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Performance of PSMA PET-CT imaging in predicting outcomes and assessing response in prostate cancer: a meta-analysis

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► ***Original article***

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ABSTRACT

Background: One of the most widespread forms of cancer in males across the globe is prostate cancer (PC), which is seeing an upward trend in illness and death. The use of Prostate-Specific Membrane Antigen Positron Emission Tomography-Computed Tomography (PSMA PET-CT) is gaining traction as a valuable imaging strategy that shows potential for diagnosing and monitoring PC. Nevertheless, existing studies on how PSMA PET-CT parameters influence patient outcomes show varying results, highlighting the need for definitive evidence to validate their predictive capabilities. ***Materials and Methods:*** The objective of this thorough examination and structured evaluation was to assess the predictive capacity of parameters derived from PSMA PET-CT in PC patients. The databases PubMed, EMBASE, Cochrane Library, and Web of Science were accessed to find research on the link between metrics generated from PSMA PET-CT and survival rates in PC patients. The meta-analysis utilized Stata version 14.0. To determine whether publication bias existed among the studies, Egger's test was employed. ***Results:*** Seventeen research investigations that included 1,103 individuals were combined. The findings from the meta-analysis indicated that TV-PSMA emerged as a crucial factor in forecasting overall survival (OS) for PC patients (HR=1.69, 95% CI 1.24-2.29), while parameters related to SUV showed no meaningful association with OS or progression-free survival (PFS). ***Conclusion:*** The PSMA PET-CT-derived TV-PSMA parameters serve as reliable predictors of OS in PC patients, while SUV-related parameters and TL-PSMA each show no significant performance in prognostic predictions. Future research should seek to validate these findings in a broader population, and these parameters should be effectively incorporated into clinical decision-making to enhance patient outcomes.

INTRODUCTION

Among male patients, prostate cancer (PC) ranks as the cancer that is diagnosed most often, accounting for nearly 15% of all cancers affecting men [(1)]. The age-standardized incidence rate (ASR) of PC is 31 per 100,000 men, with a lifetime cumulative risk of 3.9% [(2)]. Moreover, PC also stands as the fifth highest contributor to cancer-induced mortality around the globe [(3)].

Currently, the clinical diagnosis and treatment of PC are developing rapidly. The identification of the condition mainly relies on testing for prostate-specific antigen (PSA) levels in the blood combined with traditional imaging methods, encompassing CT, MRI, and whole-body bone scans [(4)]. The diverse and varied pathological characteristics of pancreatic cancer complicate both its clinical diagnosis and staging, resulting in a higher likelihood of inaccurate diagnostic outcomes, whether false negatives or positives [(5)]. Traditional imaging methods like CT scans, MRIs, and comprehensive bone scans have inherent drawbacks in accurately diagnosing prostate cancer. This may give rise to a substantial potential for misdiagnosis, which includes the possibility of receiving incorrect results that are either positive or negative [(6)]. The limitations of these techniques may adversely affect physicians' ability to develop treatment schemes for PC patients, which in turn affects the outcomes, quality of life (QoL) and the overall prognosis of patients. As a result, there is an immediate need to refine and enhance these detection methods to boost the precision and dependability of diagnoses.

Over the last several decades, innovative imaging techniques have been consistently enhanced and refined. One of the methods available is prostate-specific membrane antigen (PSMA) positron emission tomography-computed tomography (PET-CT), which serves as a noninvasive approach for visualizing PSMA-positive tumors in individuals diagnosed with prostate cancer [(7)]. The results from imaging can assist physicians in precisely detecting lesions (figure 1) [(8)]. This tool is essential for the detection of PC for

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its integration of anatomical, functional metabolic imaging, and molecular imaging, which can considerably enhance the accuracy of clinical disease diagnosis [9]. Derived parameters include the Total Volume of PSMA-positive lesions (TV-PSMA), Total Lesion of PSMA (TL-PSMA, which refers to the total PSMA uptake in all tumor lesions, determined by multiplying the volume of each tumor lesion by its average standardized uptake value (SUVmean), the highest standardized uptake value (SUVmax), SUVmean, and the peak standardized uptake value (SUVpeak).

PSMA is a protein that spans the cell membrane and features a binding site on its exterior. It is found in significant amounts on the membranes of prostate cell structures, including prostate cancer tissues. This substance is recognized as an effective indicator for both imaging and focused treatment of cancerous tumors, particularly in the case of prostate cancer [10]. PSMA, although mostly associated with the prostate, can also be identified in smaller traces within a variety of other organs. Notably, the expression of PSMA is increased in the neovascularization of multiple tumors, which is especially pronounced in PC [11]. PSMA expression is usually at higher levels in both primary and metastatic stages of PC [12, 13].

However, the association of parameters obtained from PSMA PET-CT (TV-PSMA, TL-PSMA, SUVmax, SUVmean, and SUVpeak) with the prognosis and survival of PC patients is controversial. Some articles have argued that an increase in SUVmax predicts shorter OS [14, 15], while others have reached the opposite conclusion, suggesting that an increase in SUVmax predicts longer OS [16-19] Some articles concluded that an increase in TV-PSMA predicted shorter progression-free survival (PFS) [14, 16, 18, 20-22], while others believed that an increase in TV-PSMA implied a lower risk of death and predicted longer PFS [23, 24]. Similarly, the influence of various parameters derived from PSMA PET-CT on survival prognosis is inconsistent and debated across multiple studies.

To sum up, this comprehensive analysis marks a groundbreaking initiative aimed at connecting the clinical needs with scientific progress in assessing the prognosis of PSMA PET-CT imaging for individuals diagnosed with PC. This has enriched our insight into the future health status of these patients, substantiated the usefulness of PSMA-based indicators, and propelled scientific exploration ahead. This research aims to combine existing insights with new discoveries to create a robust basis for improving treatment methods and enhancing management strategies for patients diagnosed with prostate cancer.

MATERIALS AND METHODS

This analysis was performed in line with a study protocol set beforehand, which is available if requested. The research plan has been officially recorded in the PROSPERO database under the registration number CRD42024574171. The comprehensive review adhered closely to the standards set by the Cochrane Collaboration and the systematic review and meta-analysis protocols outlined by PRISMA [25].

Literature search

The research team accessed PubMed, EMBASE, Cochrane Library, and Web of Science, tailoring their search methods to suit the unique features of each database. The deadline for the literature search was set as July 12, 2024. When screening potential studies for meta-analysis, the terms “prostate-specific membrane antigen” or “PSMA”, “positron emission tomography” or “PET”, and “prostate cancer”, “prostate tumor” or “prostate malignancy”, and their abbreviations were used as keywords. In addition, various synonyms were used to enhance the comprehensiveness of the search. No restrictions were imposed on the date of publication or language of the literature.

Inclusion and exclusion criteria

Two researchers conducted independent reviews of the titles, abstracts, and complete texts to identify studies that might be eligible. Any disagreements between them were addressed by consultation and discussion with a third author, and any differences were resolved upon consensus after consultation. Literature screening was performed in Endnotes version X9.

Original articles were deemed suitable for inclusion if they fulfilled all specified criteria, including: (a) clinical research involving patients diagnosed with different forms of PC; (b) individuals undergoing PSMA PET-CT scans; (c) research exploring the connection between prostate cancer patient results and PSMA PET-CT metabolic metrics; (d) research published in the English language. The criteria for exclusion included: (a) studies conducted on animals or cellular models; (b) various other article formats (such as reviews, conference summaries, case studies, or opinion pieces); (e) duplicated publications; and (f) studies that do not provide hazard ratios (HRs) along with 95% confidence intervals (CIs) for PFS or OS.

Data extraction

In this research, two separate reviewers conducted an initial examination of the titles and abstracts from all chosen studies to eliminate any articles that did not align with the study's goals. Afterward, the information obtained from the selected studies comprised the title, the name of the chief contributor and the year it was made public, the region or country of the research, the sample size, the age demographics of subjects, the period over which

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they were followed up, the study outcome metrics, the subtypes of PC studied, and the therapeutic strategies adopted, as depicted in table 1.

By analyzing the entire texts of suitable articles, the essential characteristics of the study were determined. Outcome indicators of PSMA PET-CT imaging encompassed TV-PSMA, TL-PSMA, SUVmax, SUVmean, SUVpeak, and their HRs and 95% CIs were also extracted. In cases where HR was not reported directly, the estimation of HR along with its 95% confidence interval was conducted through Kaplan-Meier curves, utilizing Engauge Digitizer version 2.24 and Richard Steven's Excel workbook [26].

Quality evaluation

Two authors assessed the quality of every cohort study that was part of the review using the NOS, and any differences in their assessments were addressed through discussions with a third author. Research that received scores ranging from 4 to 6 points was categorized as having moderate quality, while studies scoring 6 points or higher were classified as high quality, which served as the established criteria for this report.

Statistical analysis

Hazard ratios accompanied by 95% confidence intervals were computed to reflect the effective impact. Cochrane's Q test was employed to examine the diversity present in the studies, while the extent of this variability was measured using the I^2 statistic. A P-value for the Q statistic below 0.1 or an I^2 value above 50% suggests considerable variability among the studies, prompting the use of a random-effects model (REM) to combine the effect sizes (HR values); otherwise, a fixed-effects model (FEM) was leveraged. In addition, an analysis using meta-regression techniques was carried out to reveal possible contributing elements contributing to variability, with the significance threshold (α) for the meta-analysis established at 0.05. In instances of significant variability, sensitivity and subgroup analyses were performed, provided there were enough articles available. Publication bias was assessed using the Egger's test when the number of articles was six or greater, where a p-value below 0.05 indicates a meaningful statistical sign of bias. Publication bias was assessed and rectified by trim and fill technique in published works.

RESULTS

Literature screening results and fundamental characteristics

The literature search yielded 17,582 studies, from which 7,292 duplicates were eliminated, in addition to 10,072 articles that did not align with the necessary literature types or the study's goals. Of the 218 articles screened by title and abstract reading, 87 irrelevant articles were excluded, and the remaining 131 articles were downloaded to read the full text. Regrettably, the complete texts for four articles could not be accessed. As a result, the texts of the other 127 studies were reviewed, leading to the inclusion of 17 qualifying studies, all of which were cohort studies [14-23, 27]. This study involved 1,103 patients from six countries.

Table 1. General characteristics of included studies.

Author,year	Country	Case Numbers	Mean age	Tumor location	Treatment options	Median follow-up time (month)	Outcome	NOS
John,2023[12]	Australia	127	75.0	mCRPC	177Lu-PSMA	24	PFS,OS	7
Seifert,202019[13]	Germany	85	73.1	Advanced Prostate Cancer	177Lu-PSMA	NG	OS	6
Pathmanan-dave,2023[14]	Australia	56	68.0	mCRPC	177Lu-PSMA	26	PFS,OS	7
Acar,2019[15]	Turkey	19	66.0	mCRPC	ADT combined with docetaxel therapy	19	PFS,OS	6
Mollica,2024[16]	Italy	49	76.0	mCRPC	ARTA	16	PFS,OS	6
Widjaja,2021[17]	Germany	71	72.1	mCRPC	177Lu-PSMA	NG	OS	7
Simsek,2021[18]	Turkey	52	67.0	mCRPC	taxane	NG	OS	7
Güven,2023[19]	Turkey	42	63.5	mCSPC	ADT combined with docetaxel therapy	25.3	OS	8
Zou,2020[20]	China	59	69.0	Newly diagnosed cancer	None	14	PFS	6
Murad,2023[21]	Canada	74	68.3	oligometastatic prostate cancer	MDT	25	PFS	8
Li,2024[22]	China	71	70.0	Treatment-naïve prostate cancer	ADT	14	PFS	6
Chen,2023[25]	China	75	70.0	High-Risk Prostate	ADT combined with docetaxel therapy	30	PFS	8
Ferdinandus,2020[26]	Germany	50	NG	mCRPC	177Lu-PSMA	31.4	OS	6
Hartrampf,2023[27]	Germany	103	71.0	mCRPC	177Lu-PSMA	NG	OS	7
Seifert,2020[28]	Germany	40	73.7	Advanced Prostate Cancer	177Lu-PSMA	NG	OS	7
Seifert,2021[29]	Germany	110	72.0	Advanced Prostate Cancer	177Lu-PSMA	NG	OS	7
Widjaja,2023[30]	Germany	20	72.1	mCRPC	177lu-PSMA	NG	PFS	6

mCRPC: Metastatic Castration-Resistant Prostate Cancer mCSPC: Metastatic Castration-Sensitive Prostate Cancer ADT: Androgen Deprivation Therapy MDT: Multidisciplinary Team. ARTA: Androgen Receptor Targeted Alpha Therapy OS: Overall Survival PFS: Progression Free Survival NG: Not Given.

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Quality assessment results

This research involved an in-depth evaluation of the caliber of the chosen research articles, employing the NOS for systematic evaluation. According to the extensive review, seven of the studies assessed were awarded six stars, ten awarded seven stars, and three awarded eight stars. As a result, every research effort was conducted with a high standard, establishing a strong basis for the trustworthiness of the findings in this investigation (table 2).

Meta-analysis results

The 17 articles included were meta-analyzed. The results are depicted in table 3.

Nine articles focused on elevated TV-PSMA for forecasting OS [14, 16-18, 20, 21, 28-30], with 545 PC patients. Significant heterogeneity was noted among studies (I^2=83.8%, P=0.001). Therefore, a REM was used to pool the HRs and their 95% Cls. The aggregate HR was 1.69 (95% Cl: 1.24, 2.29, P=0.001). An evaluation of sensitivity was conducted, revealing that omitting any of the studies did not lead to notable alterations in the findings of the research (figure 2A).

Subgroup analyses were implemented because of the high heterogeneity among the studies. Table 4 demonstrates the subgroup analysis results. The publications were categorized into two distinct groups according to their geographical origin. There was no significant decrease in heterogeneity in both subgroups (I^2=85.9%, P=0.001; I^2=79.9%, P=0.026). The aggregate HR calculated using a REM was 1.64 (95% CI: 1.20, 2.25, P=0.002) and 2.01 (95% CI: 0.35, 11.62, P=0.436), respectively. This result suggested that the region of publication was not a source of heterogeneity in TV-PSMA for predicting OS. Further subgroup analysis was conducted based on treatments. Heterogeneity was significantly reduced in the chemotherapy subgroup (I^2=0%, P=0.929); the combined hazard ratio calculated with a FEM was 4.36 (95% CI: 2.64, 7.22), P=0.139. There was no considerable change in heterogeneity in the radiotherapy subgroup (I^2=75.6%, P=0.003); the combined hazard ratio calculated using a REM was 1.18 (95% CI: 0.96, 1.48, P=0.003). This result revealed that the treatment method may be a source of heterogeneity in TV-PSMA for predicting OS. Patients were analyzed in two subgroups based on their mean age. Heterogeneity was significantly reduced in the ≤70-year-old subgroup (I^2=0%, P=0.928), yielding an aggregate HR of 4.57 (95% CI: 2.75, 7.59, FEM, P=0.001). In the subgroup of individuals over 70 years old, there was no notable alteration in heterogeneity (I^2=73.2%, P=0.005), yielding an aggregate HR of 1.17 (95% CI: 0.95, 1.45, REM, P=0.139). This result suggested that the age of patients may be a source of heterogeneity in TV-PSMA regarding OS. Three articles focused on elevated TL-PSMA for forecasting OS, with 171 PC patients [17, 21, 30]. Significant heterogeneity was noted among studies (I^2=71.5%, P=0.030). Therefore, a REM was used to pool the HRs and their 95% Cls. The combined hazard ratio was 3.00 (95% Cl: 0.44, 20.21, P=0.030). An evaluation of sensitivity was conducted, revealing that omitting any of the studies did not lead to notable alterations in the findings of the research.

Nine articles utilized elevated SUVmax for forecasting OS, with 604 PC patients [14-19, 28, 29, 31]. Because of moderate heterogeneity among studies (I^2=50.8%, P=0.001), a REM was used to pool the HRs and their 95% Cls. The aggregate HR was 0.99 (95% Cl: 0.99, 1.00) (P=0.030) (figure 2B).

Table 2. Quality assessment results of included literature.

Study		Selection				Comparability	Outcome			Total score
		Representativeness of the exposure group	Selection method of non-exposed group	Determination method of Exposure factors	Control for conditions	Control for important factors	Full evaluation of the result	Appropriate follow-up time	Full follow-up of exposed and non-exposed groups	
John *et al.*[12]	2023	★	★	★		★	★	★	★	7
Seifert *et al.*[13]	2020	★	★	★			★	★	★	6
Pathmanandave *et al.*[14]	2023	★	★	★		★	★	★	★	7
Acar *et al.*[15]	2019	★	★	★			★	★	★	6
Mollica *et al.*[16]	2024	★	★	★			★	★	★	6
Widjaja *et al.*[17]	2021	★	★	★		★	★	★	★	7
Simsek *et al.*[18]	2021	★	★	★		★	★	★	★	7
Güven *et al.*[19]	2023	★	★	★		★★	★	★	★	8
Zou *et al.*[20]	2020	★	★	★			★	★	★	6
Murad *et al.*[21]	2023	★	★	★		★★	★	★	★	8
Li *et al.*[22]	2024	★	★	★			★	★	★	6
Chen *et al.*[25]	2023	★	★	★		★★	★	★	★	8
Ferdinandus *et al.*[26]	2020	★	★	★			★	★	★	6
Hartrampf *et al.*[27]	2023	★	★	★		★	★	★	★	7
Seifert *et al.*[28]	2020	★	★	★		★	★	★	★	7
Seifert *et al.*[29]	2021	★	★	★		★	★	★	★	7
Widjaja *et al.*[30]	2023	★	★	★			★	★	★	6

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Table 3. Meta-analysis results.

Outcomes	Cohort count	Case count	HR(95%CI)-Model	P	Heterogeneity	
					I^2(%)	P-value
OS						
TV-PSMA	9	545	1.69 (1.24,2.29)	0.001	83.80%	0.001
TL-PSMA	3	171	3.00 (0.44,20.21)	0.030	71.50%	0.030
SUVmax	9	604	0.99 (0.99,1.00)	0.030	47.40%	0.055
SUVmean	5	405	0.94 (0.91,0.98)	0.001	0.00%	0.462
SUVpeak	3	228	0.99 (0.98,1.00)	0.160	24.10%	0.268
PFS						
TV-PSMA	9	550	1.06 (0.89,1.25)	0.201	84.90%	0.001
TL-PSMA	3	172	0.77 (0.30,1.96)	0.589	5.40%	0.347
SUVmax	6	407	0.99 (0.86,1.14)	0.011	64.95%	0.014
SUVmean	2	198	0.73 (0.28,1.88)	0.226	62.40%	0.103

OS: Overall Survival PFS: Progression Free Survival TV-PSMA: Total Volume of Prostate-specific membrane antigen TL-PSMA: Total Lesion of Prostate-specific membrane antigen SUVmax: Maximum Standardized Uptake Value SUVmean: Mean Standardized Uptake Value SUVpeak: Peak Standardized Uptake Value.

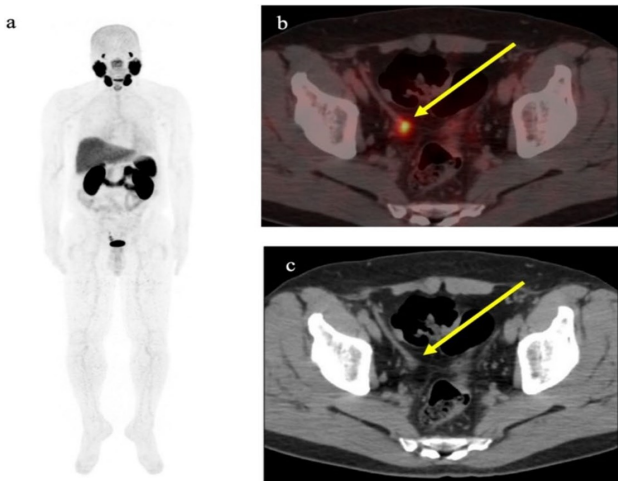

Figure 1. PSMA PET-CT imaging of a patient with biochemical recurrence of prostate cancer revealed focal radioactivity uptake extending from the right seminal vesicle to the vas deferens area. Notably, no significant radioactivity accumulation was detected in other regions, which is indicative of metastatic spread. **(a)** Maximum intensity projection image. **(b)** Transaxial PET/ CT fusion image. **(c)** Transaxial CT.

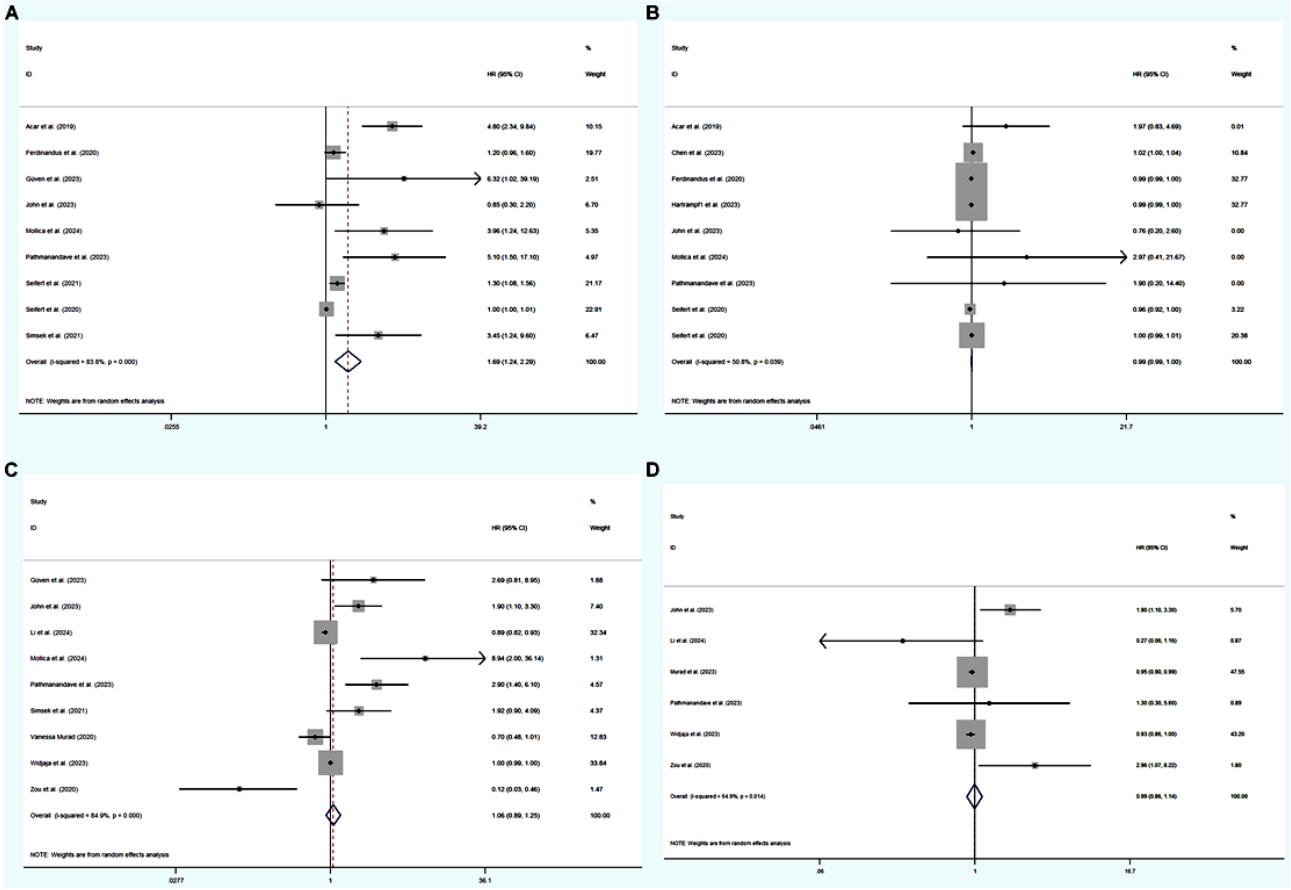

Figure 2. A; Forest plot of hazard ratios for TV-PSMA in relation to overall survival. **B;** Forest plot of hazard ratios for SUVmax in relation to overall survival. **C;** Forest plot of hazard ratios for TV-PSMA in relation to progression-free survival. **D;** Forest plot of hazard ratios for SUVmax in relation to progression-free survival.

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Table 4. Subgroup analysis results.

Subgroup		Number of included studies	Heterogeneity test		Meta analysis results	
			I^2	P	HR (95%CI)	P
TV-PSMA OS	Overall	9	83.80%	0.001	1.69 (1.24,2.29)	0.001
	Area					
	Europe	7	85.90%	0.001	1.64 (1.20,2.25)	0.001
	Oceania	2	79.90%	0.026	2.01 (0.35,11.62)	0.436
	Treatment options					
	chemotherapy	4	0.00%	0.929	4.36 (2.64,7.22)	0.139
	radiotherapy	5	75.60%	0.003	1.18 (0.96,1.48)	0.003
	Age					
	≤70	4	0.00%	0.928	4.57 (2.75,7.59)	0.001
	>70	5	73.20%	0.005	1.17 (0.95,1.45)	0.139
SUVmax OS	Overall	9	50.80%	0.001	0.99 (0.99,1.00)	0.030
	Treatment options					
	chemotherapy	3	40.00%	0.189	1.29 (0.75,2.20)	0.356
	radiotherapy	6	0.00%	0.513	0.99 (0.99,0.99)	0.001
	Age					
	≤70	3	21.40%	0.280	1.15 (0.79,1.68)	0.467
	>70	6	1.50%	0.407	0.99 (0.99,0.99)	0.001
TV-PSMA PFS	Overall	9	84.90%	0.001	1.06 (0.89,1.25)	0.201
	Area					
	Oceania	2	0.00%	0.367	2.21 (1.42,3.43)	0.001
	Europe	5	77.60%	0.001	1.36 (0.84,2.21)	0.206
	Asia	2	87.90%	0.001	0.37 (0.05,2.59)	0.316
	Age					
	≤70	5	84.80%	0.001	1.13 (0.46,2.74)	0.960
	>70	4	88.70%	0.001	1.01 (0.87,1.17)	0.200
SUVmax PFS	Overall	6	64.90%	0.014	0.99 (0.86,1.14)	0.011
	Area					
	Oceania	2	0.00%	0.634	1.81 (1.08,3.03)	0.023
	Europe	2	0.00%	0.590	0.94 (0.91,0.98)	0.009
	Asia	2	85.30%	0.009	0.95 (0.09,9.91)	0.967
	Age					
	≤70	3	59.50%	0.085	1.37 (0.65,2.91)	0.411
	>70	3	79.20%	0.010	1.01 (0.51,2.00)	0.987

OS: Overall Survival PFS: Progression Free Survival TV-PSMA: Total Volume of Prostate-specific membrane antigen SUVmax: Maximum Standardized Uptake Value.

Subgroup analyses were implemented given the moderate heterogeneity among the studies. The articles were classified into two subgroups based on the treatment. Heterogeneity was significantly reduced in the radiotherapy subgroup (I^2=0%, P=0.513), yielding an aggregate HR of 0.99 (95% CI: 0.99, 0.99, FEM, P=0.001). There was no significant change in heterogeneity in the chemotherapy subgroup (I^2=40.0%, P=0.189), yielding an aggregate HR of 1.29 (95% CI: 0.75, 2.20, REM, P=0.356). The findings indicated that the approach to treatment could contribute to variability in SUVmax in relation to overall survival. Patients were separated into two subgroups based on their mean age. Heterogeneity was significantly reduced in the >70-year-old subgroup (I^2=1.5%, P=0.407), yielding an aggregate HR of 0.99 (95% Cl: 0.99, 1.00, FEM, P=0.001); heterogeneity was also significantly reduced in the ≤ 70-year-old subgroup (I^2=21.4%, P=0.280), yielding an aggregate HR of 1.15 (95% Cl: 0.79, 1.68, REM, P=0.467). This result suggested that the age of patients may be a source of heterogeneity in SUVmax regarding OS.

Five articles used increased SUVmean for forecasting OS, with 405 PC patients [14, 15, 28, 29, 31]. Owning to no heterogeneity among studies (I^2=0%, P=0.462), a FEM was used to pool the HRs and their 95% Cls. The aggregate HR was 0.94 (95% Cl: 0.91, 0.98) (P=0.001).

Three articles focused on increased SUVpeak for forecasting OS, encompassing 228 PC patients [15, 29, 31]. Given relatively low heterogeneity among studies (I^2=24.1%, P=0.268), a FEM was used to pool the HRs and their 95% Cls. The aggregate HR was 0.99 (95% Cl: 0.98, 1.00) (P=0.160).

Nine articles used increased TV-PSMA for forecasting FPS, encompassing 550 PC patients [14, 16, 18, 20-24, 32]. Owing to significant heterogeneity among studies (I^2=84.9%, P=0.001), a REM was used to pool the HRs and their 95% Cls. The aggregate HR was 1.06 (95% Cl: 0.89, 1.25, P=0.201), as illustrated in figure 2C. Sensitivity analysis was performed. The research conducted by Widjaja *et al.* [30] and Li *et al.* [22] did not contribute to variability, yet they resulted in inconsistent combined outcomes.

Subgroup analyses were carried out because of the high heterogeneity among studies. The articles were separated into three subgroups based on the region of publication. Heterogeneity was considerably lower in the Oceania subgroup (I^2=0%, P=0.367). A FEM was

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employed, yielding an aggregate HR of 2.21 (95% CI: 1.42, 3.43). There was no significant change in heterogeneity in the European and Asian subgroups (I^2=77.6%, P=0.001; I^2=87.9%, P=0.001). The combined hazard ratio calculated using a random effects model was 1.36 (95% CI: 0.84, 2.21, P=0.206) and 0.37 (95% CI: 0.05, 2.59, P=0.316), respectively. This result suggested that the region of publication may be a source of heterogeneity in TV-PSMA regarding FPS. Additional analysis of subgroups was conducted according to the average age of the participants. There was no significant change in heterogeneity in the >70-year-old subgroup (I^2=88.7%, P=0.001) or the ≤70-year-old subgroup (I^2=84.8%, P=0.001). The combined hazard ratio calculated using a random effects model was 1.01 (95% CI: 0.87, 1.17, P=0.200) and 1.13 (95% CI: 0.46, 2.74, P=0.960), respectively. This result unveiled that the age of patients was not a source of heterogeneity in TV-PSMA regarding FPS.

Three articles reported increased TL-PSMA for forecasting FPS, encompassing 172 PC patients [21, 22, 24]. With no significant heterogeneity among studies (I^2=5.4%, P=0.347), a FEM was used to pool data. The aggregate HR was 0.77 (95% Cl: 0.30, 1.96, P=0.589). An analysis of sensitivity was conducted, revealing that omitting any of the studies did not lead to notable alterations in the findings of the research.

Six articles investigated increased SUVmax for predicting FPS, with 407 PC patients [14, 16, 22, 24, 32]. Owing to significant heterogeneity among studies (I^2=64.9%, P=0.014), a REM was used to pool data, yielding an aggregate HR of 0.99 (95% CI: 0.86, 1.14, P=0.011), as depicted in figure 2D. Sensitivity analysis was performed. The analysis revealed that the research by Widjaja *et al*. [30] and Li *et al*. [22] was not responsible for any discrepancies, but they resulted in erratic overall results.

Subgroup analyses were implemented due to the high heterogeneity among studies. Table 4 shows the subgroup analysis results: The articles were classified into three subgroups based on the region of publication. The heterogeneity among studies was notably diminished in both groups: Oceania (I^2=0%, P=0.634), and European (I^2=0%, P=0.590). The combined hazard ratio calculated with a FEM was1.81 (95% CI: 1.08, 3.03, P=0.023) and 0.94 (95% CI: 0.91, 0.98, P=0.005), respectively. There was no significant change in heterogeneity in the Asian subgroup (I^2=85.3%, P=0.009); the combined hazard ratio calculated using a random effects model was 0.95 (95% CI: 0.09, 9.91, P=0.967). This result unraveled that the region of publication may be a source of heterogeneity in SUVmax for forecasting FPS. A more detailed examination of subgroups was carried out, focusing on the patients' average age. There was no considerable change in heterogeneity in the >70-year-old subgroup (I^2=79.2%, P=0.010) or the ≤70-year-old subgroup (I^2=59.5%, P=0.085). The combined hazard ratio calculated using a random effects model was 1.01 (95% CI: 0.51, 2.00, P=0.987) and 1.37 (95% CI: 0.65, 2.91, P=0.411). This result unveiled that the age of patients was not a source of heterogeneity in SUVmax regarding FPS. Two articles focused on elevated SUVmean for forecasting FPS, encompassing 198 PC patients. [12, 22] Owing to significant heterogeneity among studies (I^2=82.4%, P=0.103), a REM was used to pool data. The aggregate HR was 0.73 (95% CI: 0.26, 1.86, P=0.226). The analysis of subgroups was not feasible because there were too few pertinent studies available.

Meta-regression analysis

To ascertain potential sources of heterogeneity, meta-regressions were performed with area, type of cancer, treatment method, sample size, and age as covariates.

The results on OS unraveled that for TV-PSMA, the variation in treatment approach (P=0.007) and the age of patients (P=0.002) contributed to the observed heterogeneity, whereas area (P=0.581), number of samples (P=0.177), and type of cancer (P=0.706) did not. For SUVmax, patient age (P=0.026), area (P=0.034), and treatment method (P=0.030) may be sources of heterogeneity, whereas the type of cancer (P=0.604) and number of samples (P=0.720) were not. For TL-PSMA, SUVmean, and SUVpeak, meta-regression could not be implemented owing to a small sample size.

The results on PFS unveiled that for TV-PSMA, type of cancer (P=0.061) may be a source of heterogeneity, whereas area (P=0.672), number of samples (P=0.946), treatment approach (P=0.864), and patient age (P=0.604) were not. For TL-PSMA, SUVmax, SUVmean, and SUVpeak, meta-regression could not be carried out given a sample size. The results are depicted in table 5.

Table 5. Meta-regression results.

Covariate	β	Standard error	95%CI	P
TV-PSMA(OS)				
area	-0.174	0.300	(-0.884,0.536)	0.581
sampsize	-0.011	0.007	(-0.028,0.006)	0.177
tumor location	-0.179	0.456	(-1.259,0.900)	0.706
treatment options	0.608	0.160	(0.229,0.987)	0.007
age	-0.911	0.433	(-1.116,0.934)	0.002
SUVmax(OS)				
area	0.010	0.004	(0.001,0.018)	0.034
sampsize	-0.001	0.001	(-0.001,0.001)	0.720
tumor location	0.004	0.007	(-0.014,0.022)	0.604
treatment options	0.029	0.011	(0.004,0.055)	0.030
age	0.004	0.011	(-0.021,0.029)	0.026
TV-PSMA(PFS)				
area	-0.100	0.226	(-0.635,0.435)	0.672
sampsize	-0.001	0.013	(-0.032,0.030)	0.946
tumor location	-0.442	0.198	(-0.911,0.026)	0.061
treatment options	-0.033	0.184	(-0.469,0.403)	0.864
age	-0.408	0.753	(-2.190,1.373)	0.604

OS: Overall Survival PFS: Progression Free Survival TV-PSMA: Total Volume of Prostate-specific membrane antigen SUVmax: Maximum Standardized Uptake Value.

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Publication bias test

In this study, Egger's test was performed on all the included articles. The results unraveled that there may be publication bias in TV-PSMA for forecasting OS (P=0.002), no publication bias in SUVmax for forecasting OS (P=0.374), TV-PSMA for forecasting PFS (P=0.669), or SUVmax for PFS (P=0.426). The asymmetric funnel plot of TV-PSMA for OS was corrected for publication bias using the trim-and-fill method. After three iterations, it was determined that the results of 3 studies needed to be imputed, leading to a total of 12 studies post-correction. Following the trim-and-fill adjustments, the analysis yielded P=0.074 and HR=1.32 (95% CI: 0.973-1.78). No further signs of publication bias were detected, and the funnel plot seemed to be symmetrical. The outcomes of the publication bias assessment are shown in table 6.

Table 6. Publication bias test results.

	Cohort count	Begg's test		Egger's test	
		Z	Pr>|z|	t	P
OS					
TV-PSMA	9	0.420	0.677	4.690	0.002
SUVmax	9	0.730	0.466	0.950	0.374
PFS					
TV-PSMA	9	0.000	1.000	0.450	0.669
SUVmax	6	-0.560	0.573	0.890	0.426

OS: Overall Survival PFS: Progression Free Survival TV-PSMA: Total Volume of Prostate-specific membrane antigen SUVmax: Maximum Standardized Uptake Value.

DISCUSSION

This research employs an extensive analysis and synthesis of existing literature to assess the forecasting importance of various factors derived from PSMA PET-CT in individuals diagnosed with prostate cancer. Evidence suggests that TV-PSMA is an important measure of OS in PC patients. Conversely, TL-PSMA and metrics related to SUV did not show significant relevance in forecasting OS and PFS. Earlier research has primarily concentrated on how PSMA PET-CT contributes to diagnosing and staging PC, while there has been limited investigation into how its derived metrics affect patient outcomes. Utilizing a comprehensive dataset that encompassed 17 articles involving 1,103 subjects, this research demonstrated the promise of PSMA PET-CT for prognostic forecasting and offered stronger evidence to bolster investigations in this field.

Over the past ten years, the role of PSMA PET-CT in identifying both initial and returning cases of PC has grown significantly. The use of this approach in the early identification, classification, and monitoring of biochemical recurrence following therapy, and targeted PC treatment has been extensively recognized in various research, greatly impacting how patients are managed [33, 34]. In terms of prognosis, as a prognostic biomarker, PSMA PET-CT has the following theoretical advantages over conventional histologic grading [35]: First, utilizing the abundant PSMA expression within PC cells as a biomarker can offer valuable insights for diagnosing and predicting outcomes. Due to the varying cancer characteristics, PSMA PET-CT can discern between tumors of lesser severity and those of greater severity [36], which aids healthcare professionals in formulating a more effective treatment strategy to enhance patient survival rates. Second, PSMA PET-CT offers a noninvasive assessment of systemic tumor metastasis, in contrast to conventional PC diagnosis, which relies on prostate biopsy-an invasive procedure that can lead to complications such as infection and rectal bleeding, potentially negatively impacting patient prognosis [36]. Third, compared with biopsied tissues that only reflect local tumor characteristics, PSMA PET-CT can evaluate the diversity within tumors and offer a more detailed overview of tumor features[37], which is conducive to assessing the survival prognosis of patients more accurately.

Previous studies have not conclusively demonstrated that PSMA PET-CT metrics can forecast the survival of PC patients. In the present study, TV-PSMA was identified as an important predictive instrument for determining survival outcomes in those suffering from PC, whereas TL-PSMA with SUV-related parameters lacked this capacity. Previous research has concentrated on SUV parameters linked to tumor metabolism but does not fully account for the impact of tumor burden. In contrast, TV-PSMA can reflect both tumor metabolic activity and tumor load, and this combined metric may provide a more accurate prediction of disease progression. Moreover, the calculation of TL-PSMA may be affected by SUVmean data, which may reduce its predictive accuracy for disease progression. Therefore, TV-PSMA, as a parameter that integrates metabolic activity and tumor load, may demonstrate higher efficacy in predicting tumor progression and patient survival prognosis compared to SUV-related parameters. The limitation of SUVmax, SUVmean, and SUVpeak, which are used to measure tracer uptake levels in the lesion area, lies in their inability to comprehensively capture the tumor's biological behavior [38]. Changes in the patient's body weight and its resulting variation in tissue composition, such as an increase in the proportion of adipose tissue, may affect SUV measurements because tracer uptake by adipose tissue is usually relatively low, which may result in relatively high SUV measurements[39, 40].

A recent investigation highlighted this relationship, revealing that changes in body mass index (BMI) and body composition can greatly affect Standardized Uptake Value (SUV) readings [41]. Respiratory and motion artifacts in patients are critical factors impacting the accuracy of SUV measurements. These artifacts may result in the

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misestimation of tumor volume, thereby influencing the clinical evaluation of disease progression. Errors due to differences in respiratory cycles should not be overlooked, especially for relatively small lesions that are more sensitive to respiratory motion [42]. This may limit the accuracy of SUV parameters in predicting small-volume tumors. Furthermore, the infiltration of inflammatory cells and the associated inflammatory response may amplify the glycolytic function of neoplastic cells. Thus, the glycolytic function of tumor cells might be enhanced, which could elevate the absorption of the tracer, making it more challenging to distinguish between cancerous and normal tissue and increasing the likelihood of false-positive findings [43]. Variations in technical aspects significantly contribute to inaccuracies, including discrepancies in the scanner's acquisition and reconstruction settings, as well as miscalibrations between the PET imaging device and the dose measurement instrument [44], which can influence the accuracy of SUV measurements. In addition, variations in the imaging equipment model selected in different studies may also affect the predictive capacity of SUV parameters.

TV-PSMA, as a parameter for quantifying tumor volume, offers a comprehensive evaluation of the total tumor burden, surpassing the limitations of SUV -related metrics, which are restricted to measuring only the point of maximal uptake [45, 46]. The tumor volume measured by TV-PSMA presents a more direct correlation with tumor pathophysiological characteristics, such as tumor growth rate, invasiveness, and metabolic activity, thus reflecting the actual tumor load more comprehensively [47]. In contrast, TV-PSMA measurements can be performed by automated or standardized VOI plotting methods, such as the structured reporting system proposed by PSMA-RADS, to reduce operator subjectivity and inter-operator variability [48].

TV-PSMA enables direct volumetric comparisons between different lesions, facilitating the identification of the most aggressive areas of the disease20-a capability that SUV parameters lack. Furthermore, in pre- and post-treatment evaluations, changes in TV-PSMA demonstrate greater sensitivity to alterations in tumor volume compared to changes in SUV, thereby facilitating earlier evaluation of treatment efficacy [49]. Despite these advantages of TV -PSMA, SUVmax remains an important metric in practical applications because it is fast, easy to measure, and in many cases sufficient for clinical decision-making. In some cases, a combination of TV-PSMA and SUVmax may provide more comprehensive information.

At present, traditional 18F-fluorodeoxyglucose (18F-FDG) PET-CT scans are extensively employed for identifying gastric cancer, lung cancer, malignant melanoma, and various other illnesses [50]. The approach is fundamentally centered on the enhanced glucose uptake of cancerous tissues, which aids in distinguishing malignant cells from normal ones using 18F-FDG PET-CT scanning. A new investigation has shown that metrics obtained from FDG PET-CT imaging possess considerable forecasting potential for anticipating death and the advancement of disease in those suffering from suffering from non-small cell carcinoma of the lungs [51]. Nonetheless, the performance of 18F-FDG PET-CT in detecting PC is restricted because only a few types of PC (such as aggressive, poorly differentiated, or undifferentiated types) exhibit high rates of glycolysis [52, 53]. PSMA PET-CT leverages the elevated levels of PSMA found on PC cell surfaces to identify PSMA-positive areas for imaging, resulting in enhanced precision. [7] Conversely, PSMA PET-CT demonstrates enhanced results when contrasted with 18F-FDG PET-CT regarding SUVmax and the ratio of target to nontarget tissues, indicating that PSMA PET-CT shows enhanced performance in differentiating tumors from healthy tissues [54-56]. This enhanced contrast helps clinicians more accurately formulate treatment plans, which may improve the prognostic survival of PC patients. A new investigation utilizing decision analysis techniques in individuals with prostate cancer revealed that incorporating PSMA PET-CT resulted in a notable decrease in death rates, with 75 fewer fatalities for every 1,000 patients. Compared to traditional imaging methods, there is a rise of 988 years of life gained and an improvement of 824 quality-adjusted life years for every 1,000 patients [57]. This indicates that data extracted from PSMA PET-CT imaging has the capacity to reliably predict and augment survival rates for PC patients. There are specific drawbacks associated with this investigation. Firstly, the included articles were predominantly retrospective, and there were no multicenter large-sample investigations. The small patient population had a negative impact on the research's quality and contributed to variations, which could have compromised the precision of the findings. Secondly, this study indicated significant heterogeneity when pooling the HRs of TL-PSMA regarding OS and SUVmean regarding PFS. Even after exploring various potential factors contributing to heterogeneity via meta-regression, subgroup analysis, and sensitivity analysis, a definitive cause remained elusive. Therefore, this heterogeneity may originate from variables not included in the current analysis, such as the setting of PSMA-derived data thresholds and baseline levels in various studies, differences in the model and initial parameters of the imaging equipment used, and inter-experimenter variability in subjective judgment. Thirdly, publication bias was found in TV-PSMA regarding OS in the included studies. The trim-and-fill method tackled the problem of biased publication results, highlighting its existence in the studies analyzed, which might sway the final interpretations of the

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meta-analysis findings. Finally, the small number of clinical study articles on PSMA PET-CT resulted in insufficient data for this investigation, unstable findings of some studies, and lack of convincing results about the prognostic impact of SUV-related parameters for further evaluation. We need extensive future studies to validate our results and investigate the prospective gains from implementing PSMA PET-CT in healthcare environments.

CONCLUSION

The evidence gathered from this research points to the fact that parameters from PSMA PET-CT related to TV-PSMA can be strong indicators of OS in PC patients. In contrast, the performance of SUV-related parameters (SUVmax, SUVmean, SUVpeak) and TL-PSMA in predicting the prognosis of PC is still open to interpretation. Nevertheless, owing to the restricted participant count, additional research is necessary to validate our results in an expanded cohort of individuals receiving treatment. The factors should be integrated into clinical decision-making to ameliorate patient outcomes.

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