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Review Article

The Diagnostic Performance of ^{68}Ga-PSMA-11 PET/MRI for the Biochemically Recurrent Prostate Cancer: A Systematic Review and Meta-analysis

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Abstract

Background: Our meta-analysis aimed to evaluate the diagnostic performance of ^{68}Ga-PSMA-11 PET/MRI for biochemical recurrence of prostate cancer.

Methods: We systematically and comprehensively searched all available studies until May 2023 in the PubMed and Embase databases. Studies evaluating ^{68}Ga-PSMA-11 PET/MRI in men with prostate cancer biochemical recurrence were included. We appraised the quality of studies using a tailored Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool. For each meta-analysis, we used the DerSimonian and Laird method. We first transformed proportions with the Freeman-Tukey double arcsine transformation, and then confidence intervals were calculated using the Jackson method. Meta-regression and sensitivity analysis were conducted to explore heterogeneity sources. Furthermore, we conducted subgroup analysis according to the PSA levels.

Results: Overall, 13 studies with 738 patients were included in the analysis. The pooled overall detection rates of ^{68}Ga-PSMA-11 PET/MRI in detecting recurrent PCa after definitive treatment were 74% (95% CI, 68%-79%). For patients with PSA under 0.5 ng/mL, the detection rate was 55 %. The detection rates were 79 %, 76 % and 87 % for the subgroup PSA levels of 0.5−0.99, 1.0–1.99 and over 2.0 ng/mL.

Conclusion: ^{68}Ga-PSMA-11 PET/MRI has a good detection rate for biochemical recurrence of prostate cancer. However, large sample, multi-center studies are still needed to verify and expand on our conclusion.

Keywords: Prostate cancer; Biochemical recurrence; Meta-analysis

Introduction

Prostate cancer (PCa) is the second most commonly diagnosed cancer, 29% of newly diagnosed cancers among U.S. men were PCa and the sixth leading cause of death worldwide (1). The pathogenesis of PCa is very complicated and has not been completely elucidated, however, environmental and genetic factors are thought to play an important role (2). There are currently a variety of treatments PCa, including endocrine therapy, radiotherapy, and surgical treatment (3). However, biochemical recurrence (BCR) occurs in 20%-40% and 30%-50% of patients after radical surgical resection and radical radiotherapy within 10 years (4). BCR was defined as rising prostate-specific antigen (PSA), although different cut-off values have been proposed, PSA value > 0.2

ng/mL with at least one confirmatory rise. (4). Patients with shorter PSA doubling time (PSADT), the higher the risk of death (5). The latest studies demonstrated that PSADT<3 months after radical resection had a 19.6-fold increased risk of death from BCR (6). Moreover, patients with BCR have a higher risk of developing lymph node, distant metastases and mortality (7). Meanwhile, the American Urology Association (AUA) guidelines also suggest that in the absence of effective medical intervention, 46% of BCR will translate to clinical recurrence or even bone metastasis within 12 to 24 months, seriously endangering human health and life (8).

The commonly used evaluation of BCR mainly relies on imaging methods, including computed tomography (CT), magnetic resonance imaging (MRI) and single-photon emission computed tomography (SPEC), but these examination methods are often not effective in early detection of BCR, especially when PSA levels dropped (9). Many researchers have used multi parametric magnetic resonance imaging (mpMRI) for detection of BCR (10). MpMRI of the prostate commly consists of T2-weighted imaging (T2WI), diffusion weighted imaging (DWI), apparent diffusion coefficient (ADC), and dynamic contrast enhanced MRI (DCEMRI), which help further improve diagnostic accuracy (11). However, this method still has a limited ability to detect tumors, about 20%-35% of BCR could be missed (12). Hybrid PET (positron emission tomography)-MRI technology scanners give the ability to perform simultaneous PET-MR prostate studies and has provided excellent soft tissue contrast and time resolution.(13). Prostate specific membrane antigen (PSMA) is a 100 kDa transmembrane glycoprotein that was originally found on prostate epithelial cells, highly upregulated in PCa (14). Therefore, PSMA is regarded as an optimal imaging and therapy target in PCa (15). Radiolabeled PSMA ligand Glu-NH-CO-NH-Lys-(Ahx)-^{68}Ga-HBED-CC, also known as ^{68}Ga-PSMA-11, is currently the most popular radiotracer used for PET imaging of BCR (16).

Nowadays, metabolic imaging techniques, specifically positron emission tomography employing PSMA targeted agents, have been acknowledged as valuable methodologies for enhancing the diagnosis of BCR (17,18). Systematic reviews of PSMA PET in BCR to date mainly focuses on the detection efficiency of ^{68}Ga PSMA PET/CT, few have assessed the performance of ^{68}Ga-PSMA-11 PET/MRI in detecting BCR. Therefore, this study was conducted to evaluate comprehensively the detection effect of 68Ga-PSMA-11 PET/MRI on BCR.

Materials and Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for conducting and reporting systematic reviews (17). The prospective protocol was created and registered in the International Prospective Register of Systematic Reviews (PROSPERO CRD42022319307).

Search Strategy

We comprehensively searched all available literature until May 2023 in the PubMed and Embase databases. The keywords were based on the following: (PET-MRI OR "positron emission tomography/magnetic resonance imaging" OR PET-MR OR "positron emission tomography/magnetic resonance") AND (regeneration OR recurrent OR relapse OR Recrudescence) AND (Prostatic Cancers OR Prostatic Cancer OR Prostate Cancers OR Prostate Cancer OR Prostatic Neoplasm OR Prostate Neoplasm OR Prostate Neoplasms OR Prostate tumor OR prostatic tumor). The reference lists of identified publications were hand-searched for potentially relevant studies.

Inclusion and Exclusion Criteria

Studies were eligible for inclusion if all the following criteria applied: (a) Patients were suspected of BCR underwent ^{68}Ga-PSMA-11 PET/MRI; (b) sample size>10.

The exclusion criteria were (a) duplicated articles; (b) abstract, editorial comments, letters, case reports, reviews, or meta-analyses; (c) clearly irrele-

vant titles and abstracts; (d) non-English full-text articles.

Two researchers independently screened titles and abstracts of the retrieved articles according to the aforementioned inclusion and exclusion criteria, and then evaluated the full-text version of the remaining articles to determine their eligibility for inclusion. Disagreements between the researchers were resolved by consensus.

Quality Assessment

Two researchers independently assessed the quality of the included studies, using the Quality Assessment tool for Diagnostic Accuracy Studies (QUADAS-2) tool (18). Studies were assessed for selection of patient, index test, reference standard, flow and timing. These domains were then assessed according to the risk of bias and were rated regarding applicability as high, low, unclear. Any discrepancies were resolved by consensus with a third reviewer.

Data Extraction

Two researchers independently conducted data extraction for all included articles. The extracted data included the author, year, study characteristics (country, study design), patient characteristics (number of patients, age, median PSA, Gleason score), technical aspects (scanner model, injection dose, uptake time, image analysis). Detection rates were tabulated using the corresponding raw data provided from each of the included studies. Disagreements concerning eligibility among the researchers were resolved by consensus.

Statistical Analysis

We assessed heterogeneity using the I^2 statistic. A forest plot was constructed in the random-effect model if the significant heterogeneity was observed ($I^2 > 50\%$), else, the fixed model would be applied for statistical analysis. For each meta-analysis, we used the DerSimonian and Laird method. We first transformed proportions with the Freeman-Tukey double arcsine transformation, and then confidence intervals were calculated using the Jackson method. Meta-regression and sensitivity analysis were conducted to explore heterogeneity sources. Furthermore, we conducted subgroup analysis according to the PSA levels. The publication bias was evaluated using Egger's test. A statistically significant *P*-value was two-tailed and with the threshold of 0.05. Statistical analyses were performed in R software environment for statistical computing and graphics version 4.1.2.

Results

Literature Search and Study Selection

Initial search of the literature yielded 276 publications. After excluding 150 duplicated studies, 126 studies were screened by title and abstract. Based on the title or abstract,105 studies were excluded. The remaining 21 articles were carefully assessed by full text, and another 8 were excluded for the following reasons: not in English (n=2); data unavailable (n=6). Finally, 13 articles evaluating diagnostic performance of ^{68}Ga-PSMA PET/MRI for the biochemically recurrent prostate cancer were eligible for meta-analysis. Study selection process is summarised in a PRISMA flow diagram shown in Fig. 1.

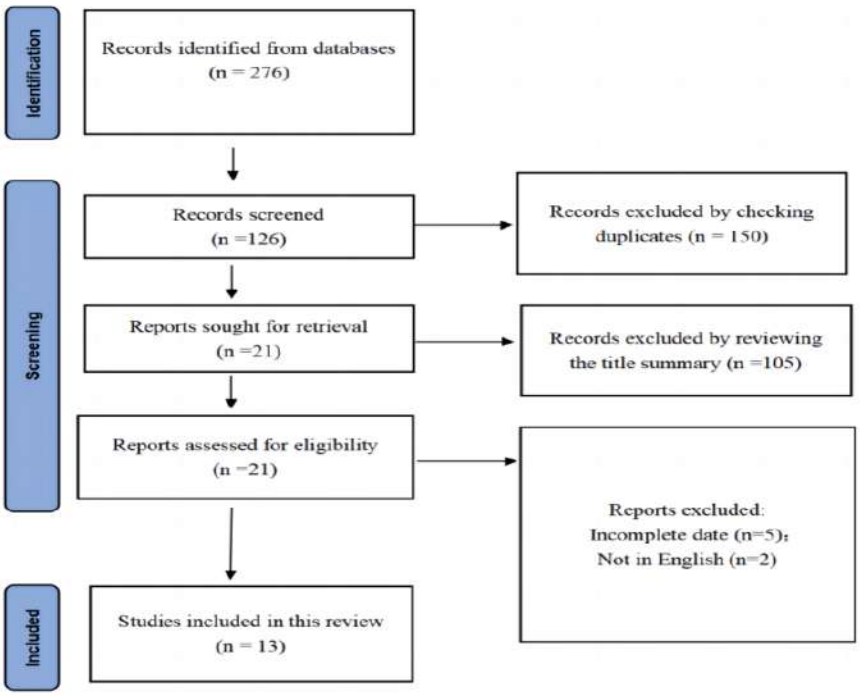

Fig. 1: The flow diagram of study selection

Study Description and Quality Assessment

The 13 eligible studies included 738 previously treated patients with BCR were published between 2014 and 2022 and had a sample size ranging from 10 to 165. The study and patient characteristics are summarized in Table 1. The technical aspects of ^{68}Ga-PSMA-11 PET/MRI are presented in Table 2. Detection rate are demonstrated in Table 3. Figure 2 demonstrates our evaluation of these studies regarding the risk of bias according to the QUADAS-2 tool. Overall, there was a moderate risk of bias due to index test. Regarding patients' selection, reference standard, and flow and timing of most studies, the risk of bias was low.

Table 1: Study and patient characteristics of the included studies. Pro prospective, Retro retrospective, RP radical prostatectomy, RT radiation therapy, NA not available

Author	*Year*	*Country*	*Study design*	*PSA level (ng/ml)*	*Age (year)*	*Inclusion interval*	*Treatments before PET*	*Gleason Score*
Guberina et al. (19)	2019	Germany	Retro	1.64	83	2015-2017	RP	NA
Jentjens et al. (20)	2021	Belgium	Pro	0.79	67.5	2015-2016	RT/RP	8-9(42.9%)
Joshiet al. (21)	2020	Australia	Pro	0.69	68	2016-2017	RP/RT	7
Kranzbühler et al. (22)	2017	Swiss	Retro	0.99	69	2016.4-2016.12	RP	Gleason=6(8.9%) Gleason=7(44.6%) Gleason≥8(33.9%)
Lake et al. (23)	2017	USA	Pro	7.1±6.6	68.3	2016.3-2016.9	RP/RT	Gleason=6(16%) Gleason=7 (50%) Gleason≥8(30%)
Lawhn-Heath et	2019	USA	Pro	2.1	68.5	2016.1-	RP/RT	Gleason=6(25.6%)

Table 1: Continued…

al. (24)						2016.10		Gleason=7 (47.4%) Gleason≥8(27%)
Lütje et al. (25)	2017	Germany	Retro	3.9	70.5	2014.11-2016.3	RT	NA
Mapelli et al. (26)	2022	Italy	Pro	1.88	70	2020-2021	RP/RT	Gleason=6(11.4%) Gleason=7 (34.2%) Gleason≥8(45.7%)
Martinez et al. (27)	2022	USA	Pro	5.56	69	NA	RP/RT	NA
Baratto et al. (28)	2021	USA	Pro	4.27	81	NA	RP/RT	NA
Burger et al. (29)	2019	Swiss	Pro	3.1±2.2	68	2016-2018	HIFU	Gleason=7 (90%) Gleason≥8(10%)
Maurer et al. (30)	2015	Germany	Retro	1.7	63	NA	RP/RT	NA
Maurer et al. (31)	2014	Germany	Retro	1.9	63	NA	RP/RT	NA

Table 2: Technical aspects of included studies

Author	*Year*	*Scanner Modality*	*Ligand dose*	*Time (min)*	*Image analysis*
Guberina et al. (19)	2019	Biograph mMR, Siemens Healthcare GmbH, Erlangen, Germany	115 MBq	76	quantitative
Jentjens et al. (20)	2021	GE Healthcare	1.86MBq/kg	121	quantitative
Joshiet al. (21)	2020	HBED-CC, ABX AG,Germany	150 MBq	45–60	quantitative
Kranzbühler et al. (22)	2017	GE Healthcare, Waukesha, WI, USA	123.34 ± 16.1 MBq	60	quantitative
Lake et al. (23)	2017	Signa, GE Healthcare	201.5 ± 52.9	65±11	quantitative
Lawhn-Heath et al. (24)	2019	3-T time-of-flight Signa PET/MRI, GE Healthcare	199.8 ± 48.1 MBq	63±10	quantitative
Lütje et al. (25)	2017	Siemens Healthcare	118 ± 23 MBq	175±45	quantitative
Mapelli et al. (26)	2022	SIGNA PET/MRI; General Electric Healthcare, Waukesha, WI, USA	129–288 MBq	60	quantitative
Martinez et al. (27)	2022	Siemens Biograph mMR	148 MBq	90	quantitative
Baratto et al. (28)	2021	Discovery Molecular Insights; GE Healthcare	155.4 MBq	90	quantitative
Burger et al. (29)	2019	Signa PET/MR; GE Healthcare	85MBq	60	quantitative
Maurer et al. (30)	2015	NA	122±17 MBq	NA	quantitative
Maurer et al. (31)	2014	NA	122±17 MBq	NA	quantitative

Table 3: Detection rate at different PSA levels

Author	*Year*	*Patients*	*Total*	*PSA <0.5*	*0.5 <PSA <1*	*1.0 <PSA <2.0*	*PSA>2.0*
Guberina et al. (19)	2019	93	63	NA	NA	NA	NA
Jentjens et al. (20)	2021	34	34	NA	NA	NA	NA
Joshiet al. (21)	2020	30	21	NA	NA	NA	NA
Kranzbühler et al. (22)	2017	56	44	12	20	5	20
Lake et al. (23)	2017	55	49	NA	NA	8	NA
Lawhn-Heath et al. (24)	2019	78	64	15	27	24	27
Lütje et al. (25)	2017	25	14	NA	NA	5	NA
Mapelli et al. (26)	2022	35	26	10	15	10	15

Table 3: Continued…

Martinez et al. (27)	2022	165	108	NA	NA	35	NA
Baratto et al. (28)	2021	50	37	2	9	6	9
Burger et al. (29)	2019	10	6	NA	NA	NA	NA
Maurer et al. (30)	2015	76	56	13	26	13	26
Maurer et al. (31)	2014	31	27	NA	NA	8	NA

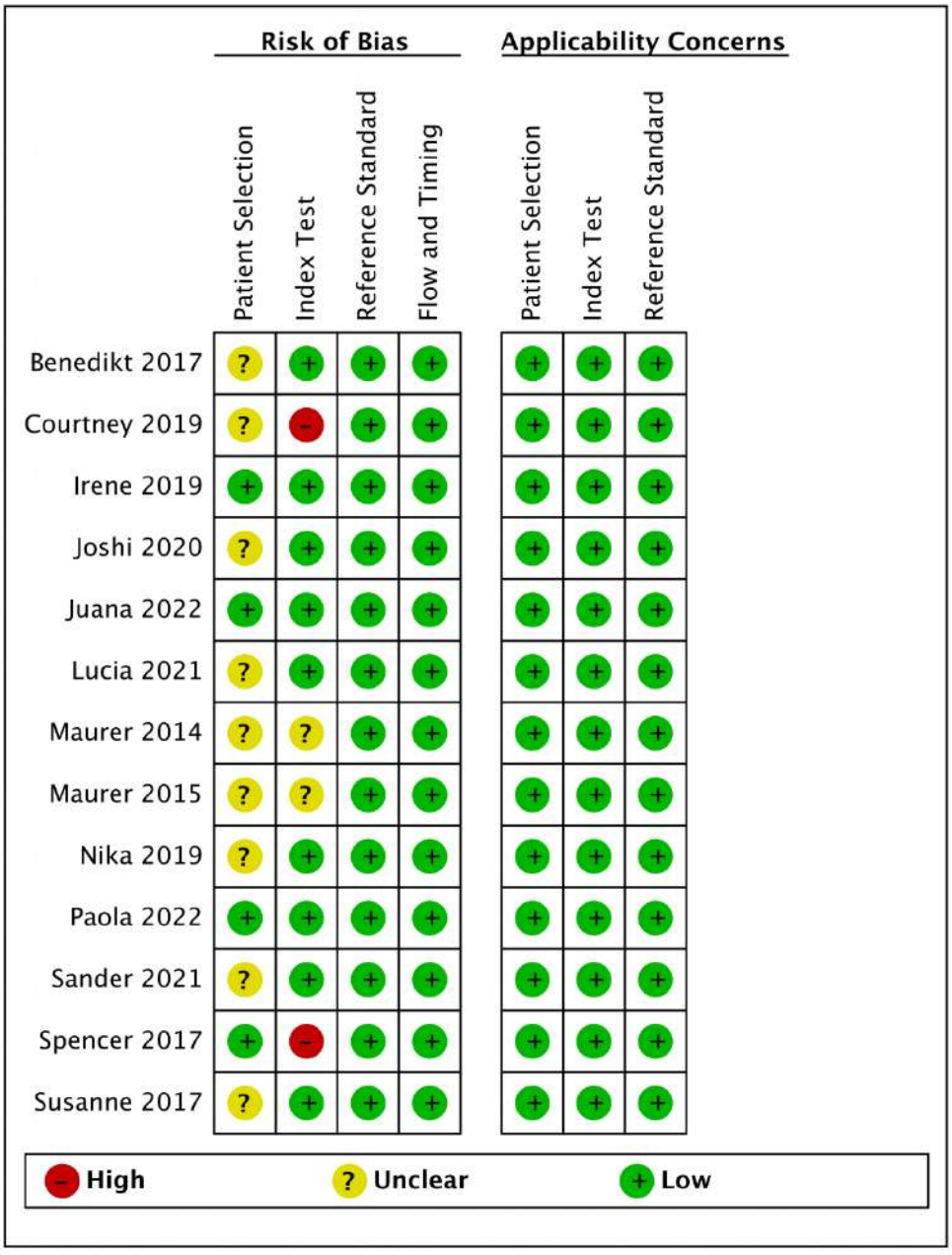

Fig. 2: Summary risk of bias and applicability concerns of the included studies

Meta-Analysis Results

Overall Detection Rates

Overall, 13 studies with 738 patients were included in the analysis. The pooled overall detection rates of ^{68}Ga-PSMA-11 PET/MRI in detecting BCR were 74% (95% CI, 68%-79%) (Fig. 3).

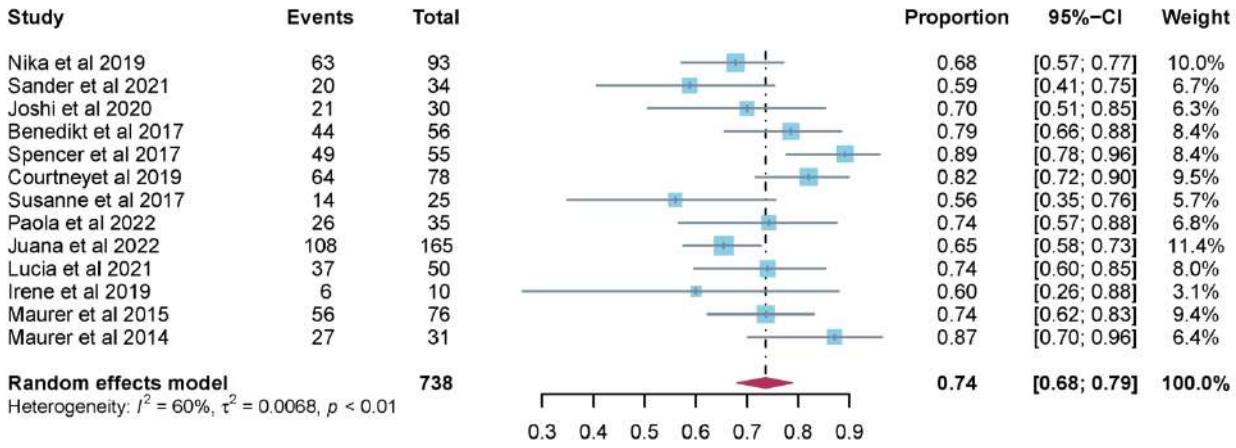

Fig. 3: Forest plot showing the pooled overall detection rates of ^{68}Ga-PSMA-11 PET/MRI in BCR

There was high heterogeneity in ^{68}Ga- PSMA-11 PET/MRI. According to the results, meta-regression couldn't find out the source of heterogeneity for ^{68}Ga-PSMA-11 PET/MRI in detecting BCR. Moreover, we carried out sensitivity analysis. Sensitivity analysis by excluding data from Spencer et al. (24) demonstrated a pooled detection rate of 72% (95% CI, 68%–75%), with acceptable heterogeneity (I^2 = 41.5%) (Table 4). Then Egger's test (P=0.914) were used to detecting publication bias showed that publication bias did not reach significance, besides, there is no publication bias by observing the funnel chart (Fig. 4).

Table 4: Sensitivity analysis of overall detection rate for ^{68}Ga-PSMA-11 PET/MRI

^{68}Ga-PSMA-11 PET/MRI	*Detection rate (95% CI)*	*I^2*
Guberina et al. (19)	0.73(0.70-0.77)	59.20%
Jentjens et al. (20)	0.73(0.70-0.78)	56.40%
Joshiet al. (21)	0.73(0.69-0.76)	60.60%
Kranzbühler et al. (22)	0.72(0.69-0.76)	59.40%
Lake et al. (23)	0.71(0.68-0.75)	41.50%
Lawhn-Heath et al. (24)	0.71(0.68-0.76)	54.50%
Lütje et al. (25)	0.73(0.70-0.76)	56.20%
Mapelli et al. (26)	0.73(0.69-0.76)	60.80%
Martinez et al. (27)	0.75(0.71-0.78)	53.30%
Baratto et al. (28)	0.73(0.69-0.76)	60.80%
Burger et al. (29)	0.73(0.69-0.76)	59.70%
Maurer et al. (30)	0.73(0.69-0.76)	60.80%
Maurer et al. (31)	0.72(0.69-0.75)	55.30%

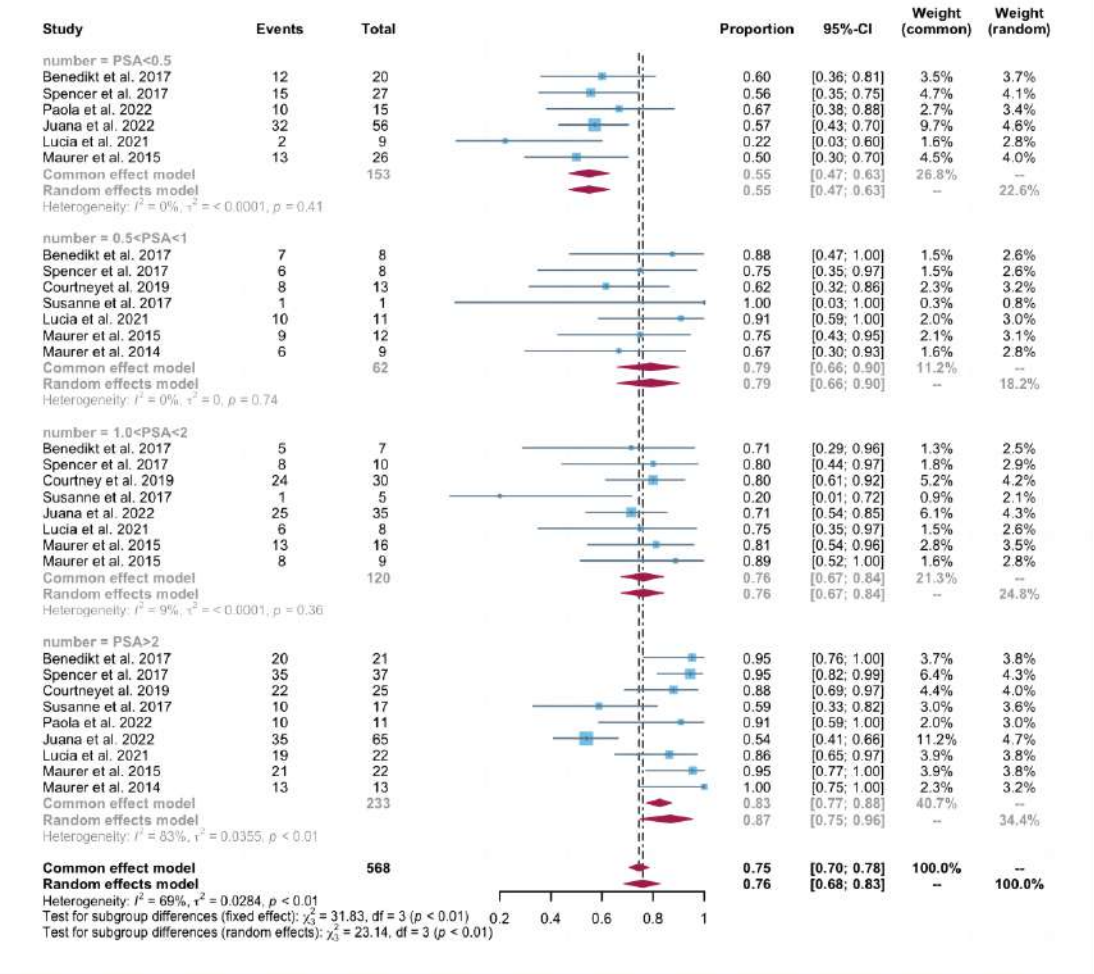

Fig. 4: Funnel plot of the pooled overall detection rates of BCR detected by ^{68}Ga-PSMA-11

Subgroup Analysis

We provided PSA levels pre ^{68}Ga- PSMA-11 PET/MRI on the basis of data in study, and then we pooled these dates to analyze the association between different PSA levels subgroups and detection rates (Fig. 5). For patients with PSA under 0.5 ng/mL, the detection rate was 55%. The detection rates were 79%, 76 % and 87% for the subgroup PSA levels of 0.5−0.99, 1.0–1.99 and over 2.0 ng/mL.

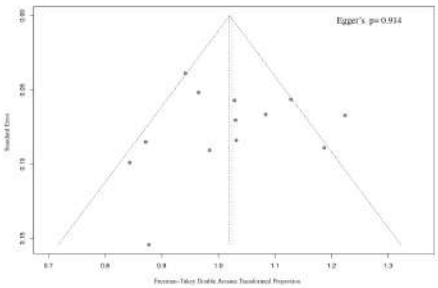

Fig. 5: Forest plot showing the subgroup analysis detection rates of ^{68}Ga-PSMA-11 PET/MRI in BCR

Discussion

To meet current medical needs, precise knowledge of the scope of the lesions is extremely important in clinical medicine. Molecular imaging can be used for detection of cancer as an accurate imaging diagnosis, such as the application of ^{68}Ga-PSMA-11 PET/MRI. Totally, 13 studies with 738 patients were included in the analysis. According to our analysis, the pooled overall detection rates of ^{68}Ga-PSMA-11 PET/MRI in detecting BCR were 74%. The findings of the review were consistent with the findings of the previous meta-analysis. The subgroup analysis findings indicate a positive correlation between the blood level of PSA and the detection rate of ^{68}Ga-PSMA-11 PET/MRI, emphasizing the significance of monitoring PSA values.

In the United States in 2022, prostate, lung, and colorectal cancer account for almost half of all cases of male cancer (48%), as well as 27% of confirmed cases of PCa (32). According to research, BCR may be caused by various factors, including aging, obesity, family history of PCa, and gene mutations (33). Depending on the individual risk category, most patients will recur after initial curative treatment (34). A diagnosis of local recurrence will determine whether salvage radiation therapy or systemic therapy is needed (i.e., androgen deprivation therapy, chemotherapy, or immunotherapy) (35). Thus, for oncologists treating patients with suspected BCR, detecting sites of relapse and characterizing extent of disease provide crucial information for treatment planning (36). Frequently, PCa is detected after an initial measurement of elevated PSA levels (37). There is, however, limited correlation between PSA levels and tumor burden, and patients with poorly differentiated tumors may develop metastatic disease in the absence of elevated PSA levels (38). Imaging examinations can detect subtle or occult recurrence and metastasis, offer non-invasive diagnosis of BCR (39). Radiopharmaceutics (^{68}Ga) are injected into the body, where they attach to prostate cancer cells via PSMA ligands by imaging in combination with PET/CT or PET/MRI to produce a new imaging technique called ^{68}GA-PSMA PET (40). It offers the potential to accurately stage recurrences of cancer and provide more personalised treatment (41). BCR patients commonly undergo ^{68}Ga-PSMA-11 PET/CT to locate recurrent disease, as it has been shown to be superior to conventional diagnostic imaging in this regard (42). Giorgio et al. published a meta-analysis reporting a detection rate of 74.1% for PSMA PET/CT in BCR patients (43). In parallel, a head-to-head comparative study showed that compared with mpMRI, ^{68}Ga-PSMA-11 PET/CT has a trend of higher sensitivity and diagnostic accuracy in detecting PLNMs in patients with prostate cancer (44). However, ^{68}Ga-PSMA-11 PET/CT offers limited anatomic detail of the zonal anatomy of the prostate gland and may miss bone marrow lesions, thus limiting its value in recurrence of tumor and in directing targeted biopsies (45). In ^{68}PSMA-11 PET-MRI, the multiparametric potential of PSMA-PET and the high soft tissue contrast of MRI are combined to provide a whole-body assessment with high performance, well suited to the locoregional evaluation of the prostate bed and pelvis (46).

In the previously published meta-analysis, rang et al. analyzed the detection rate of ^{68}Ga-PSMA-11 PET/MRI for BCR. In their study, only seven studies were included assessing the application value of ^{68}Ga-PSMA-11 PET/MRI, with a pooled detection rate of 76%. A recent update meta-analyse in Huasong et al. revealed that ^{68}Ga-PSMA-11 PET/CT and ^{68}Ga-PSMA-11 PET/MRI seem to have equivalent performance in detecting BCR (47). The pooled overall detection rates of ^{68}Ga-PSMA-11 PET/CT and ^{68}Ga-PSMA-11 PET/MRI in detecting recurrent PCa after definitive treatment were 89% and 92%. Compared to PET/CT, PET/MRI does offer better soft tissue resolution and less radiation exposure. Meanwhile, the current study demonstrated that the use of ^{68}Ga-PSMA PET/MRI to detect BCR appears to be more cost-efective relative than usual care, ^{68}Ga-PSMA was potentially cost saving and slightly more effective 0.07 life years(48). The detection rate of ^{68}Ga-PSMA-11

ranged from 55.8% to 82.8% with the median PSA less than 5 ng/mL.

There were several limitations that should be analyzed when interpreting the results of this meta-analysis. First, only thirteen studies with 738 patients were finally included in this meta-analysis, and both computer and manual search strategies were adopted; therefore, high-quality studies with larger sample sizes are required to confirm the diagnostic value of ^{68}GaPSMA-11 PET-MRI in BCR. In addition, most papers do not use pathological biopsy as the gold standard to combine sensitivity and specificity, we evaluated the detection rate of ^{68}GaPSMA-11 PET-MRI.

Conclusion

68Ga-PSMA-11 PET/MRI has a good detection rate for biochemical recurrence of prostate cancer. Meanwhile, 68GaPSMA-11 PET-MRI demonstrate a potentially promising detection rate with low PSA levels in BCR. However, owing to the limitations, further large-scale and well-designed studies are required to verify and expand on our conclusion.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

Conflict of interest

The authors declare that they have no conflict of interest.

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