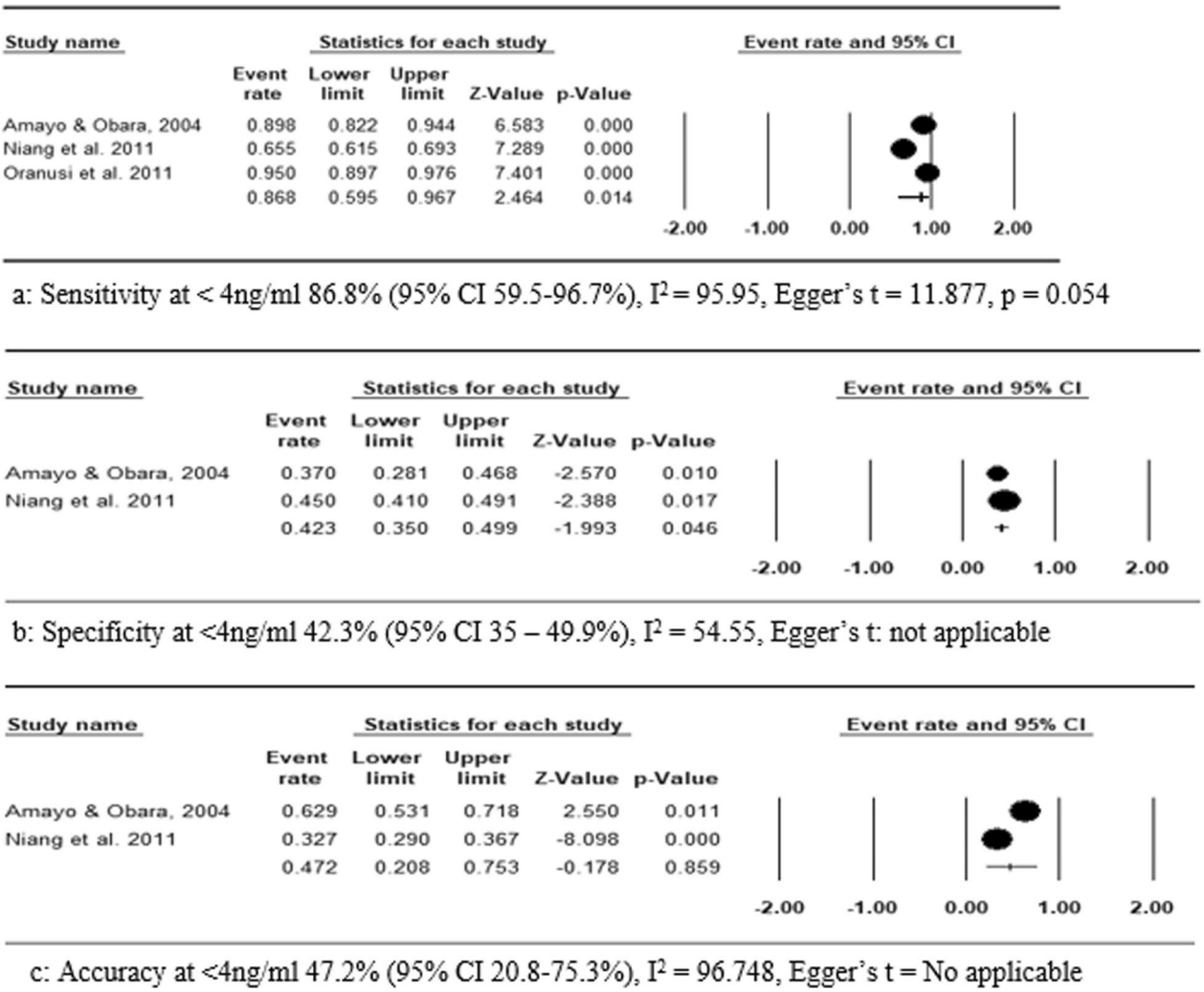
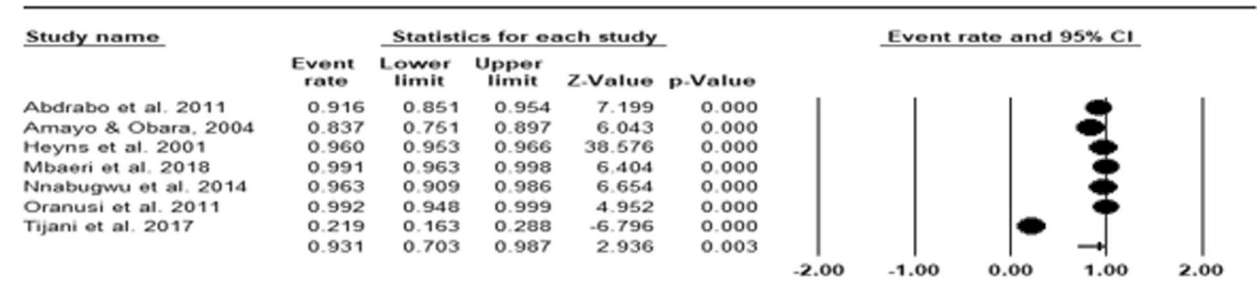
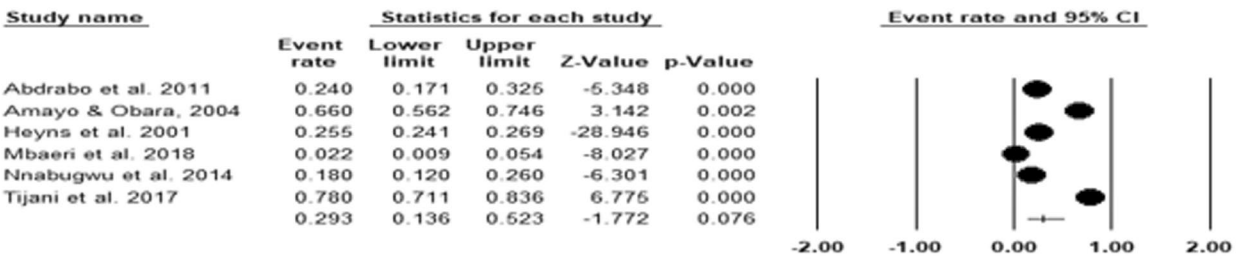


Fig. 2 Pooled Sensitivity, Specificity and Accuracy of PSA at < 4 ng/ml

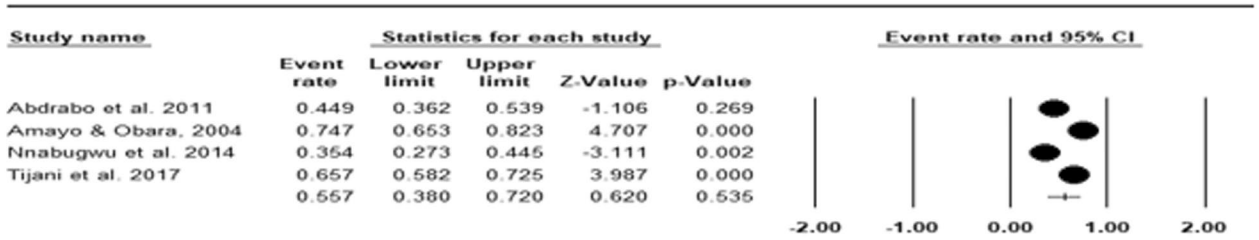
and keywords/free text terms were included in the pilot search. The most sensitive technique was picked and reported after many combinations of these terms. The sensitivity judgment was made based on appearances.



a: Sensitivity at 4-10ng/ml 93.1% (95% CI 70.3 – 98.7%), $I^2 = 98.8$, Egger's t = 0.409, p = 0.699



b: Specificity at 4-10ng/ml 29.3% (95% CI 13.6-52.3%), $I^2 = 98.02$, Egger's t = 0.574, p = 0.597



c: Accuracy at 4-10ng/ml 55.7% (95% CI 38 – 72%), $I^2 = 93.23$, Egger's t = 0.177, p = 0.876

Fig. 3 Pooled Sensitivity, Specificity and Accuracy of PSA at 4-10 ng/ml

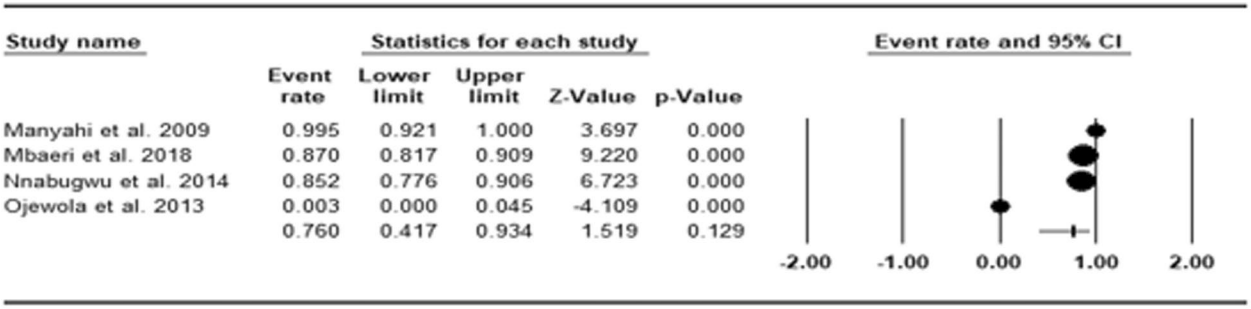
The strategy was tweaked to fit the remaining databases' syntax and subject headers (MEDLINE, CINAHL, African Journal Online and Academic Search Complete). For possible identification of relevant studies, a reference list of selected papers and reviews was searched.

2.4 Study records and data management

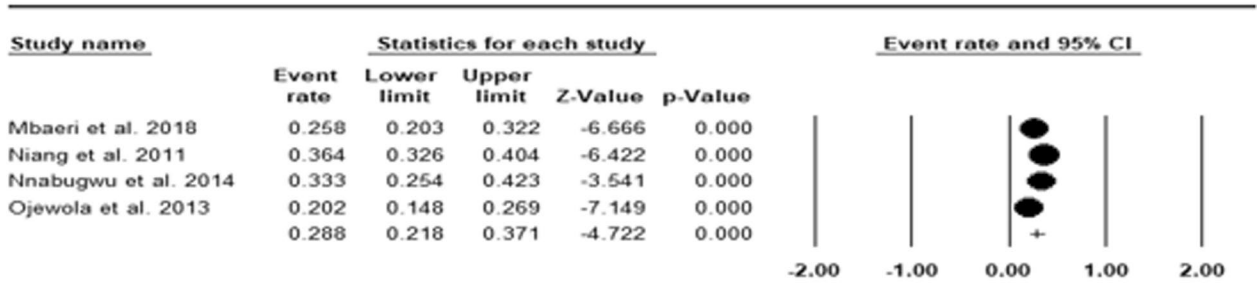
The results of the literature search were directly exported to EndNote 8, where they were de-duplicated. We checked all bibliographic entries in EndNote 8 after removing duplicate copies, and then chose articles that met the inclusion criteria. We used piloted and fine-tuned screening template with eligibility questions to help with the screening process.

2.5 Selection process

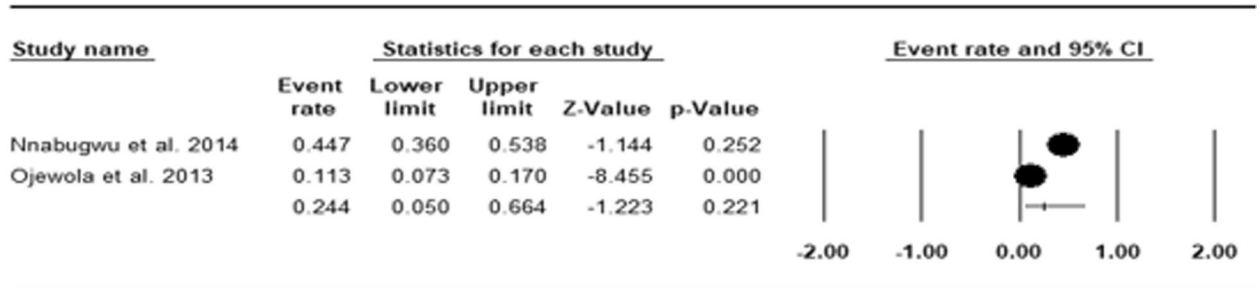
The first screening of the title and abstract to identify those that met the inclusion criteria was conducted by NM. A trained research assistant downloaded full-text versions of selected articles. OCJ and NID undertook full-text screening with conflict resolved in consultation with NM. A PRISMA diagram (Fig. 1) was used to show the flow of studies throughout the selection process, as well as the grounds for exclusion.



a: Sensitivity at >10ng/ml 76% (95% CI 41.7 – 93.4%), I^2 = 91.45, Egger's t = 0.549, p = 0.638)



b: Specificity at >10ng/ml 28.8% (95% CI 21.8 – 37.1%), I^2= 84.4; Egger's t = 1.791, p = 0.215



c: Accuracy at >10ng/ml 24.4% (95% CI 5.0 – 66.4%), I^2 = 97.33, Egger's t = Not applicable

Fig. 4 Pooled Sensitivity, Specificity and Accuracy of PSA at > 10 ng/ml

2.6 Data extraction and data items

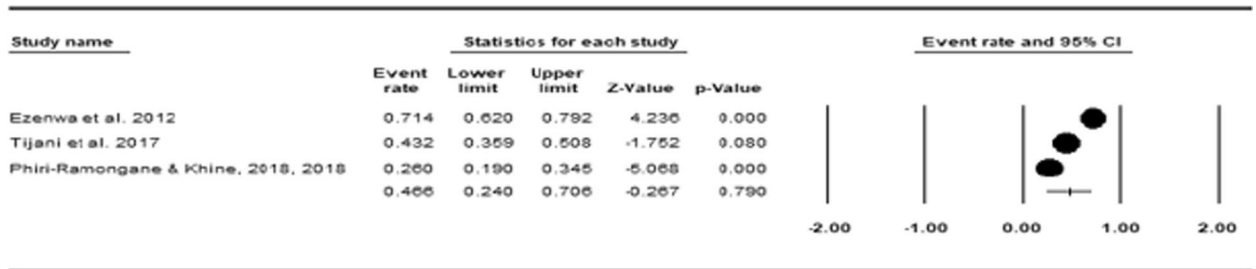
To collect relevant data from each included study, a pre-piloted data extraction template was employed. EOA undertook the data extraction, with study data verified by MN. Sensitivity, specificity, and prevalence were obtained, and where published estimates were not available, we obtained them from two-by-two tables for the index and reference tests where complete data were available.

2.7 Quality appraisal and risk of bias assessment

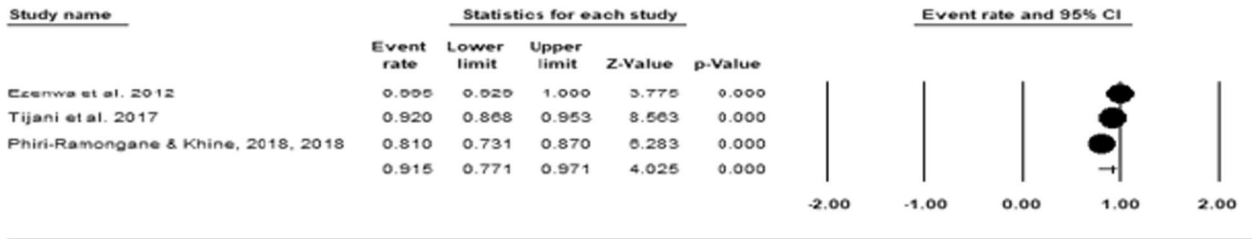
To strengthen the review's rigor, we used the QUADAS-2 method [21] to assess the risk of bias and applicability of all included research. Three investigators carried out this independently (CJO, EOA and IDN). In consultation with MN, conflicts were resolved.

2.8 Data synthesis and assessment of heterogeneity

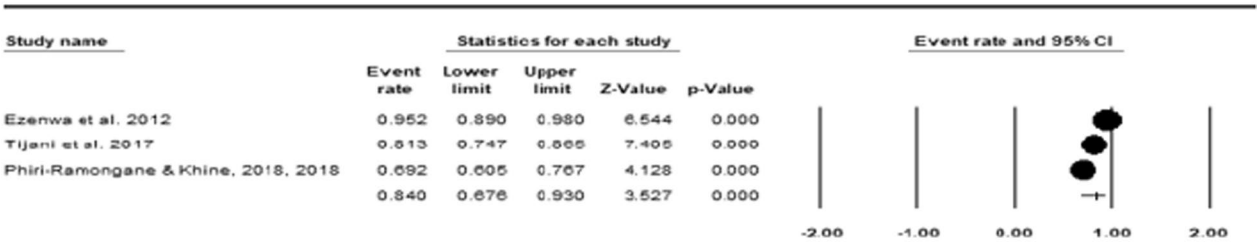
Measures of heterogeneity, i.e. study characteristics, were classified by year of publication and presented in an evidence table in a narrative format (Table 1). We employed a random-effect model of meta-analysis to pool the indices of diagnostic accuracy. In line with the Cochrane Handbook for Systematic Reviews of Intervention [22], we computed measure of heterogeneity (I^2) and interpreted it as follows: 0–40% indicated low heterogeneity,



a: Sensitivity of %fPSA at ≤10% (46.6 (CI 24.0-70.6, $I^2 = 95.4$, Egger's t = 0.2453, p = 0.8469)



b: Specificity of %fPSA at ≤10% (91.5% (CI 77.1-97.1, $I^2 = 85.0$, Egger's t = 1.306, p = 0.4161)



c: Accuracy of %fPSA at ≤10% (84.0% (CI 67.6-93.0, $I^2 = 90.3$, Egger's t = 1.6893, p = 0.3388)

Fig. 5 Pooled Sensitivity, Specificity and Accuracy of %fPSA at ≤ 10%

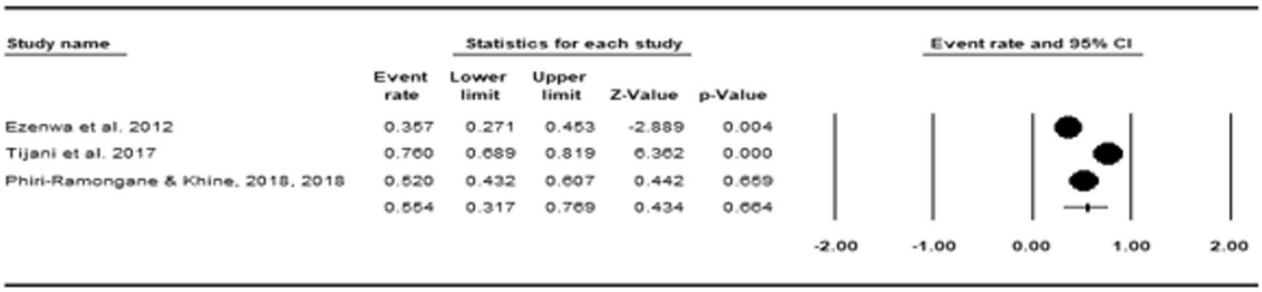
30–60% represented moderate heterogeneity, 50–90% represented substantial heterogeneity, and 75–100% indicated considerable heterogeneity.

2.9 Data analysis

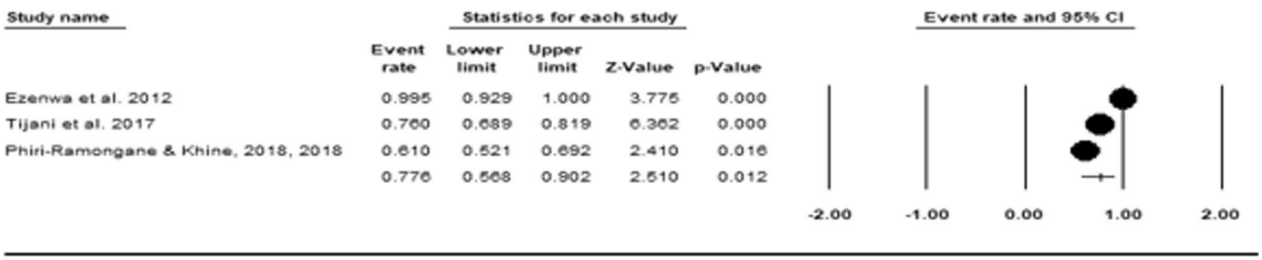
Data analysis was performed with the Statistical Package for Social Sciences (SPSS) version 2, while meta-analysis was performed with the Comprehensive Meta-Analysis version 3. We pooled data (sensitivity, specificity and accuracy) per cut-off values to obtain the summary estimates and 95% confidence intervals. We assessed the correlation between age, PSA and %fPSA using Pearson correlation coefficient. To assess publication bias, Egger's test was utilized. A p-value of < 0.05 was considered to be statistically significant.

3 Results

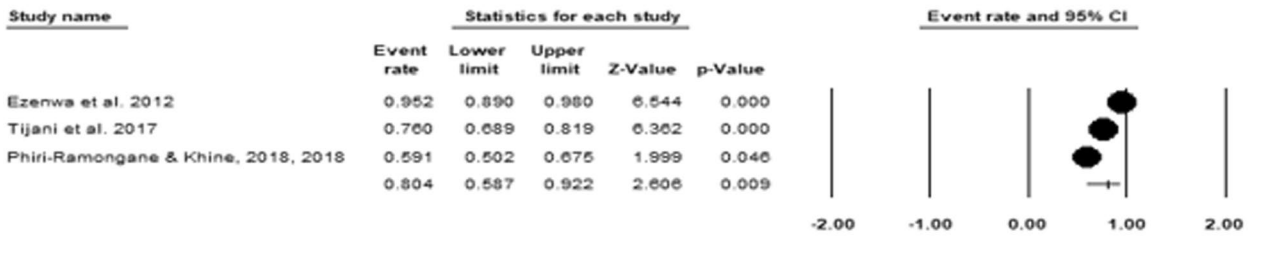
A total of 6861 records were identified from PubMed (5245), Medline (59), CINAHL (6), Academic Search Complete (947) and African Journal Online (604). Following de-duplication, title and abstract screening, we eliminated 996 records that were deemed irrelevant, leaving 5865 articles for the title and abstract screening. Twenty-one (21) full text were downloaded and screened. Ultimately, 13 studies met the eligibility criteria and were included in the systematic review (Fig. 1). Studies were spread across six countries namely Nigeria (seven)[12, 13, 18, 23–26], South Africa (two)[27, 28], Kenya (one) [29], Senegal (one)[30], Sudan (one)[31], and Tanzania (one)[32]. Of the 13 studies, ten studies reported sensitivity of PSA, specificity of PSA or both (Table 1).



a: Sensitivity of %fPSA at ≤15% (55.4% (CI 31.7-76.9, $I^2 = 95.3$, Egger's t = 1.199, p = 0.4425)



b: Specificity of %fPSA at ≤15% (77.6% (CI 56.8-90.2, $I^2 = 88.6$, Egger's t = 1.128, p = 0.4618)



c: Accuracy of %fPSA at ≤15% (80.4% (CI 58.7-92.2, $I^2 = 93.6$, Egger's t = 1.476, p = 0.3791)

Fig. 6 Sensitivity, specificity and accuracy of %fPSA at ≤ 15%

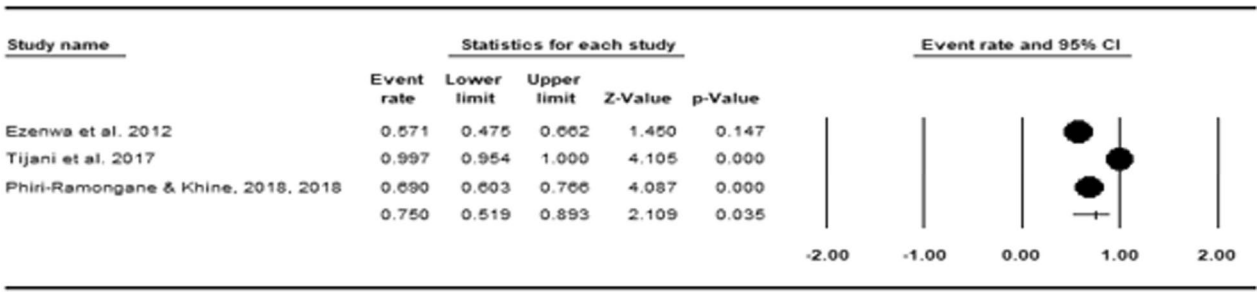
We identified two PSA surrogates namely percent free PSA (%fPSA) reported in three studies [12, 26, 28] and PSA density reported in only one study [13] (Table 2). We conducted two meta-analyses to pool the diagnostic accuracy of PSA and %fPSA respectively. In the analysis of diagnostic accuracy of PSA, 10 studies (Table 1) were involved in pooling PSA sensitivity while 8 were involved in pooling PSA specificity. Three studies were involved in pooling the diagnostic accuracy of %fPSA (Table 2).

Five studies examined the sensitivity and specificity of the PSA combined with the digital rectal examination (Table 3). The highest sensitivity (100%) was recorded at PSA = 4–10 ng/ml.

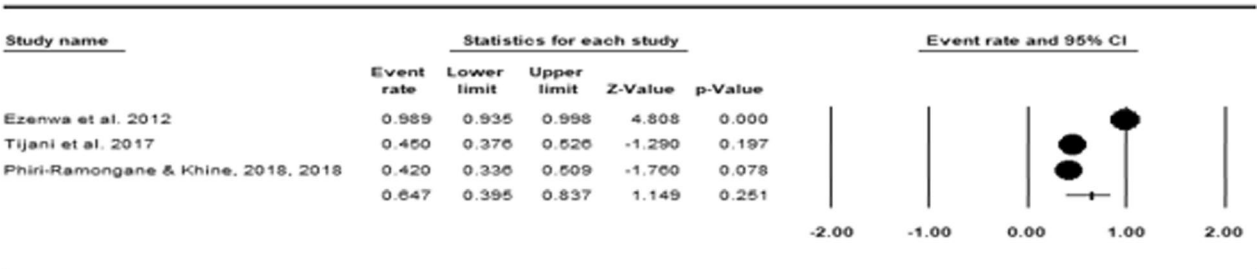
In sub-Saharan Africa, the pooled PSA sensitivity, specificity and accuracy at < 4 ng/ml were 86.8% (95% CI 0.60–0.97, $I^2 = 96$), 42.3% (95% CI 0.35–0.50, $I^2 = 54.6$) and 47.2% (95% CI 0.21–0.75, $I^2 = 96.7$), respectively (Fig. 2). The pooled PSA sensitivity, specificity and accuracy at 4-10 ng/ml were 93.1% (95% CI 0.70–0.99, $I^2 = 98.8$), 29.3% (95% CI 0.14–0.52, $I^2 = 98.0$) and 55.7% (95% CI 0.38–0.72, $I^2 = 93.2$), respectively (Fig. 3); while at PSA > 10 ng/ml were 76% (95% CI 0.42–0.93, $I^2 = 91.5$), 28.8% (95% CI 0.22–0.37, $I^2 = 84.4$) and 24.4% (95% CI: 0.05– 0.66, $I^2 = 97.3$) (Fig. 4). There was no publication bias throughout ($p > 0.05$). The PSA cut-off of 4–10 ng/ml possessed the best diagnostic accuracy of 55.7% (Fig. 3c).

There was moderate positive correlation between PSA sensitivity and age which was statistically significant (r = 0.536; $p < 0.05$). However, no statistical significant correlation was found between PSA specificity and age (r = −0.303; $p > 0.05$).

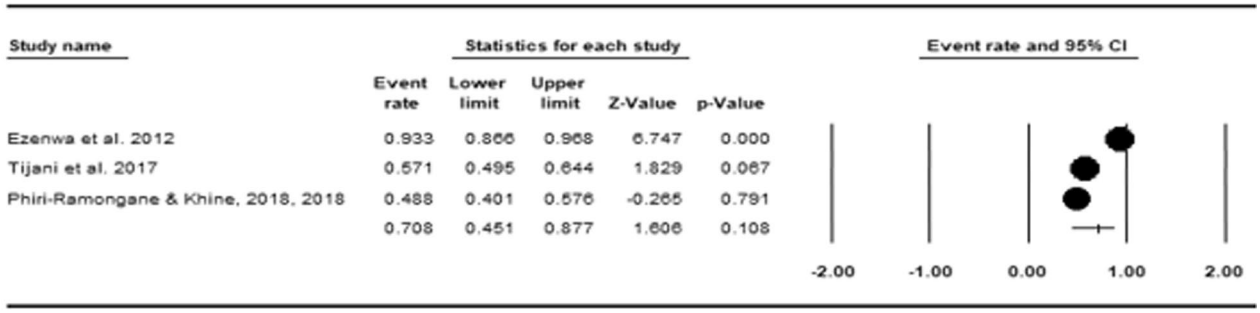
The pooled %fPSA sensitivity, specificity and accuracy at various cut-offs obtained from the forest plots (Figs. 5, 6, 7, 8 and 9) are summarized in Table 4.



a: Sensitivity of %fPSA at ≤20% (0.75% (CI 51.9-89.3), $I^2 = 88.3$, Egger's t = 1.971, p = 0.2989)



b: Specificity of %fPSA at ≤20% (64.7% (CI 39.5-83.7), $I^2 = 92.2$, Egger's t = 4.054, p = 0.1540)



c: Accuracy of %fPSA at ≤20% (70.8% (CI 45.1-87.7), $I^2 = 94.9$, Egger's t = 2.291, p = 0.2620)

Fig. 7 Pooled Sensitivity, Specificity and Accuracy of %fPSA at ≤ 20%

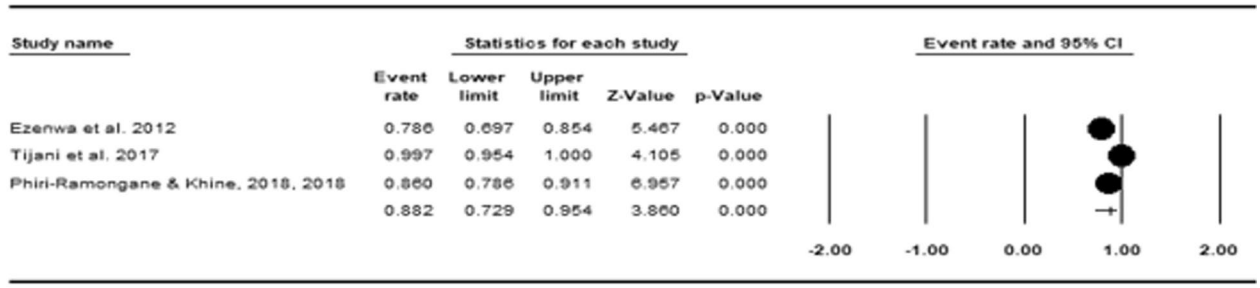
The pooled sensitivity of %fPSA increased with increasing cut-off values, while specificity decreased with increasing cut-off values. The %fPSA cut-off of ≤ 10 possessed the best diagnostic accuracy of 84% (95% CI 67.6–93.0%, $I^2 = 90.3$). There was no publication bias across the cut-offs ($p > 0.05$).

Weak and statistical insignificant negative correlation was found between %fPSA sensitivity and age ($r = -0.322$; $p > 0.05$). There was also no statistically significant correlation between %fPSA specificity and age ($r = -0.076$; $p > 0.05$).

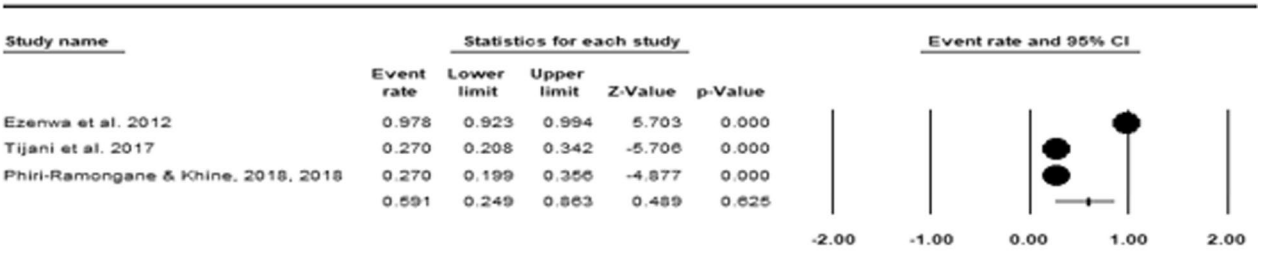
Our results show that most of the studies included in this review possessed a low risk of bias (Appendix 1).

4 Discussion

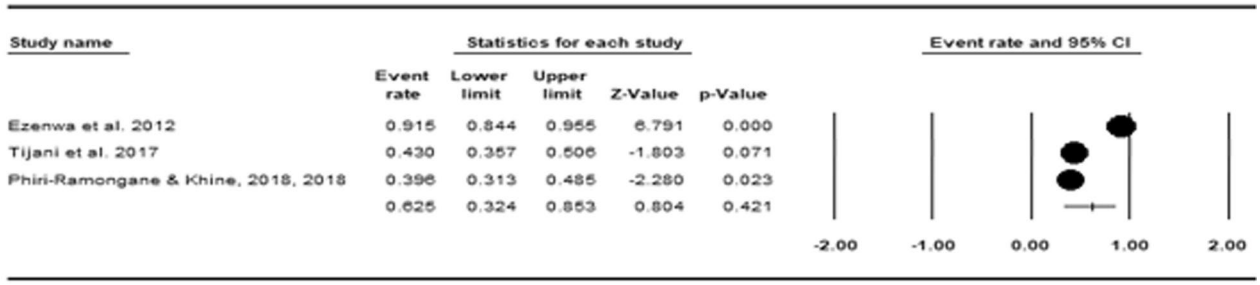
This is one of the first systematic reviews aggregating data on the diagnostic accuracy of PSA in sub-Saharan Africa. We found that the pooled sensitivity (86.8%) and specificity (42.3%) of PSA at < 4 ng/ml was higher than that reported by Maphayi et al. (53.3% and 37.1% respectively) [19]. We also observed that the PSA cut-off that gave the best accuracy (55.7%) for predicting PCa was 4–10 ng/ml. Some studies had suggested a biopsy threshold of 4 ng/ml [33], while other algorithms had given thresholds as high as 10 ng/ml [34], above which prostate biopsy for histology should be done to rule out malignancy.



a: Sensitivity of %fPSA at ≤25% (88.2% (CI 72.9-95.4), $I^2 = 82.0$, Egger's t = 2.557, p = 0.2374)



b: Specificity of %fPSA at ≤25% (59.1% (CI 24.9-86.3), $I^2 = 96.0$, Egger's t = 6.387, p = 0.099)

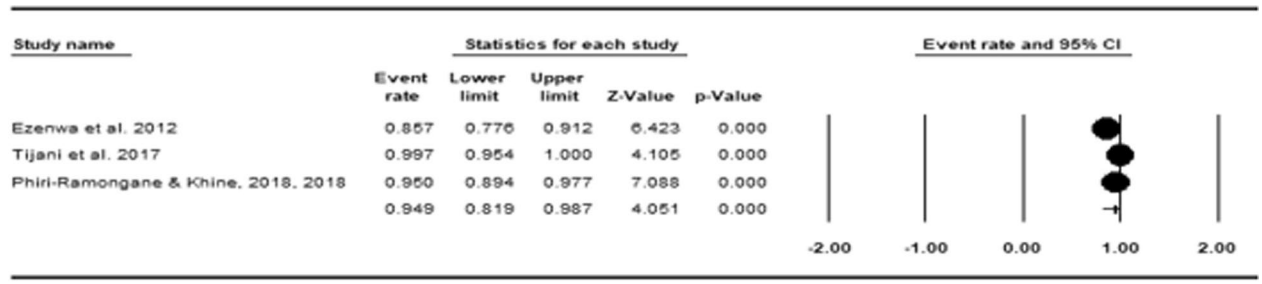


c: Accuracy of %fPSA at ≤25% (62.5% (CI 32.4-85.3), $I^2 = 93.3$, Egger's t = 3.056, p = 0.2013)

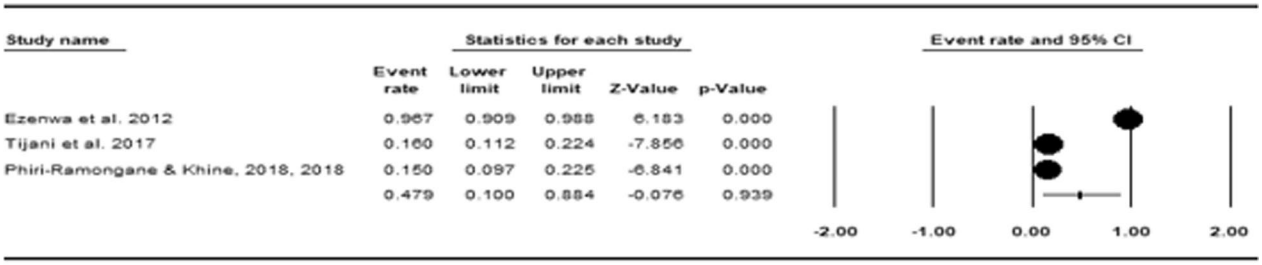
Fig. 8 Pooled Sensitivity, Specificity and Accuracy of %fPSA at ≤ 25%

We identified some studies that described sensitivity and specificity of PSA and digital rectal examination (DRE) (Table 3). It has been established that combination of PSA and DRE can be used to predict PCa, with sensitivity rates as high as 100% having been reported [23, 25, 32]. Milwa et al. gave a diagnostic accuracy of 87% using DRE and PSA [35]. Similarly, Tijani et al. reported that raised PSA and abnormal DRE gave a positive predictive value (PPV) of 95.2% [36]. A Ghanaian study even suggested using a nomogram that combines DRE, PSA and PSAD (which gave an area under the curve (AUC) of 84.8%) may be a better and accurate assessment for predicting patients with PCa than using them individually [37]. Despite these, PSA is still considered the primary screening test while other measures are secondary screening tests [38].

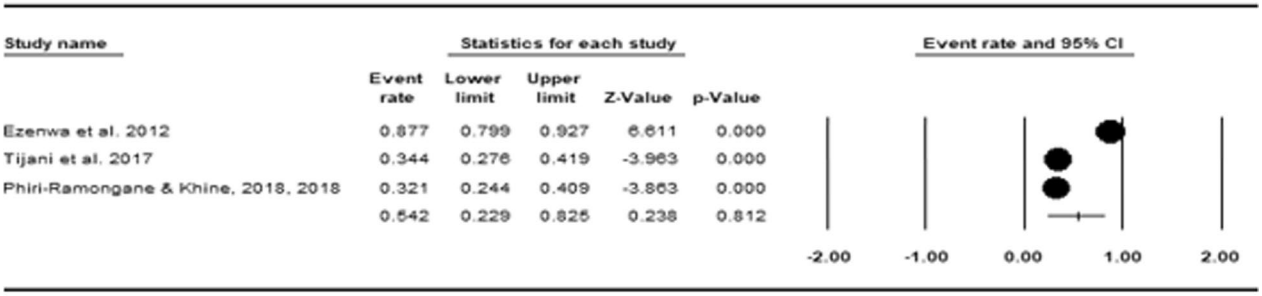
When PSA values fall within the range of 4–10 ng/ml (also called the "grey zone"), free PSA can be performed, and the ratio of the free:total PSA expressed as a percentage gives the %freePSA. A prospective, multi-center clinical trial in the United States of America observed that a lower percentage of fPSA was associated with a higher risk of PCa, and %fPSA was an independent predictor of PCa (Odds ratio [OR],3.2; 95%CI 2.5 – 4.1; $p < 0.001$) [39]. They gave the %fPSA cutoff of ≤ 25% as an ideal level (with 95% sensitivity) to differentiate prostate cancer from benign prostatic disease [39]. But we observed that in males from sub-Saharan Africa, the best diagnostic



a: Sensitivity of %fPSA at ≤30% (94.9% (CI 81.9-98.7), $I^2 = 83.1$, Egger's t = 2.427, p = 0.2488)



b: Specificity of %fPSA at ≤30% (47.9% (CI 10.0-88.4), $I^2 = 97.5$, Egger's t = 3.869, p = 0.1610)



c: Accuracy of %fPSA at ≤30% (54.2% (CI 22.9-82.5), $I^2 = 97.1$, Egger's t = 2.624, p = 0.2318)

Fig. 9 Pooled Sensitivity, Specificity and Accuracy of %fPSA at ≤ 30%

accuracy (84%) was with cut-off ≤ 10% which had a pooled sensitivity of 46.6% and specificity of 91.5%. The implication of this is that using higher cut-offs may lead to overdiagnosis with resultant unnecessary biopsies and its antecedent complications in the African population.

Table 4 Pooled[#] sensitivity, specificity & diagnostic accuracy of %free PSA in sub-Saharan Africa (*n* = 3)

%fPSA cut-off	Sensitivity (%)	Specificity (%)	Accuracy (%)
≤ 10	46.6 (24.0 – 71.0)	91.5 (77.1 – 99.1)	84.0 (67.6 – 93.0)
≤ 15	55.4 (31.7 – 76.9)	77.6 (56.8 – 90.2)	80.4 (58.7 – 92.2)
≤ 20	75.0 (51.9 – 89.3)	64.7 (39.5 – 83.7)	70.8 (45.1 – 87.7)
≤ 25	88.2 (72.9 – 95.4)	59.1 (24.9 – 86.3)	62.5 (32.4 – 85.0)
≤ 30	94.9 (81.9 – 98.7)	47.9 (10.0 – 88.4)	54.2 (22.9 – 82.5)

[#] Summary estimate (95% Confidence Interval)

Our findings are contrasted by the meta-analysis by Huang et al., where they showed that the free/total PSA ratio (which is an approximation of the %fPSA) had a low pooled sensitivity of 70% and specificity of 55% for the diagnosis of PCa but this was not at any particular cut-off [40]. The discrepancy could be due to the variance in cut-off values and regional differences. We reviewed sub-Saharan African studies with various levels of PSA, while Huang et al. [40] were restricted to non-African studies that utilized PSA levels between 4 and 10 ng/ml.

Apart from %fPSA, the other PSA surrogate identified in this review was PSA density (PSAD) [13]. Only one study examined sensitivity and specificity of PSAD to detect PCa and observed the maximum discriminatory cut-off was 0.04 ng/ml/cm^3 with sensitivity 95.88%, specificity 27.8%, and AUC of 82% [13]. When used for PSA in the grey zone (4 – 10 ng/ml), 0.04 ng/ml/cm^3 gave

a better sensitivity (86.7% vs 33.3%) than the internationally accepted cut-off value of 0.15 ng/ml/cm^3, which led them to conclude that 0.04 ng/ml/cm^3 may be a more appropriate cut-off for evaluating Nigerian men with symptomatic prostatic enlargement [13]. This supports the report by Shenoy et al. that general PCa screening guidelines may be inappropriate for black men because the course of the disease is different for them due to social and genetic characteristics [41]. Based on this, it is important to delineate appropriate cut-off values for males in sub-Saharan Africa.

Overall, we agree that PSA should not be used alone in screening or diagnosis of PCa. A South African study of 227 patients showed that using a prostate biopsy decision pathway consisting of PSAD > 0.1 ng/ml/cm^3, %fPSA ≤ 12% and PSA ≥ 4 ng/ml as an indication for biopsy, would have prevented 21.1% of biopsies and 16.7% of clinically insignificant PCa diagnoses [42]. In our study, we recommend that a combination of PSA 4–10 ng/ml and %fPSA ≤ 10% may be a good pointer to an abnormal prostate gland in males from sub-Saharan Africa, and should guide the decision for prostate biopsy.

Age is an important factor to consider when using PSA to screen for PCa because serum PSA varies with age even in healthy individuals. We observed a moderate positive correlation between PSA sensitivity and age that was statistically significant (r = 0.536; $p < 0.05$). This is corroborated by the study of Abbiyesuku et al. that demonstrated a significant positive correlation between age and serum PSA value over the entire age range (r = 0.523; $P = 0.001$) of both healthy individuals and those with prostate abnormalities [43].

5 Limitations

The number of articles included in this review were few based on our criteria, which may have limited the power of our findings. Also, there was considerable heterogeneity among the included studies which could be due to clinical and methodological differences among the individual studies.

6 Conclusions

In sub-Saharan Africa, the PSA cut-off 4–10 ng/ml possessed the highest pooled sensitivity while PSA < 4 ng/ml had the highest pooled specificity. Considering PSA surrogates, %fPSA cut-off at ≤ 10% possessed the highest specificity, but the lowest sensitivity. Consequently, PSA cut-off at 4–10 ng/ml, as well as %fPSA ≤ 10%, showed the best diagnostic accuracy respectively. Thus, a combination of these two may be a more appropriate criteria for deciding males who will be eligible for prostate biopsy in the sub-Saharan Africa region.

Abbreviations

AUC	Area under the curve
CI	Confidence interval
DRE	Digital rectal examination
MeSH	Medical subject headings
na	Not applicable
ng/ml	Nanograms per millilitre
NPV	Negative predictive value
nr	Not reported
%fPSA	Percent free PSA
PPV	Positive predictive value
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PCa	Prostate cancer
PSA	Prostate specific antigen
PSAD	Prostate specific antigen density
SD	Standard deviation
tPSA	Total PSA

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Author contributions
CJO conceived and supervised the study; EOA & MN obtained the data; CJO, IDN, EOA, MN screened and analyzed the data, CJO & MN drafted the article and IDN critically revised it for intellectual content. All authors read and approved the final version to be published.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Ethical approval for the study was obtained from the Health Research and Ethics Committee of University of Nigeria Teaching Hospital, Enugu, Nigeria (UNTH/HREC/2023/01/543). Consent to participate was not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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