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Original Article

Antibiotics has incapability of reducing unnecessary prostate biopsies: a meta-analysis involving 2,035 patients

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Abstract: Objective: To explore the effect of antibiotics on decreasing prostate specific antigen (PSA) of patients scheduled prostate biopsies (PBs) and the feasibility of reducing unnecessary PBs. Methods: A systematic search of PubMed, Embase and the Cochrane Library database was performed to identify all the studies that used antibiotics to decrease elevated PSA of patients scheduled PBs and pursued the possibility of reducing unnecessary PBs. All patients must be scheduled PBs necessarily and they were classified as "asymptomatic" if they had neither lower urinary tract symptoms (LUTS) nor laboratory test for suspected prostatitis and "symptomatic" if LUTS or/and positive laboratory test for prostatitis exist. Stata 13.0 and QUADAS-2 tool was utilized to accomplish meta-analysis. Results: Twenty-one studies involving 2035 patients were included in meta-analysis. The results showed that: a) PSA decreased more in symptomatic patients of antibiotics group than control group [Weighted Mean Difference (WMD) -0.78, 95% confidence intervals (95% CI) (-1.53, -0.03), P=0.041] but not in asymptomatic patients (P>0.05). b). The volume of PSA decreased more in symptomatic patients without prostate cancer (PCa) than symptomatic patients with PCa in antibiotics group [WMD 1.36, 95% CI (0.52, 2.20), P=0.002], but this statistical difference was not found in asymptomatic patients of antibiotics group and all patients of control group (P>0.05). c). The area under curve of summary roc curve were 0.64 [95% CI (0.60, 0.68)] and 0.66 [95% CI (0.62, 0.70)] to diagnose PCa when cutoff points were set as normal PSA (repeat PSA=2.5 ng/ml or 4 ng/ml) and responsive PSA (PSA had a meaningful decline or not). Conclusions: Antibiotics treatment cannot decrease elevated PSA of asymptomatic patients and reduce unnecessary PBs.

Keywords: Antibiotics, meta-analysis, prostate biopsy, prostate cancer, prostate specific antigen

Introduction

Prostate specific antigen (PSA) has been used world widely since the late 1980s and it is still the most important tumor marker for diagnosing and monitoring prostate cancer (PCa) [1]. With a profound impact on PCa screening, PSA and its derivatives have guidance significance to prostate biopsies (PBs)-an appropriate medical procedure to get specimens of patients with suspected PCa.

Unsatisfactorily, patients who were prescribed PBs due to elevated PSA levels between 4 and 10 ng/ml are verified PCa in 20% to 30% actually and the other patients may be recommended further PBs [2]. While, it is reported only one in ten patients would consider further PBs after procedure due to pains, discomfort and anxiety in this unfavorable experience [3]. Furthermore, in case of complications: hematuria (10-84%), hematospermia (1.1-93%), rectal bleeding (1.3%-45%), transient lower urinary tract symptoms (25%) and infectious complications resulting in 0-6.3% hospitalization, the suffering and affliction would be prolonged and aggravated, and even lead to life-threatening status [4, 5].

With a 80% sensitivity and 20% specificity [6], PSA is organ but not cancer specific to the prostate gland which makes a substantial overlap in values of PSA between PCa and other conditions (eg. differences in androgen levels, pros-

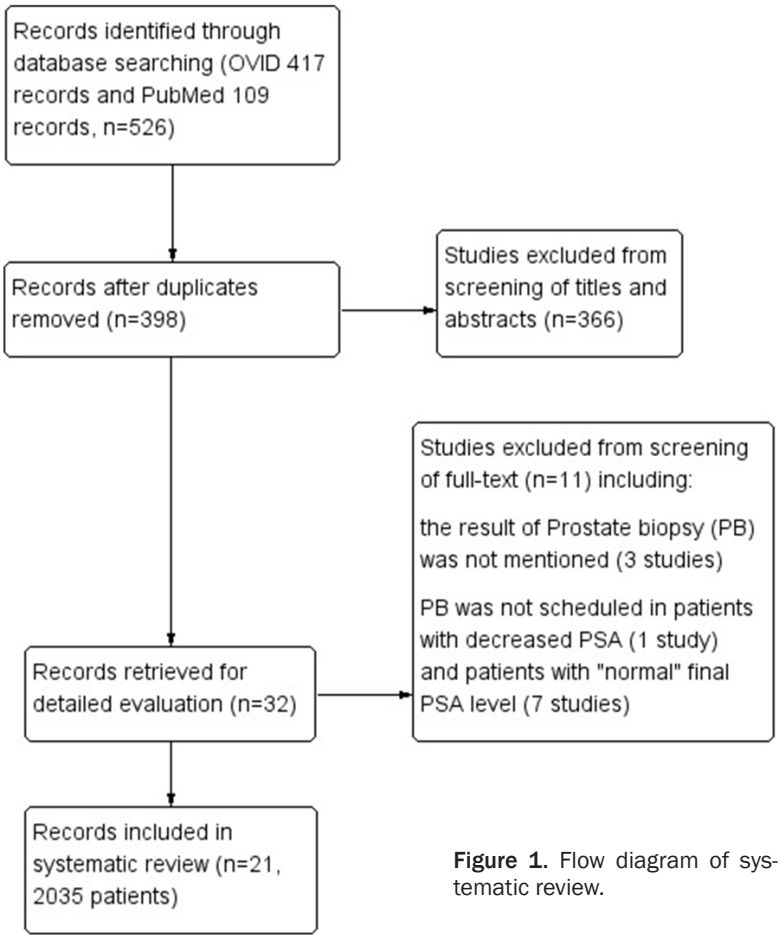

Figure 1. Flow diagram of systematic review.

tate manipulation, ejaculation, benign prostatic hyperplasia, etc) [1, 7]. Asymptomatic prostatitis, as one of confounding factors resulting in elevated PSA without obvious clinical signs, is hard to be differentiated from PCa before the histopathological examination. Although the PCa detection rate is significantly associated with the PSA velocity (PSAV) during the year prior to the biopsy, the frequency of histological inflammation is also associated with PSAV [8]. Aiming at treating asymptomatic prostatitis, antibiotics were used in many clinical centers to manage patients with moderately elevated PSA in order to confirmed or suspected nonmalignancy which may decrease the number of unnecessary PBs [2]. Evidences [9-11] supporting this kind of attempt reported a declines in PSA levels ranging from 7.1% to 43% after antibiotics treatment, but other evidences from the literature are contradictory and considered not only the useless of antibiotics in decreasing PSA but also the possible harmfulness-delaying or missing PCa diagnosis and abuse of antibiotic [8, 12].

We conducted a systematic review and meta-analysis [12] of all randomized controlled trials (RCTs) previously and drew a conclusion that the use of antibiotics might neither decrease PSA levels significantly nor avoid unnecessary biopsies. However the evidences supporting this conclusion were poor. First, the number of participants was small (656 patients). Second, owing to the limited number of RCTs, the outcomes were not classified according to whether patients were asymptomatic or not and some of outcomes were only based on 2 studies. So it is necessary to have a further systematic review and meta-analysis based on comprehensive evidences.

Methods

Search strategy

A systematic bibliographic search of PubMed, Embase and the Cochrane Library database (the Cochrane central register of controlled trials and the Cochrane Data base of Systematic Reviews) of Ovid was done from inception to 4 August 2015 for studies that reported using antibiotics to decrease elevated PSA levels of patients who scheduled PBs and pursuing the possibility of reducing unnecessary PBs. Keywords used for searching were: antibacter*; antimicrob*; antibio*; prostate specific antigen; psa; prostat*; biopsy. Original papers were scanned in the reference section to look for missing trials.

Participants

No restriction of study type, with all enrolled patients scheduled PBs necessarily, published studies that used antibiotics to decrease elevated PSA levels and pursued the possibility

Table 1. Characters of included studies

Reference	Study type	Country	Patients	Inclusive criteria			Antibacterial therapy			Cores of PBs
				PSA rage, ng/ml	DRE results	Symptomatic*	Antibiotics	Daily dose	Course	
Baltacı 2009	Prospective	Turkey	100	4-10	Negative	N	Ofloxacin	400 mg once/day	20 days	12
Busato 2015	Prospective	Brazil	106	4-10	Negative	N	Ciprofloxacin	500 mg twice/day	3 weeks	≥12
Dirim 2009	Retrospective	Turkey	85	2.7-19.2	Negative	N	Levofloxacin	500 mg once/day	4-8 weeks	10
							Ciprofloxacin	500 mg twice/day		
Eggener 2013	Randomized	USA, Israel, Canada	77	>2.5	Negative	N	Ciprofloxacin	500 mg twice/day	2 weeks	≥12
Erol 2006	Randomized	Turkey	97	>4	NR	Y	Ciprofloxacin	500 mg twice/day	2-3 weeks	#
Fandella 2014	Retrospective	Italy	100	4-10	Negative	N	Levofloxacin	500 mg once/day	20 days	12
Faydaci 2012	Prospective	Turkey	108	>2.5	NR	Y	Ofloxacin	400 mg once/day	3 weeks	12
Heldwein 2011	Prospective	Brazil	202	>2.5	Negative	N	Levofloxacin	500 mg once/day	30 days	12
Karazanashvili 2001	Prospective	Georgia	61	4-10	Negative	Y	Ofloxacin	400 mg twice/day	15 days	6
							Specific antibacterial therapy			
Kaygısız 2006[&]	Prospective	Turkey	48	4-10	Negative	Y	Ofloxacin	400 mg once/day	3 weeks	10
							Specific antibacterial therapy			
Kim 2011	Prospective	Korea	86	>4	Negative	Y	Ciprofloxacin	500 mg once/day	4 weeks	10
Kobayashi 2008[&]	Prospective	Japan	51	>4	Negative	Y	Levofloxacin	300 mg once/day	4 weeks	10-18
Lorente 2002	Randomized	Spain	90	4-20	Negative	Y	Ofloxacin	400 mg twice/day	3 weeks	6
Saribacak 2014	Randomized	Turkey	100	4-10	Negative	N	Ofloxacin	400 mg once/day	4 weeks	12
Serretta 2008	Prospective	Italy	99	4-20	Negative	N	Ciprofloxacin	500 mg twice/day	3 weeks	12-21
Shtricker 2009[&]	Retrospective	Israel	135	4-10	Negative	N	Ofloxacin	Unknown	10-14 days	10
							Ciprofloxacin			
Stopiglia 2010	Randomized	Brazil	98	2.5-10	Negative	Y	Ciprofloxacin	500 mg twice/day	28 days	12
Tang 2010	Prospective	China	136	4-50	Negative	Y	Levofloxacin	500 mg once/day	2 weeks	6-13
Toktas 2013	Randomized	Turkey	140	2.5-10	Negative	Y	Levofloxacin	500 mg once/day	21 days	12
Torky 2011[&]	Prospective	Egypt	44	4-10	Negative	N	Levofloxacin	500 mg once/day	4 weeks	12
Ugurlu 2010	Randomized	Turkey	72	2.5-10	Negative	Y	Levofloxacin	500 mg once/day	3 weeks	10

*: Whether the patients had lower urinary tract symptoms or laboratory test for suspected prostatitis; PBs: prostate biopsies; NR: not required; #: the cores of PBs were according to the volume of prostate; [&]: some patients were not prescribed PBs as their own choice.

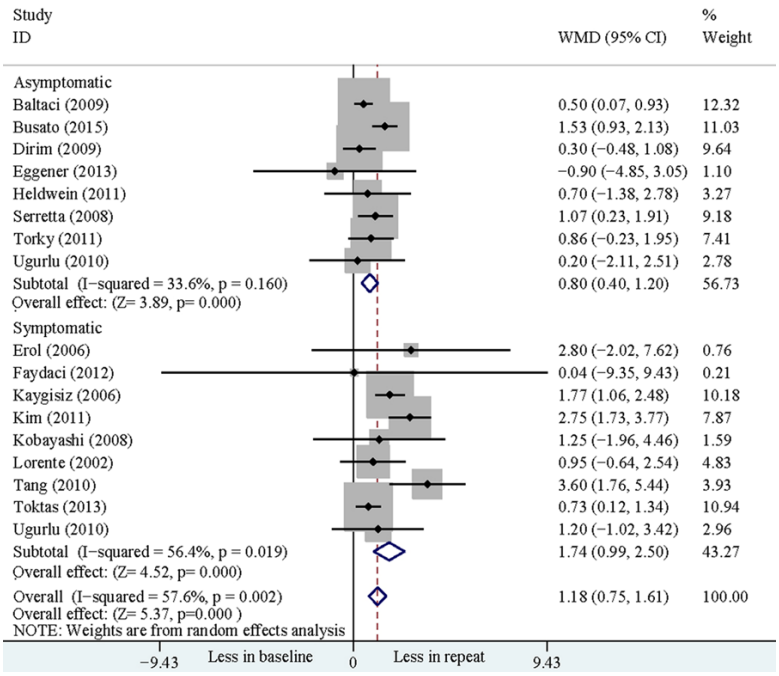

Figure 2. Baseline vs repeat PSA levels of antibiotics group (Begg's test P=0.711; Egger's test P=0.433).

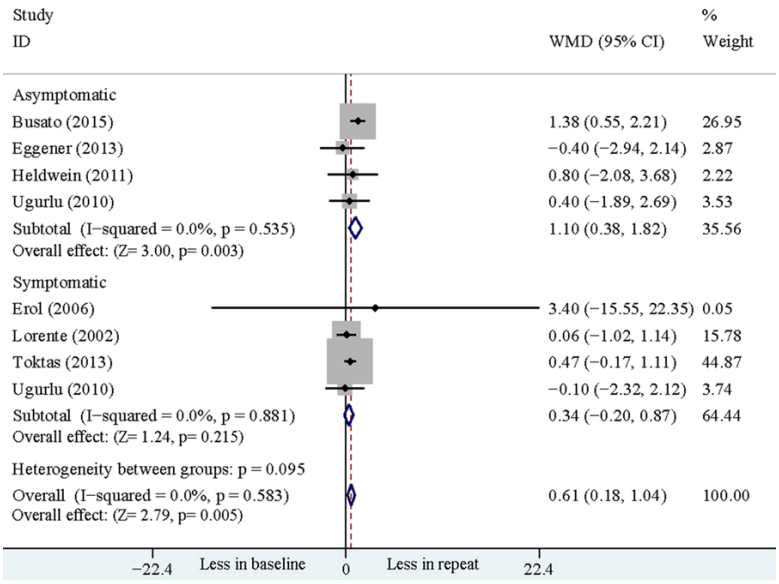

Figure 3. Baseline vs repeat PSA levels of control group (Begg's test P=0.536; Egger's test P=0.635).

of reducing unnecessary PBs were included. Patients were considered as "asymptomatic" if they had neither lower urinary tract symptoms (LUTS) nor laboratory test for suspected prostatitis and "symptomatic" if LUTS or/and positive laboratory test for prostatitis exist. Followed, studies were classified as two types with labels: "asymptomatic" and "symptomatic". The studies had some patients not be scheduled PBs under specific conditions but patients' personal choice were excluded. The duplicate publications, that two or more studies investigating the same sample and abstracts or unpublished reports were not included. Only studies published as full-text articles were included in this study.

Outcome measures

There were two types of outcomes measured in this review. a) The outcomes of interventional efficacy-the efficacy of antibiotics treatment on decreasing elevated PSA including: the levels of the baseline and repeat PSA, the volume of PSA decreased. These outcomes were compared between antibiotics group and control group or patients with PCa (PCa patients) and patients without PCa (nPCa patients); b) The outcomes of diagnostic accuracy-the feasibility of reducing unnecessary PBs including: the pooled sensitivity, pooled specificity and area under curve (AUC) of summary roc curve (SROC). These outcomes were calculated though the value of true positive (TP), false negative (FN), false positive (FP) and true negative (TN) for PCa diagnosis based on PBs (golden standard) according to two cutoff points: normal PSA (repeat PSA=2.5 ng/ml or 4 ng/ml) and responsive PSA (PSA had a meaningful decline or not).

Literature screening and data extraction

Two reviewers (Yu F, Duan G) read the title and abstracts of all potential studies and selected

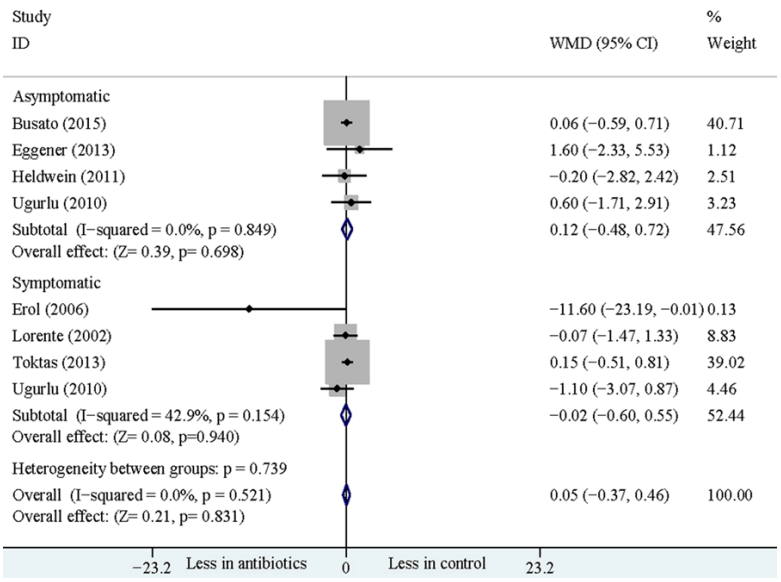

Figure 4. Antibiotics group vs control group about repeat PSA levels (Begg's test P=0.711; Egger's test P=0.280).

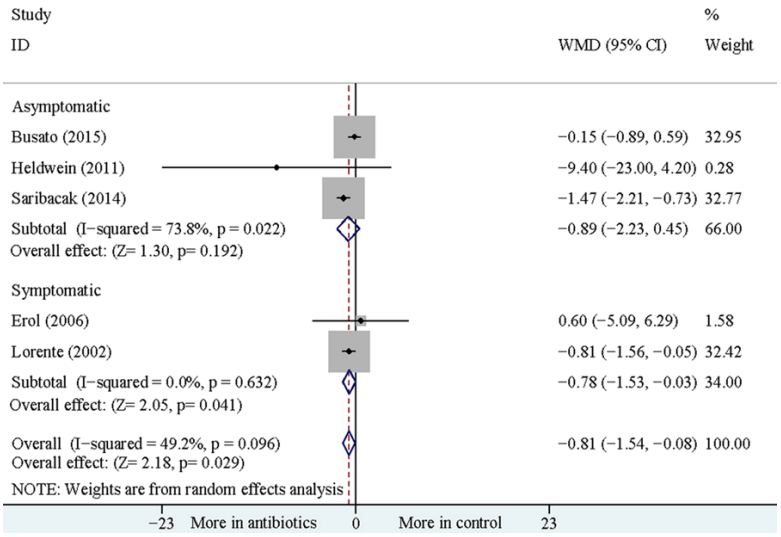

Figure 5. Antibiotics group vs control group about the volume of PSA changes (Begg's test P=0.806; Egger's test P=0.731).

eligible ones according to the predetermined inclusion and exclusion criteria independently. Discrepancies when existed were resolved by discussion between two reviewers or by assistance of third reviewer (Wei Q). Data extracted and typed in by aforementioned two reviewers (Fan Y, Duan G) through elaborative reading and utilization of a specific formulary, the third reviewer (Wei Q) checked information and discussed within team (Other authors) to resolve differences. If the study provided medians and interquartile ranges instead of means and standard deviations (SDs), we imputed the means and SDs as described by Hozo *et al.* [13]. In the presence of missing data, effort would be made to contact the authors for information. Data extracted mainly included: general information of trials, selected outcomes and methodological characteristics.

Statistical analysis of the included studies

Stata 13.0 was used to accomplish meta-analysis. The methodological quality of each selected studies with diagnostic accuracy outcomes was assessed according to the QUADAS-2 tool [14]. Continuous data was expressed as Weighted Mean Difference (WMD) along with 95% confidence intervals (95% CI). 95% CI was described in pooled sensitivity, specificity and AUC as well. All *p* values were based on two-sided tests and P<0.05 was considered statistically significant except Deeks' funnel plot asymmetry test by which significant publication bias was indicated if P<0.10 [15].

As to interventional efficacy outcomes, publication bias was tested by Begg's and Egger's test. When there was no considerable heterogeneity examined by I^2 test among the studies (P≥0.10, I^2≤50%), fixed-effect model was adopted. While considerable heterogeneity was detected (P<0.10, I^2>50%), data were rechecked to eliminate anthropogenic heterogeneous and a possible explanation was pursued. If reasonable cause was found, an effort for removal of it or a separate and sensitivity analysis would be performed. Still, heterogeneity persisting, random-effects model was utilized in the presence of clinical homo-

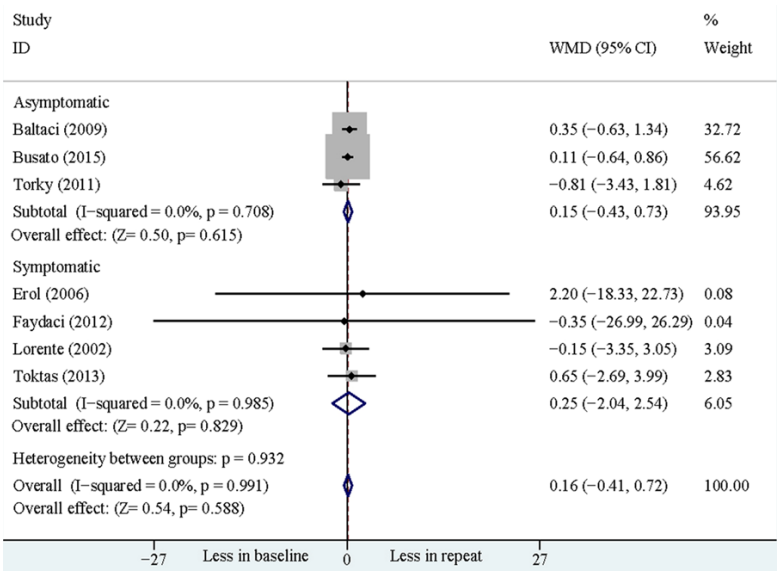

Figure 6. Baseline vs repeat PSA levels of PCa patients in antibiotics group (Begg's test P=1.000; Egger's test P=0.809).

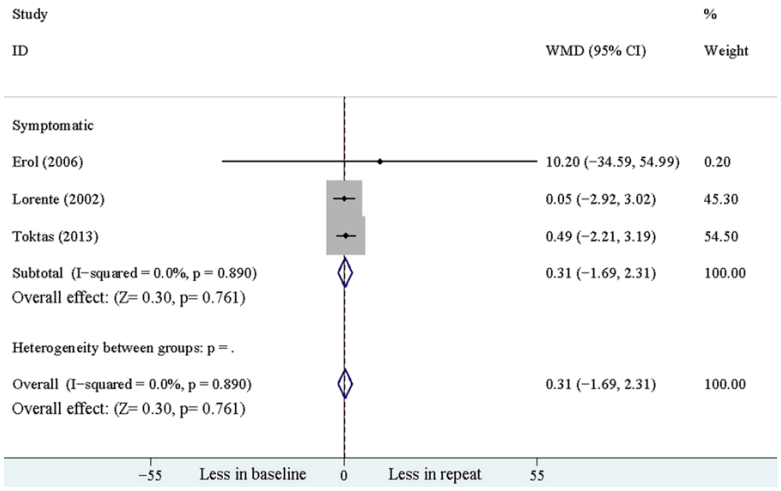

Figure 7. Baseline vs repeat PSA levels of PCa patients in control group (Begg's test P=1.000; Egger's test P=0.337).

geneity of trials. If the cause was not apparent and heterogeneity was caused by divergent data in terms of direction to results, data would not be synthesized. In case it was not possible to perform a meta-analysis of data, the results were presented in a descriptive form with individual evaluation of the results of each study.

When diagnostic accuracy outcomes were analyzed, the possible existence of a threshold effect was tested. If evidence of a threshold effect was verified, subgroup analysis would be conducted when possible. Otherwise, data would be described without synthesis. The possible publication bias was tested by Deeks' funnel plot asymmetry test and the possible heterogeneity of the studies was assessed by a chi-square test for sensitivities, specificities. In case of heterogeneity between studies was found ($P<0.10$, $I^2>50\%$), the analysis was performed following the random effects model, as well as subgroup analysis when possible.

Results

Selected trials

PubMed and Ovid were searched respectively with 109 and 417 references. After removing 128 duplicates, titles and abstracts of 398 records were read and 366 studies that did not meet the inclusion criteria were excluded. The rest 32 records retrieved for detailed evaluation, Eleven studies were excluded from screening of full-text, that including: the result of PBs was not reported in article (3 studies); PBs was not scheduled in patients with decreased PSA (1 study) and patients with "normal" (2.5 or 4 ng/ml) repeat PSA levels (7 studies). Eventually, twenty-one studies [10, 11, 16-34] were identified (2035 patients in all) and included in this meta-analysis (**Figure 1**).

Descriptive analysis of the included studies

There were 7 randomized controlled trials (RCTs), 11 prospective trials and 3 retrospective studies were included in this meta-analysis and their characters were showed in **Table 1**. One study [19] was conducted in multicenter of USA, Israel and Canada and the rest studies were carried out in several countries: eight

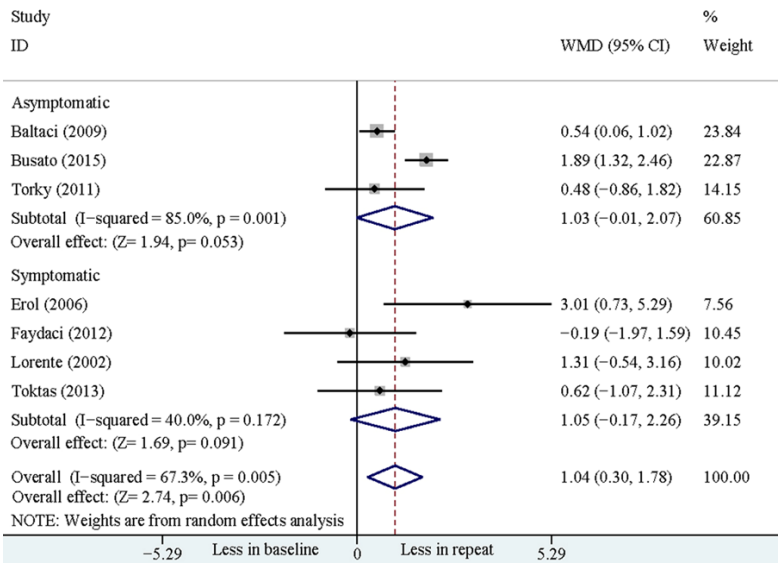

Figure 8. Baseline vs repeat PSA levels of nPCa patients in antibiotics group (Begg's test P=0.368; Egger's test P=0.960).

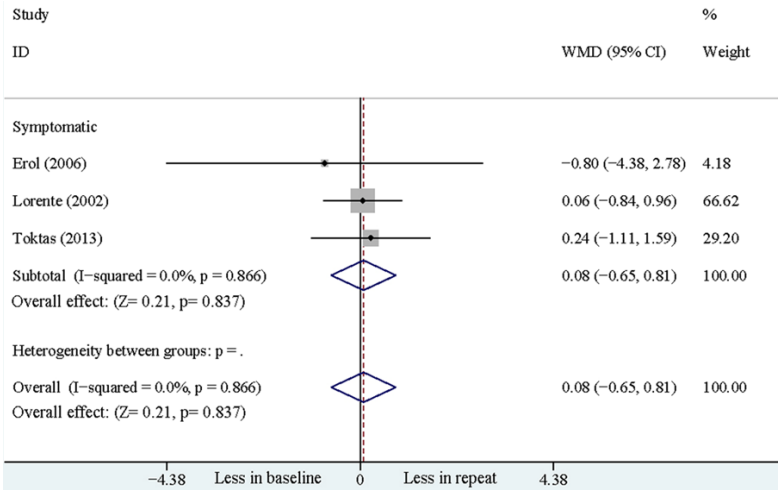

Figure 9. Baseline vs repeat PSA levels of nPCa patients in control group (Begg's test P=1.000; Egger's test P=0.511).

studies in Turkey [16, 18, 20, 22, 24, 28, 32, 34], three studies in Brazil [17, 23, 30], two studies in Italy [11, 21] and one study in Georgia [10], Korea [25], Japan [26], Spain [27], Israel [29], China [31] and Egypt [33] respectively. Inclusion criteria of these studies contained normal findings under digital rectal examination (DRE) except two studies [20, 22]. Fourteen studies [10, 11, 16-18, 21, 24, 27-30, 32-34] included patients with moderately elevated PSA level: 2.5-20 ng/ml, but 6 studies [19, 20, 22, 23, 25, 26] with unmentioned upper limit of PSA levels and 1 study [31] with PSA rage: 4-50 ng/ml. One study [34] was comparative study of patients in the presence with absence of inflammation in the expressed prostate secretion (EPS). Ten studies [11, 16-19, 21, 23, 28, 29, 33] included asymptomatic patients and other ten studies [10, 20, 22, 24-27, 30-32] included symptomatic patients. The antibiotics used on decreasing elevated PSA levels were all quinolones and specific antibacterial therapy in case specific pathogen was found. Every study scheduled PBs for all their patients, but 107 patients of four studies [24, 26, 29, 33] were not prescribed PBs as their own choice. All PBs of studies were performed under ultrasonography guided, and most of which contained a minimum of 10 cores except four studies [10, 20, 27, 31].

Meta-analysis

Variations in levels of PSA: In order to explore the efficacy of antibiotics on decreasing PSA levels, twenty studies were included in intervention meta-analysis but one study [21] with incomplete reported data which was not proper to be combined. Comparing the baseline levels with repeat levels of PSA, the difference of antibiotics group was statistically significant-showed a downward trend of PSA [WMD 1.18, 95% CI (0.75, 1.61), P<0.001]. In subgroup analysis, the differences were in both asymptomatic patients [WMD 0.80, 95% CI (0.40, 1.20), P<0.001] and symptomatic patients [WMD 1.74, 95% CI (0.99, 2.50), P<0.001] (**Figure 2**). The downward trend of PSA was weaker in control group [WMD 0.61, 95% CI (0.18, 1.04), P=0.005] and the differences were statistically significant in asymptomatic

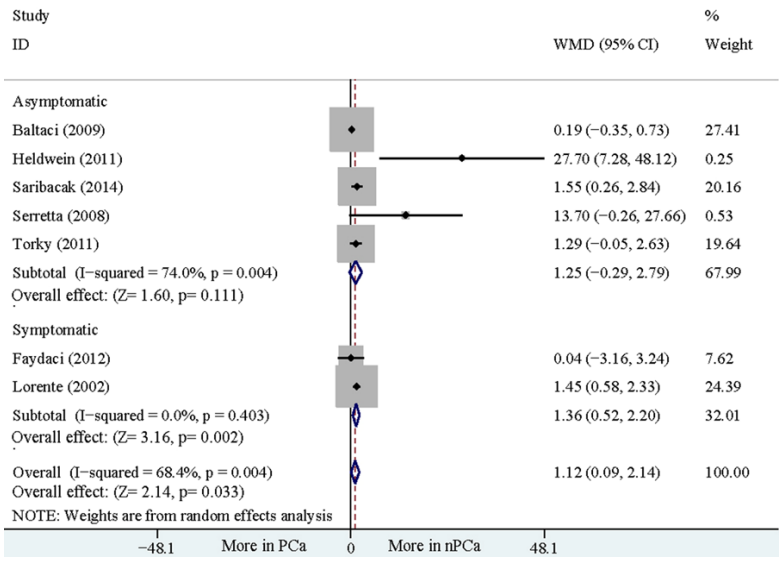

Figure 10. PCa vs nPCa patients of antibiotics group about the volume of PSA decreased (Begg's test P=0.368; Egger's test P=0.039).

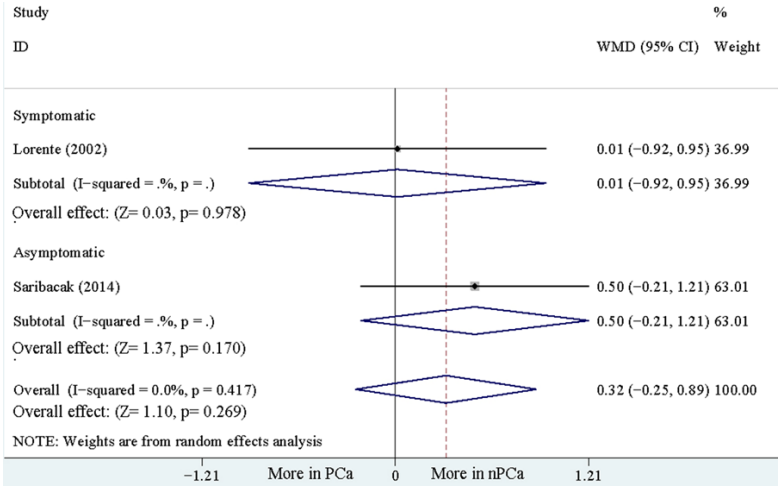

Figure 11. PCa vs nPCa patients of control group about the volume of PSA decreased.

patients merely [WMD 1.10, 95% CI (0.38, 1.82), P=0.003] but in symptomatic patients [WMD 0.34, 95% CI (-0.20, 0.87), P=0.215] (**Figure 3**). Although the repeat PSA levels of antibiotics group and control group were comparable [WMD 0.05, 95% CI (-0.37, 0.46), P= 0.831] (**Figure 4**), the volume of PSA decreased more in antibiotics group than control group [WMD -0.81, 95% CI (-1.54, -0.08), P= 0.029] (**Figure 5**). However, this kind of statistical difference was only found in symptomatic patients [WMD -0.78, 95% CI (-1.53, -0.03), P=0.041] (**Figure 5**).

As to comparing baseline with repeat PSA levels of PCa and nPCa patients, statistical difference was not found in PCa patients of both antibiotics group (**Figure 6**) and control group (**Figure 7**), but found in nPCa patients [WMD 1.04, 95% CI (0.30, 1.78), P=0.006] of antibiotics group (**Figure 8**). In comparison, this statistical difference was not found in nPCa patients (**Figure 9**) of control group. Likewise, the volume of PSA decreased more in nPCa symptomatic patients than PCa symptomatic patients of antibiotics group [WMD 1.36, 95% CI (0.52, 2.20), P=0.002] (**Figure 10**), but this kind of difference was not found in asymptomatic patients of antibiotics group (**Figure 10**) and patients of control group (**Figure 11**).

The possible of publication bias was found when PCa with nPCa patients of antibiotics group were compared about the volume of PSA decreased (**Figure 10**. Begg's test P=0.368; Egger's test P=0.039). After removing one study [23] (Heldwein et al.) that resulted in possible publication bias according to funnel plot, publication bias was not found (Begg's test P=1.000; Egger's test P=0.147) and the result of meta-analysis was unchanged. The possible of publication bias was not found in other results.

Feasibility of avoiding unnecessary PB: With different cutoff points, the repeat PSA levels and the percentage of PSA decreased were utilized to pursue the feasibility of antibiotics treatment on reducing unnecessary PBs in 18 studies. The methodological quality of these studies was moderate that each of 9 studies had one high risk of bias and 5 studies had one

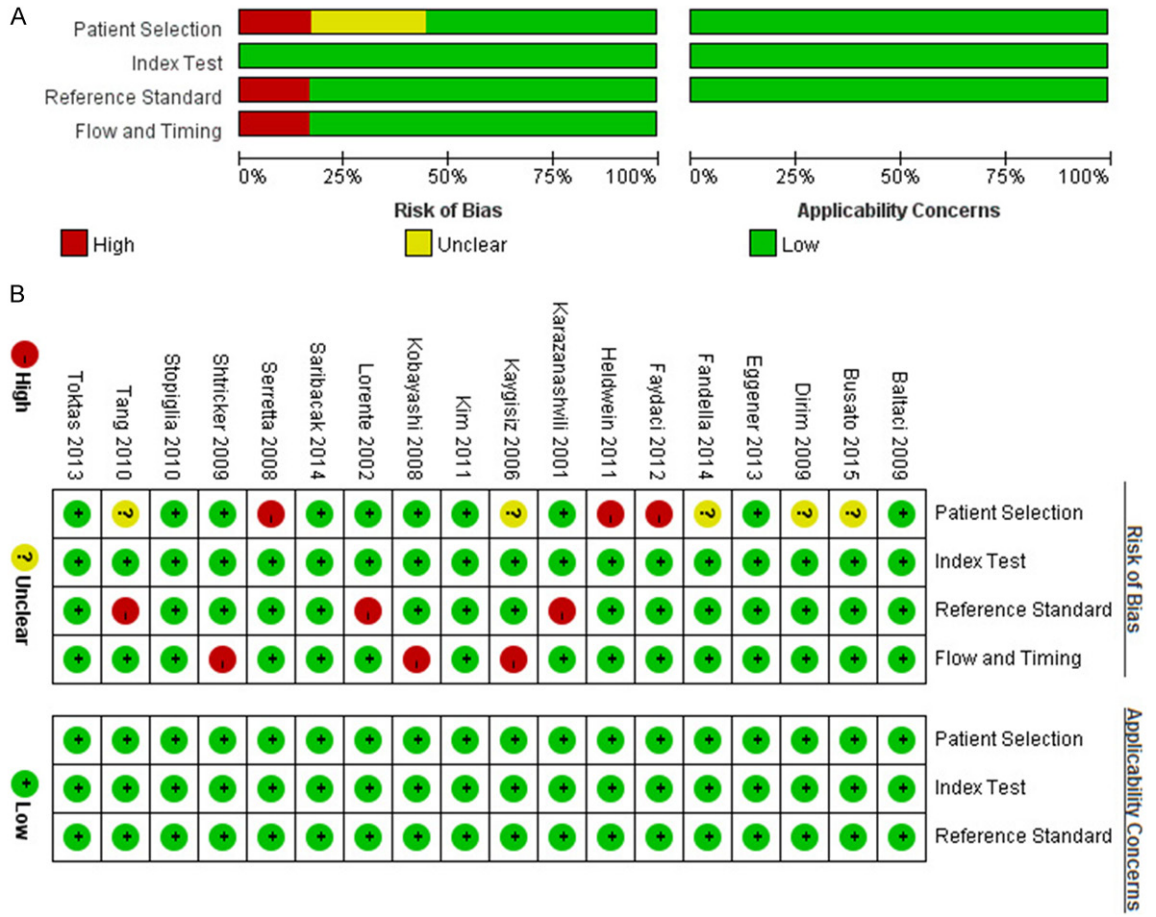

Figure 12. A: Risk of bias and applicability concerns summary: review authors' judgements about each domain for each included study. B: Risk of bias and applicability concerns graph: review authors' judgements about each domain presented as percentages across included studies.

unclear risk of bias respectively. More details are showed in **Figure 12**.

Threshold effect was not detected when cutoff point was normal PSA (**Figure 13**. P=0.10). Whereas, threshold effect was tested when cutoff point was responsive PSA (**Figure 14**. P=0.05). Publication bias was not found in both cutoff points (**Figures 15**, **16**) according to Deeks' funnel plot asymmetry test.

Due to existence of threshold effect, the sensitivities and specificities were inappropriate to be pooled when cutoff point was responsive PSA and the range of their values were 0.33-1.00 and 0.29-0.88 respectively (**Figure 17**). As to cutoff point normal PSA (**Figure 18**), heterogeneity was found between studies and analysis was performed following the random effects model. The pooled sensitivity and specificity were 0.94 [95% CI (0.86, 0.97)] and 0.20 [95% CI (0.14, 0.29)] respectively. The AUC of SROC tested under cutoff point normal PSA and responsive PSA were 0.64 [95% CI (0.60, 0.68)] and 0.66 [95% CI (0.62, 0.70)].

Discussion

In this systematic review and meta-analysis of data from studies exploring antibiotics treatment on decreasing elevated PSA levels to reduce unnecessary PBs, we found the PSA decreased eventually whether using antibiotics or not. The decline of PSA in control group was mostly attributed to the biological variation of PSA that is reported ranging from 6.2% to 58% [35]. Although existence of biological variation of PSA in antibiotics group as well, we found the volume of PSA decreased more in antibiotics group than control group. Yet, this additional

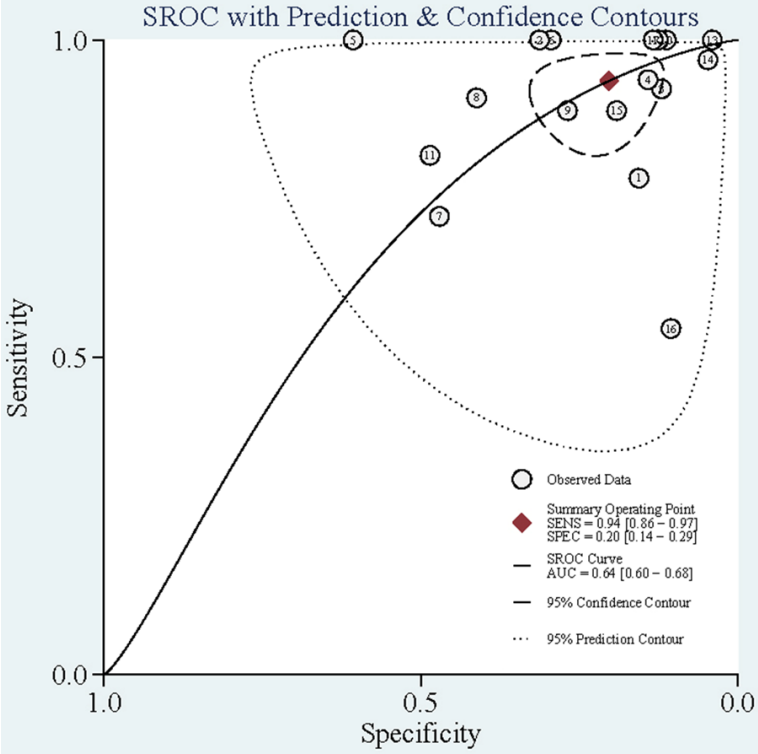

Figure 13. Cutoff point: normal PSA-area under curve (AUC) of summary roc curve (SROC). Proportion of heterogeneity likely due to threshold effect =0.10.

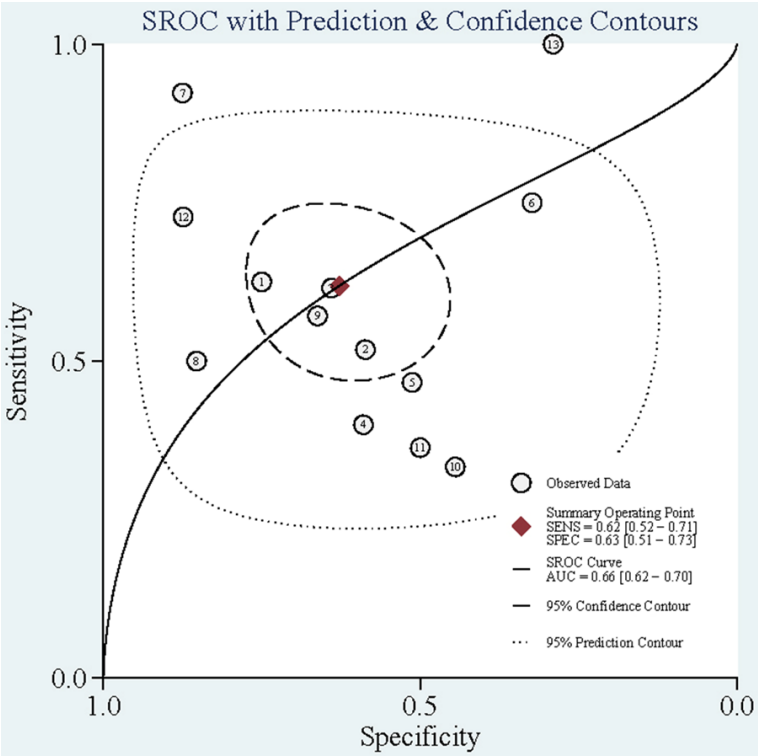

Figure 14. Cutoff point: responsive PSA-area under curve (AUC) of summary roc curve (SROC). Proportion of heterogeneity likely due to threshold effect =0.05.

decline should be ascribed to the efficacy of antibiotics on treating symptomatic patients but asymptomatic patients.

The most possibility of PSA decline after antibiotics treatment is the result of curing suspected histological prostatitis, a very common entity in pathology data of patients after PBs, which could result in rising levels of PSA [36]. As one of prospective trials we searched in database that had comparison between patients with and without prostatitis, the trial of Lee et al. [24] containing the largest number of patients (413 patients) found the cancer detection rate was 20.7% in the patients without prostatitis (negative findings on the EPS or VB_3) and 3.3% in the patients with prostatitis after antibiotics treatment respectively. There are reasonable evidences from the literature to show a decline of PSA after antibiotics treatment for prostatitis and achievement of normalization in about 42%-46% patients [37, 38]. In this meta-analysis, the efficacy of antibiotics on decreasing PSA was confirmed in nPCa patients but PCa patients and this efficacy was only found in symptomatic patients statistically. In addition, it is worth mentioning that asymptomatic patients seemed to have more spontaneous PSA decline than symptomatic patients (**Figure 3**).

Yet, prostatitis is still unsatisfactorily differentiated from prostate cancer due to the fact that inflammatory processes not only occur in association with benign prostate hyperplasia but also with carcinomatous neoplasia (in about 80% of cases) [36]. That could be one of reasons that

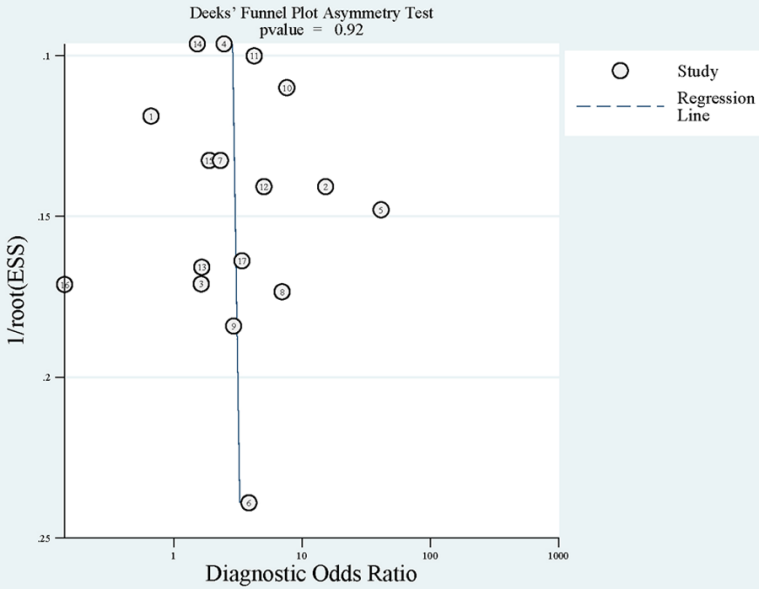

Figure 15. Publication bias of cutoff point: normal PSA.

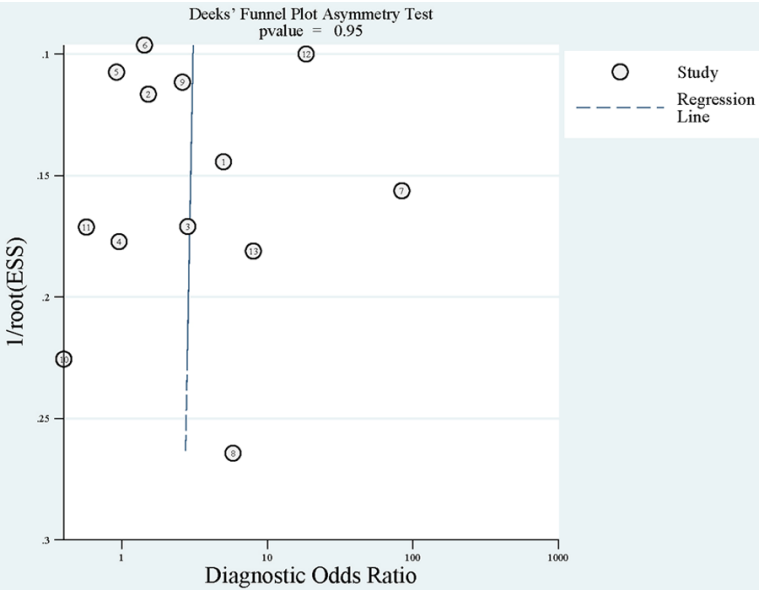

Figure 16. Publication bias of cutoff point: responsive PSA.

included asymptomatic patients and have no analysis of patients with prostatitis.

Further, with moderate methodological quality of included studies, PSA fluctuation after antibiotics treatment of these studies was regarded as a diagnostic method in this meta-analysis to explore the possibility of reducing unnecessary PBs. Setting cutoff point as normal PSA, that whether repeat PSA was less than 2.5 or 4 ng/ml or not after antibiotics treatment, the pooled sensitivity reached up to 0.94 (0.86-0.97) but specificity was as low as 0.20 (0.14-0.29) and AUC was 0.64 (0.60-0.68) merely. Likewise, When the cutoff point was set as responsive PSA, that whether PSA had meaningful decline or not after antibiotics treatment, the sensitivity and specificity fluctuated strongly around 0.62 and 0.63 and the AUC was 0.66 (0.62-0.70) (**Figure 14**). Both two cutoff points were poor in distinguishing PCa from cluster. Although the sensitivity of cutoff point normal PSA was 94%, the improvement of diagnostic accuracy of PSA (80% sensitivity and 20% specificity [6]) was limited. So, antibiotics treatment was inappropriate to be utilized to reduce unnecessary PBs at least in asymptomatic patients.

the possibility of PCa remains in patients whose PSA levels decrease to lower than 4 ng/ml even 2.5 ng/ml [25]. Among the included studies of our meta-analysis, none of studies [20, 22, 24-27, 30, 31, 34] that had patients with prostatitis as inclusive criteria or had comparison between patients with and without prostatitis was found the inefficacy of antibiotics on decreasing PSA of patients with prostatitis. Relatively, other studies [16, 17, 19, 21, 23, 29] that found inefficacy of antibiotics were all have

The trial of Heldwein *et al.* [23] has the largest number of patients (202 patients) among included studies. In accord with our result, they reported poor diagnostic accuracy to PCa of PSA fluctuation after antibiotic treatment as well and drew a conclusion that no specific PSA reduction threshold can accurately discriminate prostate cancer. In their trial, the cutoff points that 45% PSA decreased, 20% PSA decreased, repeat PSA 4 ng/ml, repeat PSA 2.5 ng/ml and baseline 20% free: total PSA ratio

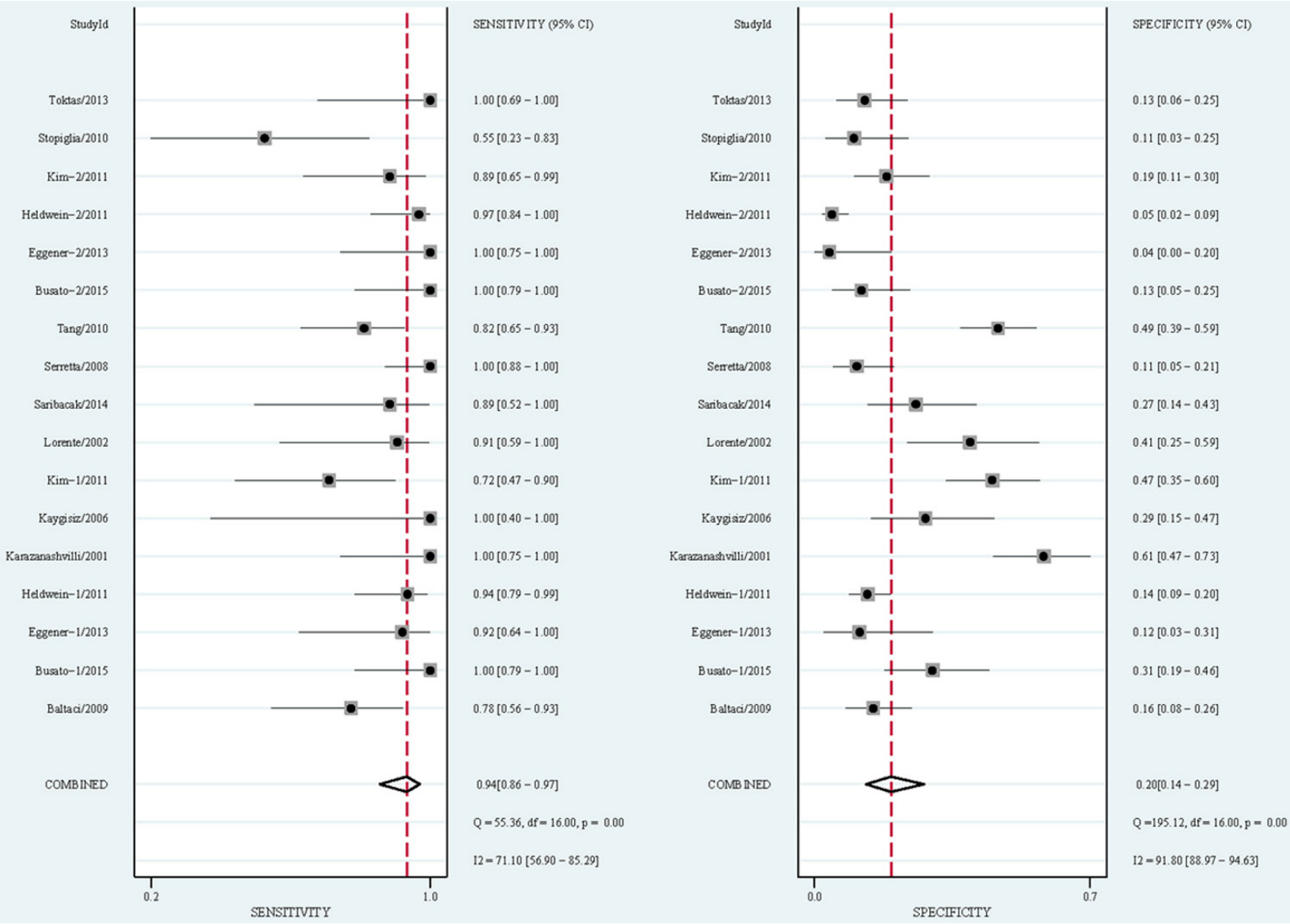

Figure 17. Cutoff point: normal PSA-the sensitivities and specificities of included studies and pooled values.

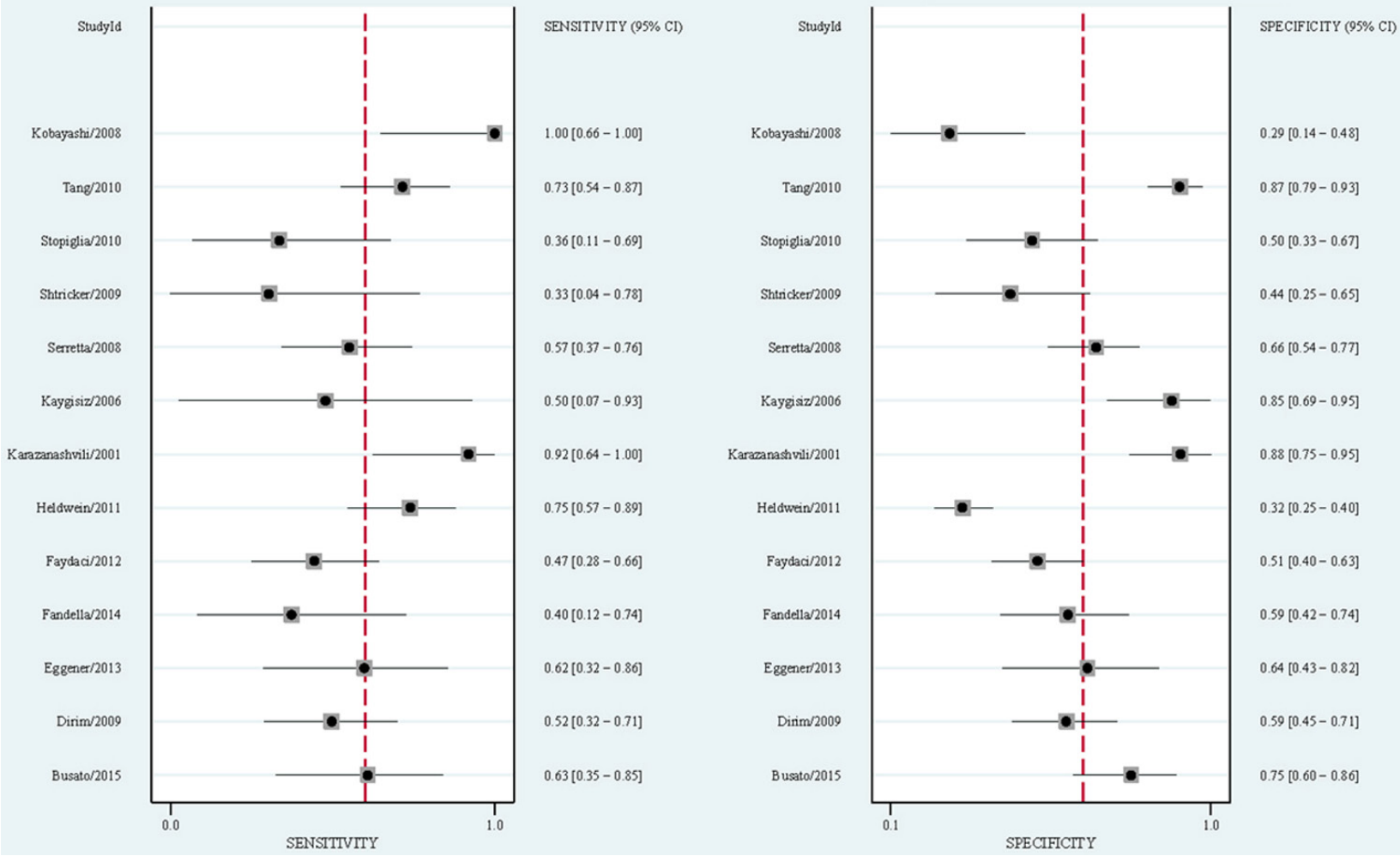

Figure 18. Cutoff point: responsive PSA-the sensitivities and specificities of included studies.

(f/t PSA) had a 90%, 75%, 94%, 97% and 89% sensitivities along with an 11%, 32%, 14%, 5% and 31% specificities. The baseline f/t PSA showed a good diagnostic accuracy (AUC= 0.716). It is regretful that we cannot analyze the possibility of f/t PSA fluctuation after antibiotics treatment on reducing unnecessary PBs due to lack of adequate data.

The antibiotics treatment has incapability of reducing unnecessary PBs. Besides, it cannot be ignored that indiscriminate use of antibiotics could lead to the development of resistant organisms and, thereby, potentially increase the risk for infectious complications [8]. In order to explore the antibiotics treatment on reducing unnecessary PBs, Holland *et al.* [39] and Akduman *et al.* [40] conducted retrospective studies of 484 and 558 patients at their institution respectively and both found that empirical treatment with fluoroquinolone was associated with a statistically significant increase in post-biopsy infectious complications. Combining these evidences with the results of our meta-analysis, we suggest the use of antibiotics should be avoided in asymptomatic patients to reduce unnecessary PBs.

There are several limitations in our meta-analysis. Firstly, due to lack of adequate data and fail to contact missing data, we did not analyze the following issue: the fluctuation of PSA derivatives after antibiotics treatment and the efficacy of them on reducing unnecessary PBs and the possibility of observation or placebo on reducing unnecessary PBs. Secondly, owing to various research methods and various result reporting patterns of included studies, some outcomes measured in this meta-analysis were only based on 2 or 3 studies and some analysis were under random-effects model. Therefore, the conclusions should be considered with caution. Beyond antibiotics, there are multiple methods to decrease PSA, such as 5α-reductase inhibitor with the effect proved by PCPT [41] and REDUCE [42] and it could prevent or delay the appearance of prostate cancer, anti-inflammatory therapy with NSAIDs (e.g. aspirin) [43] or herbal medicine [44]. These factors should be taken into account in further studies.

In summary, results from this meta-analysis suggested that antibiotics treatment can decrease elevated PSA of symptomatic patients but asymptomatic patients. This method has incapability of reducing unnecessary PBs and should be avoided in management of asymptomatic patients.

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Disclosure of conflict of interest

None.

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