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Review – Trial Protocol

Transperineal Versus Transrectal Prostate Biopsy: A Systematic Review and Meta-analysis of Randomized Controlled Trials Across Settings With and Without Magnetic Resonance Imaging Targeting

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Abstract

Background and objective: While transperineal prostate biopsy (TP-Bx) is increasingly being used to mitigate infection risk, its diagnostic equivalence to transrectal biopsy (TR-Bx) remains under investigation. Our aim was to comprehensively compare the diagnostic performance and complication profiles of TP-Bx and TR-Bx across settings with and without magnetic resonance imaging (MRI) targeting using data from randomized controlled trials (RCTs).

Methods: We performed a systematic review and meta-analysis of 12 RCTs comprising 4244 patients. Outcomes included detection of clinically significant prostate cancer (csPC), anterior tumor detection, procedural pain, infection-related complications, urinary retention, and bleeding, each analyzed in groups with and without MRI targeting for biopsy.

Key findings and limitations: Overall csPC detection rates were comparable between TP-Bx and TR-Bx (odds ratio [OR] 1.15, 95% confidence interval [CI] 0.95–1.39). There was no difference in MRI-targeted studies (OR 1.08, 95% CI 0.85–1.36), whereas TP-Bx showed superior csPC detection in settings without MRI targeting (OR 1.41, 95% CI 1.02–1.95). TP-Bx was associated with significantly fewer infectious complications (OR 0.70 for any infection; OR 0.35 for grade $\geq$3 infections), although procedural pain was higher (OR 2.05). No significant differences in urinary retention or bleeding were observed. Heterogeneity in analgesia protocols and MRI use across studies is a limitation.

Conclusions and clinical implications: TP-Bx and TR-Bx yield similar diagnostic performance for csPC in MRI-targeted procedures. However, in settings without MRI targeting, TP-Bx may offer better detection and a substantially lower infection risk. Although TP-Bx is associated with greater procedural discomfort, it can be performed safely under local anesthesia and without antibiotics, which aligns with

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antibiotic stewardship principles. These findings suggest that biopsy route selection should be individualized according to MRI availability, infection risk, and patient tolerance.

Patient summary: We compared evidence for two prostate biopsy methods: transperineal (TP) and transrectal (TR). Both were similar in detecting prostate cancer, but the TP method had fewer infections and may not require antibiotics. TP may cause slightly more discomfort, but pain is generally manageable with local anesthesia. Which approach is best may depend on factors such as the availability of MRI (magnetic resonance imaging), the risk of infection, and the patient's preference.

1. Introduction

Prostate cancer (PC) remains a major global health concern, and accurate diagnostic strategies are needed to identify clinically significant tumors that require treatment. Prostate biopsy with imaging studies is the gold standard for PC detection, with approximately 1 million biopsies performed each year according to US Medicare data sets [1]. The diagnostic pathway has evolved with the introduction of prebiopsy multiparametric magnetic resonance imaging (MRI) to improve detection of clinically significant PC (csPC; International Society of Urological Pathology [ISUP] grade group $\geq$2) [2]. Current guidelines, including the European Association of Urology (EAU) recommendations, support MRI-targeted biopsy to improve csPC detection and avoid unnecessary biopsies [3]. Consequently, biopsy strategies have increasingly shifted towards approaches that integrate MRI guidance and optimize cancer detection while minimizing harm.

Traditionally, prostate biopsy has been performed via a transrectal (TR) ultrasound-guided approach, which is effective under local anesthesia but carries a substantial risk of infection. During a TR biopsy (TR-Bx), bacteria from the rectal flora can be introduced into the prostate and bloodstream, and cause infectious complications, including urosepsis, in approximately 2–5% of cases [4]. The rise in antibiotic resistance has led to heightened concerns about sepsis after TR-Bx. As a result, the transperineal (TP) approach, which accesses the prostate through the perineum, has emerged as an alternative that virtually eliminates rectal contamination. TP biopsy (TP-Bx) can often be performed safely with minimal or no antibiotic prophylaxis, which is an important consideration for antibiotic stewardship [5]. These concerns have prompted updates to the EAU guidelines, which now strongly recommend TP-Bx to reduce infectious complications [3]. Historically, TP-Bx required general or regional anesthesia, which limited its use, but recent advances now allow local anesthetic TP-Bx procedures in outpatient settings [6].

Beyond safety, questions remain regarding the relative diagnostic performance of TP-Bx and TR-Bx, particularly for detection of csPC. Several recent studies have compared cancer detection outcomes between the two approaches using different biopsy techniques and found no clear differences [7]. A recent randomized controlled trial (RCT) involving more than 1000 patients showed a higher csPC detection rate with TP-Bx than with TR-Bx [8]. TP-Bx outperformed TR-Bx in detecting overall PC and csPC, and showed a particularly significant advantage in detecting cancer located in the anterior region of the prostate [9]. These findings align with the intuitive anatomic benefit of the TP approach, which can be used to obtain samples of anterior and apical tumor foci more effectively. However, variability in study design, biopsy protocols, and outcome definitions has led to inconsistent conclusions across the literature.

Although several meta-analyses have previously compared TP-Bx and TR-Bx approaches [7,10], the present study provides an updated synthesis that incorporates the latest large-scale RCT evidence, including the TRANSLATE trial, which was not included in prior reviews. Moreover, by stratifying analyses according to biopsy settings with and without MRI targeting, this meta-analysis reflects the evolving prostate biopsy paradigm in contemporary clinical practice and allows for a more precise evaluation of diagnostic and safety outcomes.

Given the need to maximize detection of csPC while minimizing biopsy-related morbidity, rigorous synthesis of the evidence is necessary. We therefore performed a comprehensive meta-analysis using RCTs comparing TP-Bx and TR-Bx approaches across all biopsy modalities. The primary objective was to compare the csPC detection rates between TP-Bx and TR-Bx, stratified by MRI targeting status.

2. Methods

2.1. Study protocol and registration

This systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines to ensure transparent and standardized reporting. The study protocol was prospectively registered in the PROSPERO database (CRD420251078699).

2.2. Search strategy

We systematically searched electronic databases (PubMed, Embase, and Cochrane Library) on July 17, 2025. The search

strategy was based on the following key concepts: PC, biopsy, and TP and TR approaches. The following search terms and their synonyms/related medical subject headings (MeSH) were used: "prostatic neoplasm", "prostate cancer", "biopsy", "transperineal", and "transrectal" (Supplementary Table 1). Studies involving patients who had undergone prostate biopsy and comparing TP-Bx and TR-Bx were included. Only RCTs reporting on csPC detection, anterior tumor detection, total cancer detection, infection complications, and acute urinary retention (AUR) rates were included. Conference abstracts, review articles, editorials, comments, and letters to the editor were excluded. Two authors (S.Y.C. and Y.-J.Y.) independently screened the titles and abstracts of the studies retrieved for eligibility. Disagreements were resolved via discussion or via consultation with a third author (T.T.N.).

2.3. Data extraction

Data were independently extracted by two authors, and disagreements were resolved by discussion with a third author. Study characteristics including first author, year, biopsy type, number of participants, and outcomes were extracted. The primary outcome was the csPC detection rate, with prespecified analysis in biopsy settings with and without MRI targeting. Secondary outcomes included anterior tumor detection, overall PC detection, infection-related complications, and AUR, each analyzed in the groups with and without MRI targeting. In all trials with MRI-targeted biopsy, targeted and systematic biopsies were performed concurrently and reported as combined outcomes. Therefore, outcomes specific to targeted cores alone were not available. To account for this, analyses were stratified by study design with versus without MRI targeting rather than by biopsy modality alone.

2.4. Risk-of-bias assessment

The Cochrane risk of bias tool (RoB2) was used to assess the quality of the studies. Two independent reviewers (S.Y.C. and Y.-J.Y.) evaluated the quality, and discrepancies were resolved via discussion or consultation with a third reviewer (T.T.N.).

2.5. Statistical analysis

Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to compare the diagnostic and safety outcomes, including detection rates for primary cancer, anterior tumors, and total cancer; infection-related complications; and AUR between the TP-Bx and TR-Bx techniques. Analyses for all outcomes stratified by MRI biopsy setting (with and without MRI targeting) were prespecified.

Because clinical and methodological heterogeneity was anticipated across the RCTs included, a random-effects model (restricted maximum likelihood method) was used to estimate the overall proportion of outcomes between the TP-Bx and TR-Bx groups. This approach, recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* [11], provides more conservative and generalizable estimates by accounting for potential between-study variability.

Between-study heterogeneity was assessed using Cochran's Q test and τ^2 metrics, and was visually evaluated using forest plots. I^2 values were calculated following the Cochrane guidelines [12], but are reported descriptively rather than used for interpretation, given their dependence on sample size and study precision. We calculated 95% prediction intervals to assess the expected range of true effects across studies.

Subgroup analyses and narrative exploration were conducted to interpret whether heterogeneity originated from clinical factors (eg, biopsy route, anesthesia type, or MRI-targeting protocol) or methodological differences (eg, operator experience or outcome definition). The degree of heterogeneity was also considered in interpreting the reliability and generalizability of pooled estimates.

Publication bias was not formally assessed because fewer than ten studies were included for each outcome. According to the Cochrane guidelines [12], funnel plots and statistical tests such as Egger's regression are not reliable under these conditions and are therefore not recommended. Forest plots were generated to illustrate individual study estimates and pooled effects, with squares representing study-specific estimates (size proportional to weight), horizontal lines indicating 95% CIs, and diamonds denoting pooled effects. Statistical significance was set at $p < 0.05$. All statistical analyses were conducted using Stata/MP v18 (Stata Corp., College Station, TX, USA).

3. Results

3.1. Summary of studies

Twelve RCTs ($n = 4244$ participants) met the inclusion criteria (Fig. 1) [8,13–23]. The reports were published between 2003 and 2025 and the trials were conducted across multiple regions (North America, Europe, and Asia). Most studies enrolled men undergoing initial (biopsy-naïve) prostate biopsy, although two trials [16,17] included a subset of patients who had undergone prior negative biopsies (Table 1). Sample sizes varied from 77 to 1042 men, with the largest trial [8] involving more than 1000 patients.

All of the trials included directly compared TP-Bx and TR-Bx approaches under differing protocols. Five RCTs [8,13,14,16,17] incorporated prebiopsy MRI and sampled MRI-targeted cores in addition to systematic sampling in both the TP-Bx and TR-Bx arms. The remaining seven trials [15,18–23] did not use MRI targeting and relied on standard ultrasound guidance for sampling of systematic cores (representing the pre-MRI biopsy era). Across the studies, patient demographics and procedural characteristics were generally well balanced between the TP-Bx and TR-Bx arms (Table 2). Systematic biopsy schemes were generally similar between the arms, with 10–14 cores typically obtained per patient (with the earliest study using a sextant 6-core scheme). In the trials with MRI-targeted biopsy, an additional three to five cores were obtained from each MRI-identified lesion. TP-Bx procedures were performed under local anesthesia in most studies, with two trials [14,17] using general anesthesia and two older trials [21,22] using regional (spinal or saddle-block) anesthesia; TR-Bx proce-

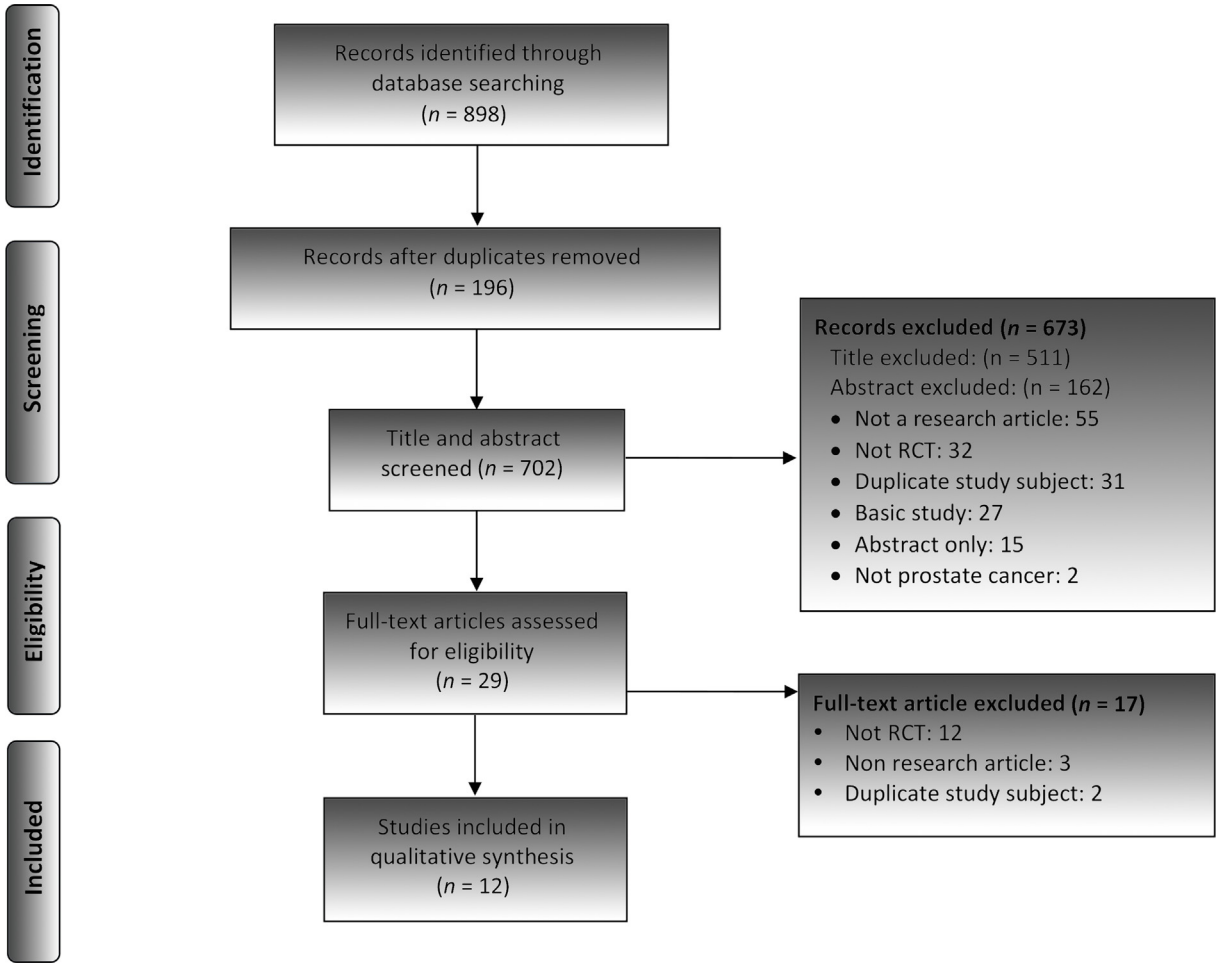

Fig. 1 – Flow chart of the study inclusion process. RCT = randomized controlled trial.

dures were typically performed under local anesthetic. Antibiotic prophylaxis strategies differed by approach. Three trials [8,13,16] omitted prophylactic antibiotics in the TP-Bx arm (using only antiseptic skin preparation) and administered targeted or standard antibiotic prophylaxis in the TR-Bx arm. By contrast, earlier studies provided all patients with routine antibiotic prophylaxis or did not specify the differences between the arms.

The primary endpoints varied among the RCTs included in the review. Most trials evaluated cancer detection as a main outcome, with five studies [8,14–17] focusing on the csPC yield. By contrast, one trial—PREVENT [13]—primarily assessed postbiopsy infectious complications as the primary outcome. Five trials [8,13,14,16,17] performed MRI-targeted biopsy using a cognitive or software-assisted method.

3.2. Cancer detection

3.2.1. ISUP grade ≥2 disease

Pooled analysis revealed no statistically significant difference in the detection rate for ISUP grade ≥2 PC between the TP-Bx and TR-Bx groups (OR 1.15, 95% CI 0.95–1.39), with low heterogeneity (I^2 = 40.7%, p = 0.1; Fig. 2). Visual inspection of the forest plot showed consistent effect directions across studies, suggesting that the variability was unlikely to influence the pooled estimate. In the studies using MRI-targeted biopsy, the ISUP grade ≥2 PC detection rate did not significantly differ between the groups (OR 1.08, 95% CI 0.85–1.36), with substantial heterogeneity (I^2 = 56.0%, p = 0.05). This heterogeneity may reflect variations in MRI protocols, targeting techniques, and operator expertise across trials. By contrast, pooled analysis for studies without MRI targeting revealed that the ISUP grade ≥2 PC detection rate was 1.41 times higher (95% CI 1.02–1.95) in the TP-Bx group than in the TR-Bx group, with no heterogeneity (I^2 = 0.0%, p = 0.9).

3.2.2. All ISUP grades

Pooled analysis revealed no significant difference in the detection rate for PC of any ISUP grade between the TP-Bx and TR-Bx groups (OR 1.11, 95% CI 0.94–1.32), with low heterogeneity (I^2 = 37.4%, p = 0.08; Table 3 and Supplementary Fig. 1), which probably reflects the consistency of the inclusion criteria and pathological grading definitions across the trials. Visual assessment of the forest plot confirmed consistent trends across studies, which supports the robustness of the overall pooled estimate. Among studies using MRI-targeted biopsy, there was no significant difference in PC detection between the TP-Bx and TR-Bx

Table 1 – Characteristics of the randomized and prospective studies included in the review: inclusion/exclusion criteria, biopsy protocols, and primary outcomes

Study	*N*	Setting	Inclusion	Exclusion	Anesthesia	Antibiotics	MRI fusion method	Planned cores (targeted)	Primary outcome
Bryant 2025 [8] TRANSLATE	1042	Bx-naïve	Suspected PC (elevated age-specific PSA, abnormal DRE or pre-Bx MRI)	PSA >50 ng/ml or entire gland replaced by tumor on MRI, symptoms of c/rUTI, IMC-Hx, need for enhanced ABP, absent rectum, not able to take lithotomy position or undergo MRI	Local	TP: chlorhexidine based skin preparation without ABsTR: ABs before and after Bx without targeted prophylaxis	Cognitive	12 (+ 3–5 per lesion)	csPC
Hu 2024 [13] PREVENT	658	Bx-naïve	Elevated PSA and/or abnormal DRE, suspicious MRI (PI-RADS 3–5)	Acute prostatitis in last 6 mo or any current bacterial infection requiring AB treatment	Local	TP: no ABsTR: targeted ABP	Visual or software-assisted registration	12 (+ 3 per lesion)	Infectious complications
Ploussard 2024 [14] PERFECT	270	Bx-naïve	Clinical suspicion of PC: PSA <20 ng/ml, suspicious MRI (PI-RADS 4–5), NUC	Stage ≥cT3a PC, ongoing ACG therapy, or untreated hemostasis disorder	Local or general	NR	SAFS	Operator's discretion (+ 3 per lesion)	csPC
Liu 2024 [15]	279	Bx-naïve	PSA ≥4.0 ng/ml, abnormal DRE, or MRI-detected lesion	ECOG ≥2, ACG use, CPD, acute UTI, Bx refusal	Local	ABP	No	10 (+ 1–2 if lesion found on TRUS)	csPC and insignificant PC
Mian 2023 [16] ProBE-PC	718	Bx-naïve + previous negative Bx	Clinical suspicion of PC	Surgically absent rectum	Local	TP: no ABPTR: 1-d ABP	SAFS	12 (+ 3 per lesion)	Infectious complications and csPC
Ber 2020 [17]	77	Bx-naïve and repeat Bx (incl. previous GG 1)	Suspicious MRI (PI-RADS 3–5)	NR	general	NR	SAFS	6 in contralateral lobe (+ 4–6 per lesion)	csPC within index lesion
Guo 2015 [18]	339	Bx-naïve	PSA > 4.0 ng/ml or abnormal DRE	>80 yr, unable to communicate effectively, symptoms of UTI, AUR, coagulation disorders	Local	ABP	No	PV >50 ml: 12 PV <50 ml: 8(+ 2 from suspicious area on TRUS or DRE)	Cancer detection
Cerruto 2014 [19]	108	Bx-naïve	PSA > 4.0 ng/ml or abnormal DRE	Acute or chronic prostatitis	Local	ABP	No	14	Cancer detection
Chae 2009 [20]	200	NR	PSA > 4.0 ng/ml, abnormal DRE, or suspicious TRUS	NR	Local	ABP	No	12	Cancer detection
Hara 2008 [21]	246	Bx-naïve	PSA 4–20 ng/ml	Acute or chronic prostatitis	Spinal or caudal block	NR	No	12	PC detection, cancer core rate, complications
Takenaka 2008 [22]	200	Bx-naïve	PSA > 4.0 ng/ml, abnormal DRE, or suspicious on TRUS	NR	Saddle blockage	ABP	No	12	PC detection, complications
Emiliozzi 2003 [23]	107	Bx-naïve	PSA > 4.0 ng/ml	Acute or chronic prostatitis	Local	ABP	No	6	PC

AB = antibiotic; ABP = AB prophylaxis; ACG = anticoagulant; AUR = acute urinary retention; Bx = biopsy; CPD = cardiopulmonary disease; NR = not reported; PC = prostate cancer; csPC = clinically significant PC; IMC-Hx = history of immunocompromise; NUC = negative urine culture; PSA = prostate-specific antigen; PV = prostate volume; DRE = digital rectal examination; MRI = magnetic resonance imaging; TP = transperineal; TR = transrectal; UTI = urinary tract infection; c/rURI = concurrent or recent UTI; PI-RADS = Prostate Imaging Reporting and Data System; GG = grade group; ECOG = Eastern Cooperative Oncology Group performance status; SAFS = software-assisted fusion system; TRUS = transrectal ultrasound.

Table 2 – Baseline patient characteristics and biopsy parameters in the studies included in the review [a]

Study	Age (yr)		PSA (ng/ml)		Prostate volume (ml)		Total cores		Systematic cores		Targeted cores	
	TP	TR	TP	TR	TP	TR	TP	TR	TP	TR	TP	TR
Bryant 2025 [8] TRANSLATE	66.1 ± 8.166 (60–72)	66.0 ± 7.366 (61–71)	8.8 ± 7.57 (5–10)	8.8 ± 6.87 (5–10)	49.8 ± 2643 (33–60)	51.2 ± 25.745 (33–63)	NR	NR	12.7 ± 3.712 (12–13)	10.4 ± 312 (8–12)	7 ± 2.17 (6–7)	5.6 ± 35 (3–7)
Hu 2024 [13] PREVENT	66 (61–71)	66 (61–70)	5.8 (4.4–8.0)	5.8 (4.6–8.3)	41 (32–57)	43 (32–59)	NR	NR	12 (12–12)	12 (12–12)	3 (2–5)	3 (2–5)
Ploussard 2024 [14] PERFECT	66.4 ± 8.366 (61–73)	67.3 ± 7.968 (61–73)	7.3 ± 3.47.0 (5.0–9.2)	7.7 ± 4.16.9 (4.9–9.7)	46.7 ± 21.942.0 (31.0–55.0)	53.6 ± 25.150.0 (35.5–64.5)	11.9 ± 3.512 (10–15)	17.4 ± 3.417	8.2 ± 3.38	13.6 ± 2.813	NR	NR
Liu 2024 [15]	70.89 ± 7.16	73.87 ± 7.08	14.22 ± 8.44	16.21 ± 9.96	45.41 ± 21.49	44.97 ± 17.71	11.00 ± 2.37	11.07 ± 2.12	NR	NR	NR	NR
Mian 2023 [16] ProBE-PC	65 (60–70)	66 (61–70)	6.9 (5.1–10.4)	7.1 (5.0–10.3)	47 (36–65)	47 (35–65)	14 (12–15)	13 (11–13)	NR	NR	NR	NR
Ber 2020 [17]	68.2 (64.2–72.2) [b]		8.9 (6.2–12.2) [b]		53 (40–82) [b]		10 (3–19)	7 (2–13)	NR	NR	NR	NR
Guo 2015 [18]	67.18 ± 6.76	67.35 ± 7.28	8.81 (3.6–56.0)	10.48 (6.2–69.0)	47.2 (12.9–97.7)	45.9 (20.0–98.0)	11.1 [c]	10.7 [c]	NR	NR	NR	NR
Cerruto 2014 [19]	66.5 ± 8.87	67.30 ± 8.05	15.95 ± 41.04	12.36 ± 39.65	56.29 ± 31.33	61.49 ± 33.39	14.0 [c]	14.0 [c]	NR	NR	NR	NR
Chae 2009 [20]	64.4 ± 9.76	66.6 ± 9.03	23.1 ± 103.67	13.8 ± 20.39	38.9 ± 19.47	43.3 ± 22.82	12.0 [c]	12.0 [c]	NR	NR	NR	NR
Hara 2008 [21]	71.0 ± 7.29	71.7 ± 7.55	8.34 ± 3.44	8.48 ± 3.90	33.2 ± 15.2	36.0 ± 17.1	12.0 [c]	12.0 [c]	NR	NR	NR	NR
Takenaka 2008 [22]	71.1 ± 7.53	72.1 ± 7.42	17.1 ± 30.1	19.6 ± 43.2	34.5 ± 18.9	37.2 ± 19.7	12.0 [c]	12.0 [c]	NR	NR	NR	NR
Emiliozzi 2003 [23]	Total cohort: 68 (52–88)		Total cohort: 8.2 (4.1–240)		NR	NR	6 [b]	6 [b]	NR	NR	NR	NR

NR = not reported; PSA = prostate-specific antigen; TP = transperineal; TR = transrectal.
[a] Results are presented as mean ± standard deviation and median (interquartile range).
[b] Overall cohort.
[c] Estimated mean.

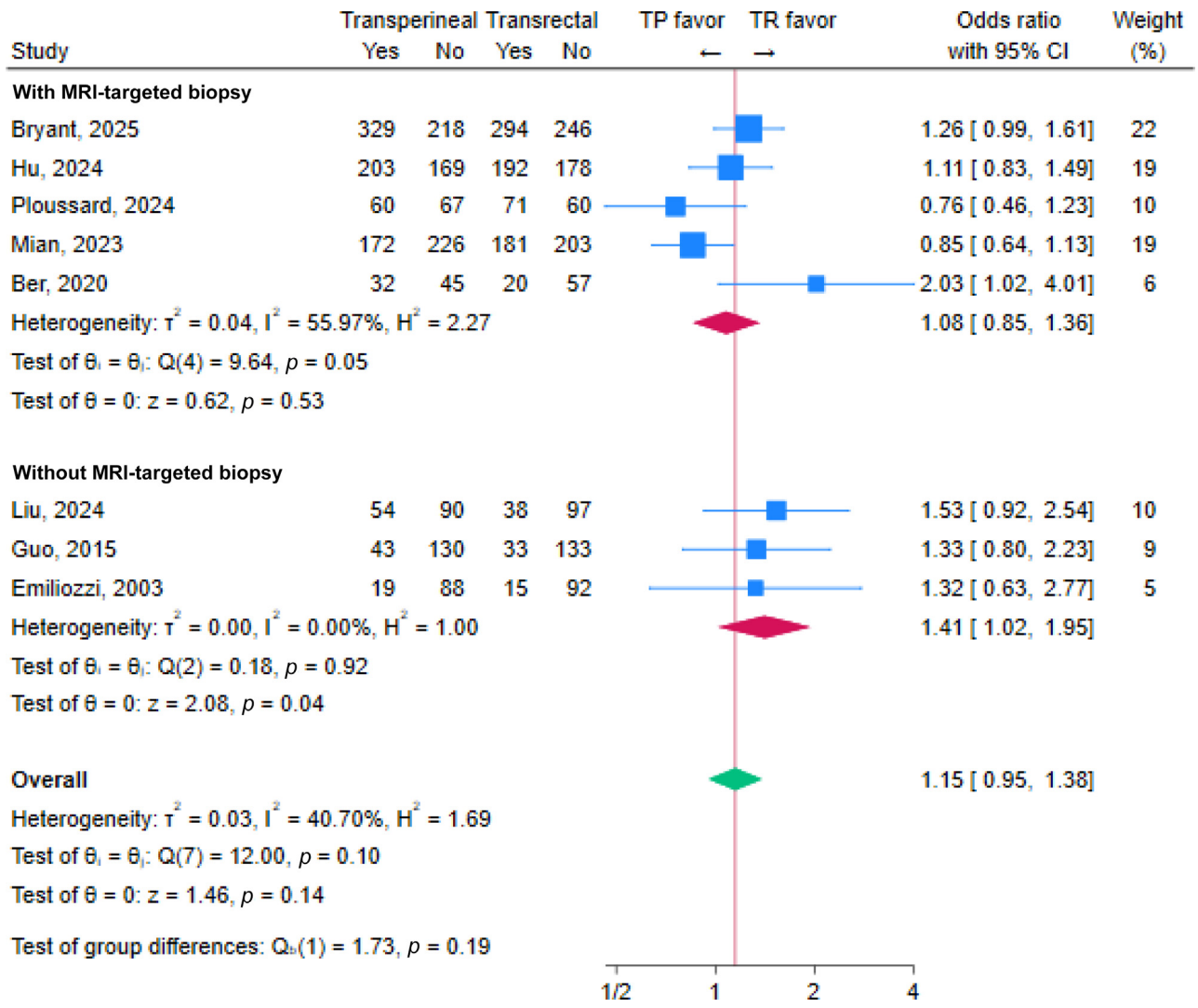

Fig. 2 – Forest plot comparing the detection rate of clinically significant prostate cancer (International Society of Urological Pathology grade ≥2) between transperineal (TP) and transrectal (TR) biopsy approaches. CI = confidence interval; MRI = magnetic resonance imaging.

groups (OR 1.15, 95% CI 0.94–1.40), with low heterogeneity (I^2 = 33.0%, p = 0.2). Similarly, among studies without MRI-targeted biopsy, there was no significant difference was observed between the TP-Bx and TR-Bx groups (OR 1.05, 95% CI 0.79–1.41), with low heterogeneity (I^2 = 48.6%, p = 0.07).

3.2.3. *ISUP grade 1 disease*

The pooled detection rate for ISUP grade 1 PC did not significantly differ between the TP-Bx and TR-Bx groups (OR 1.14, 95% CI 0.91–1.44), with low heterogeneity (I^2 = 40.8%, p = 0.1; Table 3 and Supplementary Fig. 2). Inspection of the forest plot revealed a uniform effect directions across the studies, which indicates that heterogeneity had a minimal impact on the pooled estimate. Among the studies using MRI-targeted biopsy, there was no significant difference in the PC detection rate between the TP-Bx and TR-Bx groups (OR 1.18, 95% CI 0.81–1.72), with substantial heterogeneity (I^2 = 70.7%, p = 0.03). This heterogeneity probably indicates underlying variability in study design, definitions, and sampling strategies. Pooled analysis of the PC detection rate among studies without MRI-targeted biopsy did not significantly differ between the TP-Bx and TR-Bx groups (OR 1.22, 95% CI 0.85–1.74), with no heterogeneity (I^2 = 0.0%, p = 0.7).

3.2.4. *Anterior grade ≥2 tumors*

Pooled analysis revealed no statistically significant difference in the detection rate for anterior grade ≥2 PC between the TP-Bx and TR-Bx approaches (OR 1.04, 95% CI 0.83–1.31), with no heterogeneity observed (I^2 = 0.0%, p = 0.5; Table 3 and Supplementary Fig. 3), which suggests methodological consistency for MRI targeting and lesion sampling across studies. Visual inspection of the forest plot revealed nearly identical point estimates across trials, which suggests genuine consistency for the study findings. For studies using MRI-targeted biopsy, the pooled OR was 1.03 (95% CI 0.79–1.34), with no heterogeneity observed (I^2 = 0.0%, p = 0.5). Similarly, pooled analysis for studies without MRI-targeted biopsy revealed that the detection rate for

Table 3 – Summary of the meta-analysis results for comparison of transperineal and transrectal biopsy approaches using a random-effect model

Outcome measure	Studies	Transperineal		Transrectal		OR (95% CI)	Heterogeneity metrics			
	(*n*)	Events (*n*)	Patients (*n*)	Events (*n*)	Patients (*n*)		Q	df	*p* value	I^2(%)
Overall pooled cohort										
Cancer detection										
All grades	12	1407	2335	1334	2305	1.11 (0.94–1.32)	18.13	11	0.1	37.4
ISUP grade 1	8	360	1955	328	1931	1.14 (0.91–1.44)	12.18	7	0.1	40.8
Anterior and ISUP grade ≥2	6	193	1109	189	1120	1.04 (0.83–1.31)	4.35	5	0.5	0.0
Acute urinary retention	8	27	1854	37	1825	0.73 (0.44–1.21)	1.79	7	1.0	0.0
Bleeding requiring intervention	8	4	1930	8	1910	0.69 (0.26–1.79)	1.11	7	1.0	0.0
With MRI-targeted biopsy										
Cancer detection										
All grades	5	1061	1531	1012	1523	1.15 (0.94–1.40)	6.42	4	0.2	33.0
ISUP grade 1	5	276	1531	259	1523	1.18 (0.81–1.72)	10.96	4	0.03	70.7
Anterior and ISUP grade ≥2	3	146	809	145	820	1.03 (0.79–1.34)	1.58	2	0.5	0.0
Acute urinary retention	4	15	1430	21	1416	0.74 (0.37–1.46)	1.46	3	0.7	0.0
Bleeding requiring intervention	4	4	1430	6	1416	0.75 (0.24–2.30)	0.30	3	1.0	0.0
Without MRI-targeted biopsy										
Cancer detection										
All grades	7	346	804	322	782	1.05 (0.79–1.41)	11.52	6	0.07	48.6
ISUP grade 1	3	84	424	69	408	1.22 (0.85–1.74)	0.79	2	0.7	0.0
Anterior and ISUP grade ≥2	3	47	300	44	300	1.08 (0.63–1.83)	2.74	2	0.3	27.6
Acute urinary retention	4	12	424	16	409	0.72 (0.34–1.53)	0.33	3	1.0	0.0
Bleeding requiring intervention	4	0	500	2	494	0.55 (0.09–3.41)	0.73	3	0.9	0.0

OR = odds ratio; CI = confidence interval; ISUP = International Society of Urological Pathology; Q = Cochran's Q statistic; df = degrees of freedom; MRI = magnetic resonance imaging.

anterior grade ≥2 PC did not differ significantly between the TP-Bx and TR-Bx groups (OR 1.08, 95% CI 0.63–1.83), with low heterogeneity (I^2 = 27.6%, p = 0.3).

3.3. *Infection-related complications*

3.3.1. *All complications*

The overall risk of all types of infection-related complication was significantly lower in the TP-Bx group than in the TR-Bx group (OR 0.70, 95% CI 0.51–0.97). There was no evidence of heterogeneity (I^2 = 0.0%, p = 0.4; Fig. 3), which indicates that infection-related outcomes were consistently defined and measured across included trials. Visual inspection of the forest plot revealed closely aligned effect sizes across studies, which confirms that the pooled estimate was not driven by any outlier. For studies using MRI-targeted biopsy, the pooled OR was 0.76 (95% CI 0.54–1.07). By contrast, pooled results for studies without MRI-targeted biopsy revealed a statistically significant reduction in infection risk with TP-Bx (OR 0.28, 95% CI 0.09–0.88). No significant heterogeneity was observed within each subgroup (I^2 = 0.00%).

3.3.2. *Grade ≥3 infectious complications*

The pooled risk of severe infection complications (grade ≥3, including sepsis) was significantly lower in the TP-Bx group than in the TR-Bx group (OR 0.35, 95% CI 0.14–0.90), with no evidence of heterogeneity (I^2 = 0.0%, p = 1.0; Fig. 4). The absence of heterogeneity suggests comparable definitions of complications and similar procedural protocols among studies. Visual inspection of the forest plot revealed a consistent direction and magnitude of effects, which suggests that the overall result was stable across studies. Subgroup analyses revealed a nonsignificant trend towards lower risk both in the subgroup of studies with MRI-targeted biopsy (OR 0.24, 95% CI 0.05–1.20) and the subgroup of studies without MRI-targeted biopsy (OR 0.43, 95% CI 0.13–1.35), both with no evidence of heterogeneity.

3.4. *Acute urinary retention*

The overall risk of AUR did not differ significantly between the TP-Bx and TR-Bx approaches (OR 0.73, 95% CI 0.44–1.21; Table 3 and Supplementary Fig. 4). The pooled OR was 0.74 (95% CI 0.37–1.46) for the subgroup using MRI-targeted biopsy, versus 0.72 (95% CI 0.34–1.53) for the subgroup of studies without MRI-targeted biopsy; there was no significant difference between TP-Bx and TR-Bx in either subgroup. Heterogeneity was negligible across all analyses (I^2 = 0.0%, p = 0.1). The lack of observable heterogeneity implies comparable trial designs and data collection approaches. Visual inspection of the forest plot confirmed a consistent direction of the effect across studies, which indicates that the pooled estimates were stable and not influenced by study-level variability.

3.5. *Bleeding requiring intervention*

The pooled OR for bleeding requiring intervention across all the studies was 0.69 (95% CI 0.26–1.79), with no statistically significant difference between the TP-Bx and TR-Bx approaches (Table 3 and Supplementary Fig. 5). The pooled

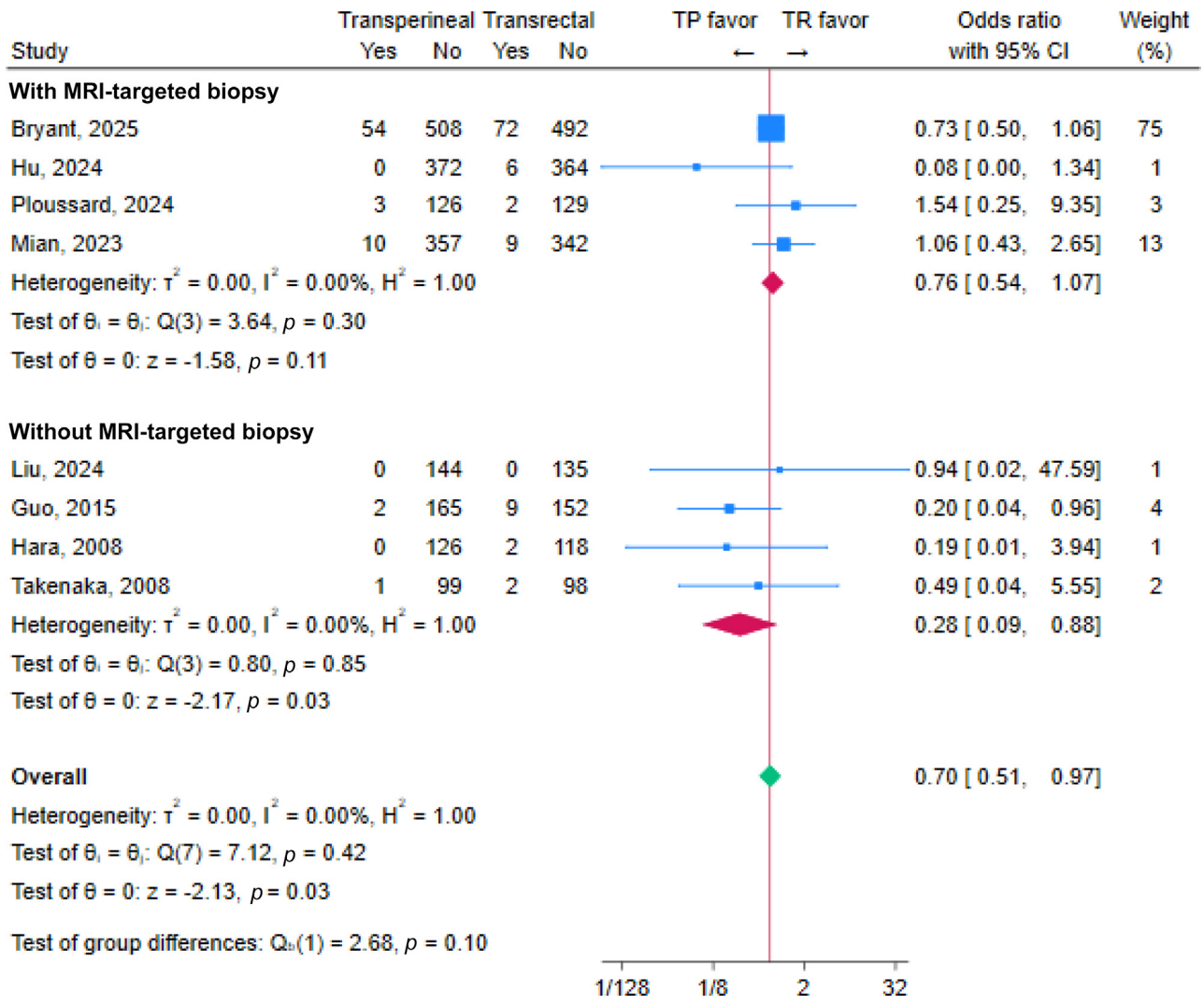

Fig. 3 – Forest plot comparing the overall risk of infection-related complications between transperineal (TP) and transrectal (TR) biopsy approaches. CI = confidence interval; MRI = magnetic resonance imaging.

OR was 0.75 (95% CI 0.24–2.30) for studies using MRI-targeted biopsy, and 0.55 (95% CI 0.09–3.41) for studies without MRI-targeted biopsy. No heterogeneity was observed in either subgroup or overall (I^2 = 0.0%, p = 0.1). The lack of heterogeneity suggests that bleeding events were consistently defined and assessed across the trials. Visual assessment of the forest plot revealed nearly identical point estimates and overlapping CIs across studies, which confirms the consistency of the findings and supports the stability of the pooled effect.

3.6. *Procedural pain*

The pooled OR for procedural pain across all studies was 2.05 (95% CI 1.19–3.53) for TP-Bx (Fig. 5). In subgroup analyses, the pooled OR was 1.55 (95% CI 0.97–2.49) for the MRI-targeted biopsy subgroup. By contrast, pooled odds for procedural pain for the subgroup without MRI-targeted biopsy were significantly higher with TP-Bx (OR 3.82, 95% CI 2.23–6.55). Moderate heterogeneity was observed for the overall analysis (I^2 = 50.9%, p = 0.08), but not within each subgroup (MRI-targeted: I^2 = 21.9%; no MRI targeting: I^2 = 0.0%). The heterogeneity for the overall analysis may be partly explained by differences in anesthesia protocols across trials. Sensitivity analyses excluding studies that used general or spinal anesthesia did not substantially change the pooled effect, which indicates that the heterogeneity observed is largely attributable to methodological differences in anesthesia rather than outcome-level variability. Furthermore, the direction of the effect was consistent across all the trials included, which suggests that heterogeneity did not materially influence the overall interpretation of procedural pain outcomes. This moderate heterogeneity probably reflects variations in anesthesia, analgesia, and operator experience across trials. Importantly, the direction and magnitude of the effects were consistent, which indicates that methodological diversity did not compromise the robustness or generalizability of the pooled estimates across different clinical contexts.

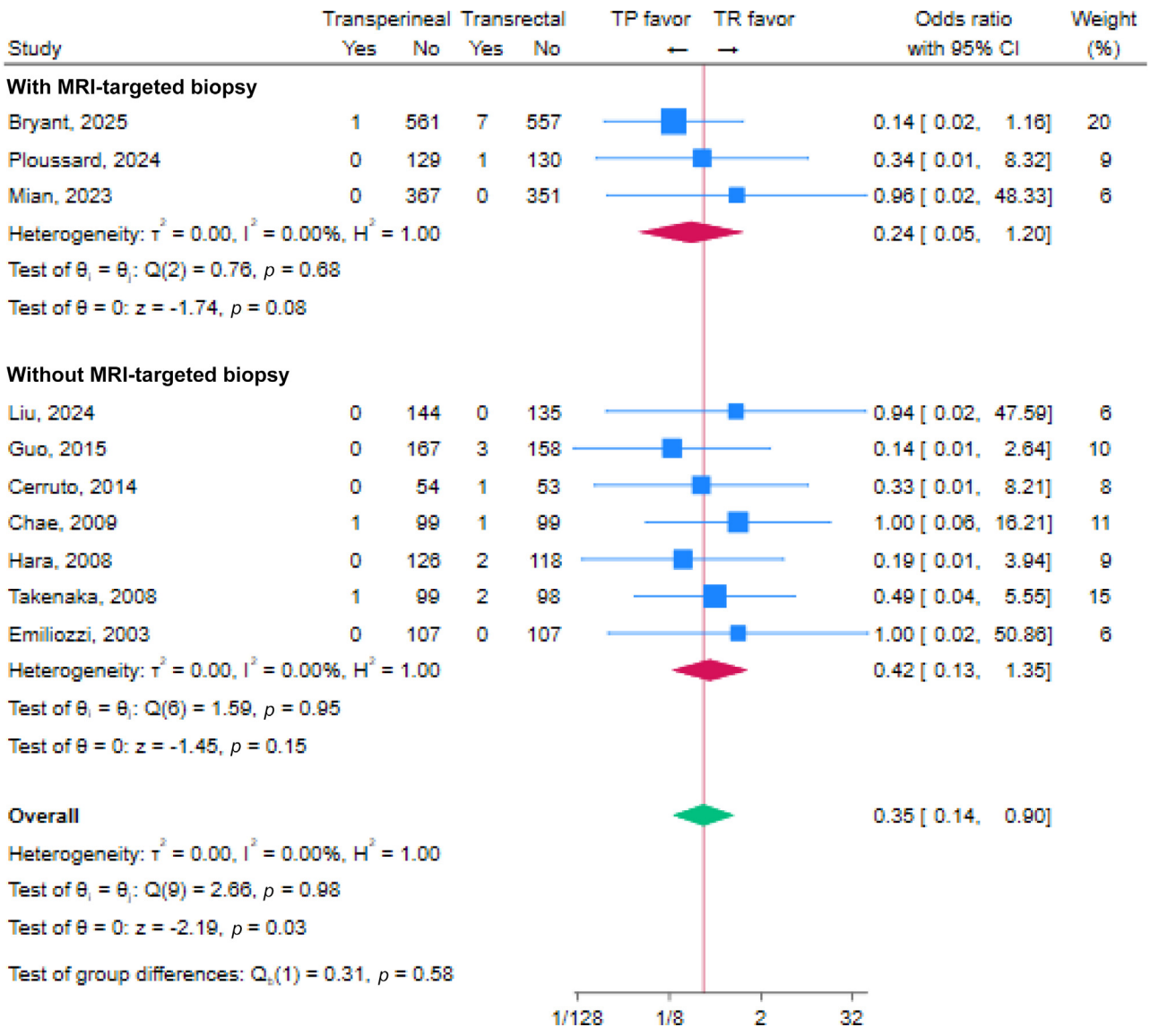

Fig. 4 – Forest plot comparing the risk of severe infectious complications (grade ≥3 infection or sepsis) between transperineal (TP) and transrectal (TR) biopsy approaches. CI = confidence interval; MRI = magnetic resonance imaging.

3.7. *Risk-of-bias assessment*

The methodological quality of the studies included was generally acceptable (Supplementary Table 2). Most trials had low risk of bias for random sequence generation, incomplete outcome data, and selective reporting. However, performance bias was high across all studies owing to the lack of participant and personnel blinding. Detection bias was mostly unclear, while other domains were assessed as having low or unclear bias without serious concerns.

4. Discussion

Our meta-analysis revealed no significant difference in csPC detection rates between the TP-Bx and TR-Bx approaches. However, in subgroup analyses restricted to biopsies without MRI targeting, TP-Bx was associated with a significantly higher csPC detection rate in comparison to TR-Bx, whereas no such difference was observed in settings with MRI targeting. Furthermore, TP-Bx was associated with significantly fewer infection-related complications versus TR-Bx. Overall, the risk of postbiopsy infection of any severity was lower with TP-Bx (pooled OR 0.70) and the risk of serious infections (sepsis or grade $\geq$3 complications) was markedly lower (pooled OR 0.35) relative to TR-Bx. Hence, patients undergoing TP-Bx had substantially lower risk of developing postbiopsy fever, urinary tract infection, or sepsis.

TP-Bx was associated with procedure-related pain. Patients in the TP group reported higher discomfort during or immediately after the procedure (pooled OR 2.05, indicating twice the odds of experiencing significant pain with TP-Bx). This suggests that there is a trade-off: TP-Bx yields safety benefits but can be less tolerable without adequate anesthesia. Although the difference in pain was statistically significant, its clinical impact appears to be moderate and

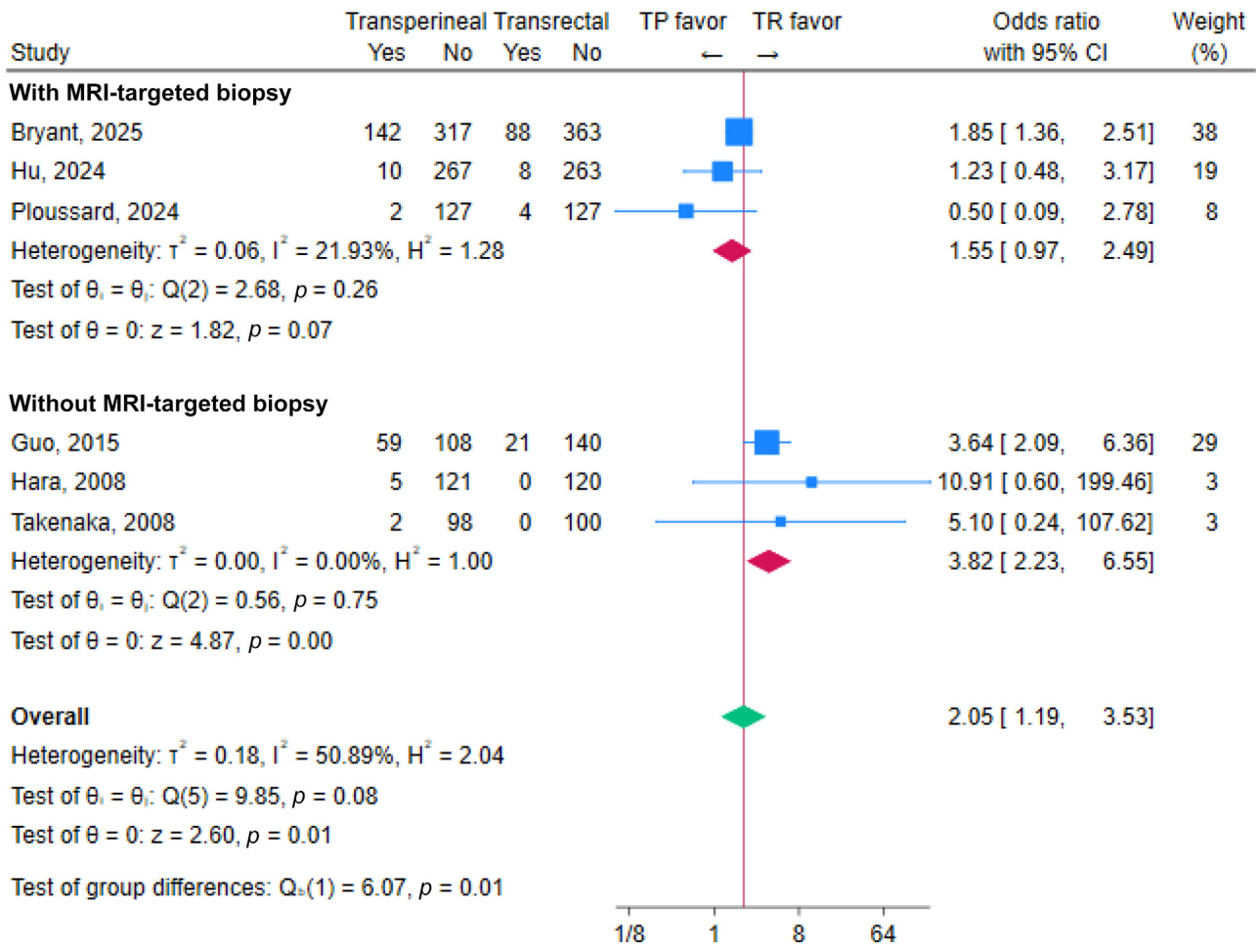

Fig. 5 – Forest plot comparing the risk of procedural pain between transperineal (TP) and transrectal (TR) biopsy approaches. CI = confidence interval; MRI = magnetic resonance imaging.

transient, as discomfort typically subsides within days and is manageable with local anesthesia. Therefore, although the TP approach may initially cause more discomfort, this does not necessarily translate into a meaningful long-term disadvantage for patients. No significant differences in other complications were observed between TP-Bx and TR-Bx.

Our findings are consistent with recent RCTs such as PERFECT [14], PREVENT [13], ProBE-PC [16], which reported similar cancer detection rates for the TP-Bx and TR-Bx approaches. Particularly in MRI-targeted settings, the biopsy route appears to have less influence on diagnostic yield. Notably, the recent TRANSLATE [8] trial revealed a higher csPC detection rate with TP-Bx than with TR-Bx. However, this conclusion was drawn from modified intention-to-treat and per-protocol analyses rather than a strict intention-to-treat approach. While these approaches are commonly used to account for real-world adherence and procedural fidelity, the lack of a strict intention-to-treat analysis may limit the comparability to other RCTs that apply standard ITT principles. According to updated CONSORT recommendations, the ITT principle—which requires subjects to remain in the group to which they were originally randomized—is critical for preserving the benefits of randomization and minimizing bias [24]. Moreover, the TRANSLATE study used cognitive fusion targeting for the MRI-guided approach. While cognitive and software-assisted fusion methods have shown similar efficacy for detection of significant cancer [25], TR targeting may be more challenging than TP targeting owing to anatomic differences between MRI and transrectal ultrasound (TRUS) [26], which could potentially affect cancer detection rates when conducted by less experienced clinicians. Furthermore, our subgroup analysis revealed that TP-Bx had a significantly higher csPC detection rate in the group without MRI targeting, whereas there was no such difference between TP-Bx and TR-Bx in the MRI-targeted group. Therefore, MRI targeting itself improves lesion localization and diagnostic precision to a degree that diminishes the influence of the biopsy route. In settings in which MRI targeting is not used, TP-Bx may offer superior anatomic access and thus higher detection rates than with TR-Bx. Although core numbers were broadly comparable between the TP and TR arms, the TP approach allows a more comprehensive distribution of sampling across the prostate, including anterior and apical zones, owing to its access via the perineum. Some MRI/TRUS fusion studies have demonstrated that TP-Bx

cores had a greater cancer core length (eg, 11 mm vs 9 mm [27]) and higher tumor involvement rates in comparison to TR-Bx, which suggests that TP-Bx may sometimes achieve deeper or more extensive sampling. It should also be noted that in contemporary RCTs, MRI-targeted biopsy is routinely performed in conjunction with systematic sampling, and targeted-only outcomes are rarely reported. Consequently, our analysis reflects the integrated diagnostic yield of both systematic and targeted cores, which mirrors real-world MRI-guided practice rather than isolated targeting performance.

Infectious complications were significantly less frequent in the TP-Bx group. This result aligns with literature data and reflects the fact that TR-Bx involves transrectal passage and exposure to rectal flora, with a higher risk of bacteremia and sepsis. In one study, clinical infection occurred in 2–5% of the patients who underwent TR-Bx, and sepsis requiring hospitalization in approximately 0.5–1.0% [28]. Prostate biopsy protocols have evolved over time from the traditional sextant biopsy (6-core) to extended systematic schemes involving 10–12 cores, as currently recommended to improve sampling adequacy [29]. The increasing use of prebiopsy MRI has also led to integration of MRI-targeted biopsy in addition to systematic biopsy, resulting in higher total core numbers—frequently exceeding 15–20 cores— in clinical practice [30,31]. With this increase in the number of biopsy cores, some studies have reported a proportional increase in procedure-related complications, including bleeding, urinary retention, and infectious events [32]. At the same time, the rise of antimicrobial-resistant organisms is a matter of global concern. Fluoroquinolone-resistant rectal flora, often implicated in post-TR-Bx sepsis, are now prevalent in up to 20–50% of men undergoing biopsy in certain regions [33,34] and represent a broader public health issue, as postbiopsy infections may limit future therapeutic options, especially in men requiring repeated interventions such as surgery, androgen deprivation therapy, and chemotherapy. Therefore, minimization of unnecessary exposure to antibiotics at the diagnostic stage may preserve the effectiveness of these agents when most critically needed. By reducing reliance on antibiotics, TP-Bx can contribute to more sustainable infection control strategies and aligns with current antibiotic stewardship goals.

Historically, TP-Bx was often performed under general or spinal anesthesia because of concerns regarding perineal discomfort [35]. However, advances in technique and analgesia have made local anesthesia a widely adopted and effective option. Most contemporary TP-Bx studies, including recent randomized trials, now use local anesthetic protocols, and often combine perineal skin infiltration with a periprostatic local block to allow outpatient procedures without a need for deep sedation or anesthesia. While the TP approach is associated with immediate discomfort at the time of needle insertion through the perineum, this is typically transient and manageable. For example, the PREVENT trial reported higher procedural pain scores for TP-Bx than for TR-Bx on the day of biopsy, but by postoperative day 7 the pain levels had markedly improved and were no longer significantly different between the groups [13]. Several recent studies have demonstrated that with optimized analgesia protocols, the pain associated with TP-Bx is comparable to that associated with TR-Bx [36].

In the MRI-targeted biopsy subgroup, there were no significant differences between TP-Bx and TR-Bx approaches across all outcomes measured, which reflects the enhanced precision of MRI-targeted biopsies. When targeting is accurate, the relative advantage of anatomic access via a TP or TR route may be diminished, which suggests that image-guided precision plays a pivotal role in diagnostic outcomes. While previous meta-analyses have focused solely on recent MRI-targeted RCTs, our study included both early and contemporary trials that encompass a broader range of biopsy techniques. This comprehensive approach increases the robustness and generalizability of our findings across various clinical contexts, including those in which MRI is not routinely available or standardized. By synthesizing evidence across varying protocols and patient populations, our meta-analysis offers practical insights for optimization of biopsy strategies according to institutional resources and clinical circumstances.

The influence of study quality on the pooled estimates was assessed using the Cochrane RoB-2 tool. Most of the trials included demonstrated low risk of bias for random sequence generation, allocation concealment, and outcome reporting, whereas performance bias was unavoidably high because of the lack of participant blinding inherent to procedural trials. To evaluate the robustness of our findings, sensitivity analyses excluding studies with "some concerns" or "high" risk of bias were conducted and yielded consistent results. Stratified interpretation according to overall risk-of-bias categories did not materially alter the direction or magnitude of the pooled estimates. These results suggest that the conclusions from this meta-analysis are unlikely to be driven by lower-quality evidence and remain robust across study quality levels.

Despite the strengths of our meta-analysis, several limitations must be acknowledged. First, although all the studies included were RCTs, methodological heterogeneity was evident across trials in terms of biopsy protocols, anesthesia type, antibiotic prophylaxis, and MRI-targeting methods. Such heterogeneity probably contributed to variability in pooled estimates and may have attenuated true intergroup differences. Specifically, the RCTs included differed in several methodological aspects. For instance, in PREVENT [13], TP-Bx was performed under local anesthesia without antibiotic prophylaxis, whereas local or general anesthesia was used in PERFECT [14]. The TRANSLATE trial [8] adopted a cognitive MRI-ultrasound fusion approach, while ProBE-PC [16] relied on a software-assisted fusion system. These variations in anesthesia, targeting technique, and sampling protocols probably contributed to the between-study heterogeneity observed in our analyses. While subgroup and sensitivity analyses were conducted to mitigate these effects, residual heterogeneity probably remains owing to unmeasured differences in operator expertise, biopsy device type, or patient selection. Nevertheless, the direction and magnitude of pooled estimates were generally consistent across analyses, which suggests that these variations did not materially compromise the robustness of the findings. In particular, differences in anesthesia protocols (local infil-

tration vs spinal vs general anesthesia) may have influenced procedural pain outcomes, and the conclusion that TP-Bx is associated with greater pain should therefore be interpreted with caution. These variations may have influenced the outcome measurements and limited direct comparisons.

Second, the definition and reporting of outcomes such as procedural pain and anterior tumor detection were inconsistent across studies, with potential to introduce information bias. In addition, it was not possible to differentiate the outcomes of targeted and systematic cores within MRI-guided biopsies, as most of the RCTs included reported combined results. This limitation precluded separate evaluation of diagnostic performance between targeted and systematic sampling strategies.

Third, while subgroup analyses were based on MRI targeting, other variables such as operator experience, biopsy device type, and number of cores could not be adjusted for because of limited data availability. Although the RCTs included in the review generally applied systematic 10–14-core schemes, it should be noted that TP-Bx in real-world practice can be performed using grid or saturation templates. These strategies allow more comprehensive and evenly distributed sampling, which may partly explain the higher cancer detection rates observed with TP-Bx in some contexts without MRI targeting. Although subgroup analyses were stratified by MRI targeting, formal meta-regression to explore sources of heterogeneity could not be conducted owing to the limited number of trials per outcome. Consequently, subgroup differences should be interpreted descriptively rather than as statistically validated interactions. Future studies with larger data sets should investigate potential effect modifiers such as biopsy protocol, anesthesia type, and operator experience to better explain the variability observed. Fourth, the majority of the studies included were conducted in high-resource health care settings; therefore, extrapolation to low-resource settings may be limited. Finally, publication bias cannot be completely excluded. Formal statistical tests such as funnel plots and Egger's regression were not performed because fewer than ten studies were available per outcome, consistent with the Cochrane handbook recommendation. Nonetheless, no clear dominance of small positive trials was observed on visual inspection of forest plots, but subtle reporting or selection biases cannot be entirely ruled out.

These findings suggest that biopsy strategies should not be applied as a "one-size-fits-all" model. While our analysis demonstrated no statistically significant difference in diagnostic performance between TP-Bx and TR-Bx in MRI-targeted settings, TP-Bx may be preferable in contexts without routine MRI availability, where minimization of infection risk and antibiotic use is a priority, or when the procedure can be safely performed under local anesthesia. Conversely, TR-Bx remains a reasonable option in MRI-targeted workflows when infection risk is low and patient comfort or procedural convenience is emphasized. Ultimately, the choice of biopsy route should be individualized on the basis of patient characteristics, institutional expertise, resource availability, and local priorities regarding infection control and antibiotic stewardship.

5. Conclusions

The results of our systematic review and meta-analysis of RCTs demonstrate that there is no statistically significant difference in diagnostic performance for csPC between TP-Bx and TR-Bx approaches, particularly when MRI-targeted techniques are used. Importantly, in studies without MRI targeting, TP-Bx was associated with a higher csPC detection rate, which indicates its diagnostic advantages in settings where MRI guidance is not available. In addition, TP-Bx was associated with a significantly lower risk of infectious complications, including sepsis, which highlights its safety advantage in the context of rising antimicrobial resistance. Although TP-Bx was associated with a higher rate of procedural discomfort, it can feasibly be performed under local anesthesia in outpatient settings, which allows wider clinical application. Taken together, these findings suggest that selection of the biopsy route should not follow a one-size-fits-all approach, but should rather be tailored according to MRI availability, infection control priorities, anesthesia feasibility, and patient preferences. Future research should further investigate the cost effectiveness, patient-reported outcomes, and long-term oncological impact of TP-Bx to guide personalized selection of biopsy strategy. Given the methodological heterogeneity identified across existing trials, future studies should focus on standardizing biopsy protocols, outcome definitions, and reporting metrics to clarify whether any differences observed reflect true clinical effects or can be attributed to variability in study design.

Author contributions: Se Young Choi had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Analysis and interpretation of data: Choi, Y.-J. Yang, Nguyen.
Drafting of the manuscript: Choi, Y.-J. Yang.
Critical revision of the manuscript for important intellectual content: Choi, Y.-J. Yang, Nguyen, E.-J. Yang.
Statistical analysis: Y.-J. Yang.
Obtaining funding: Choi.
Administrative, technical, or material support: Choi.
Supervision: Choi.
Other: Choi.

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Data sharing statement: Data are publicly available from published studies and their supplementary files. No new data were generated or collected by the authors.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euros.2025.12.008.

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