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Association between Pre-Operative Total Prostate-Specific Antigen and Survivorship of Prostate Cancer following Radical Prostatectomy: A Systematic Review

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Highlights of the Study

- Survivorship of prostate cancer (PCa) is arguably the most essential consideration when planning prostatectomy as a definitive treatment for PCa.
- The usefulness of total prostate-specific antigen (PSA) as a determinant of survivorship of PCa is reported with ambivalence.
- The study demonstrated that the sole use of pre-operative PSA in estimating post-prostatectomy biochemical recurrence should be discouraged.

Keywords
Prostate-specific antigen · Prostatectomy · Survival · Prognosis

Abstract
Objective: This review aimed to systematically quantify the association between pre-operative total prostate-specific antigen (*t*PSA) and survivorship of prostate cancer (PCa). ***Methods:*** Data sources for the review included MEDLINE, PubMed, Cochrane Library, CINAHL, Academic Search Complete, PsycINFO, and relevant reference lists. Databases were searched from inception to June 2022. The study took place between May 2022 and March 2023. We included studies that applied a quantitative approach to examine the interaction between pre-operative PSA and survivorship of PCa. Pre-operative PSA constituted the independent variable, whereas survivorship of PCa as measured by biochemical recurrence and mortality constitute the outcome variable. A risk of bias assessment was conducted with the aid of a mixed-method appraisal tool. We employed meta-analysis to quantify the association of pre-operative PSA with biochemical recurrence and mortality and computed I^2 to assess the degree of heterogeneity. ***Results:*** We found a positive weak association between pre-operative PSA and biochemical recurrence (hazard ratio [HR] = 1.074; 95% CI =

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1.042–1.106). With a median rise in PSA (≥2 ng/mL), the likelihood for biochemical recurrence increase by approximately 7.4%. There was statistically a significant association between PSA and mortality (HR = 1.222, CI = 0.917–1.630). ***Conclusions:*** Biochemical recurrence associates with pre-operative PSA in an inconsistent manner. The sole use of pre-operative PSA in estimating post-prostatectomy biochemical recurrence should be discouraged. There is need for a multifactorial model which employs a prudent combination of the most important and cost-effective biomarkers in predicting post-prostatectomy biochemical recurrence.

Introduction

Prostate cancer (PCa) is a common cause of cancer death in men, particularly African-American men [1–3]. Nearly 90% of new cases of PCa are detected when the disease is in the prostate and adjacent organs [4]. Nearly one-third of patients with PCa experience biochemical recurrence (BCR) after primary definitive treatment such as radical prostatectomy (RP) [5]. Hence, there is an urgent need to ascertain the odds for treatment success (BCR and mortality) with RP [6, 7]. Several risk assessment and classification system have been developed for predicting BCR and mortality following RP; these include the D'Amico risk stratification system [8], National Comprehensive Cancer Network (NCCN) [9], Genito-Urinary Radiation Oncologists of Canada (GUROC) [10], Memorial Sloan Kettering Cancer Center (MSKCC) preprostatectomy nomogram [11], Cancer of the Prostate Risk Assessment (CAPRA) score [12], STAR-CAP [13] and Partin's table [14, 15]. While a multivariate approach to predicting survivorship following a definitive treatment is certainly preferable [16], one factor that is predominant in most prognostic models is the prostate-specific antigen (PSA) [17]. PSA is an important factor in prognostication of post-treatment survivorship of PCa [18]. A decreased risk of PCa recurrence, biochemical progression, and/or low mortality has been linked to higher PSA levels at initial diagnosis [8]. As a rule of thumb, patients with high-grade PCa and low PSA, for example, had less favorable outcomes than those with higher PSA levels [19]. When compared to those with normal pre-operative PSA readings, individuals with pre-operative PSA values of 4–10 ng/mL had a lower risk of PCa-related death [19]. The importance of PSA in BCR is exemplified in the fact that BCR derives its definition from PSA, usually ≥0.2 ng/mL [20]. However, there exists a state of ambivalence regarding the actual power of PSA in predicting BCR following RP. This is manifested in different weightage assigned to PSA in the various prognostic and classification systems. For example, according to the D'Amico classification system, the determination of BCR and metastasis could be based on a high PSA (>20 ng/mL) criteria with or without an additional criteria of clinical stage ≥ T2c or biopsy GG 4–5 [8]. In the GUROC prognostic model, the risk of BCR is high-intermediate and extreme at PSA ≥10 and >30, respectively [21]. In Partin's table, risk of recurrence is highest at PSA 6.1–10 and >10 [14]. This conflict testifies to the lack of uniformity in gauging the predictive ability of PSA vis-à-vis survivorship of PCa [22]. Toward resolving this ambivalence, there is a need to examine the relationship between PSA and survivorship of PCa. Hence, our study aimed to evaluate the relationship between pre-operative *t*PSA and survivorship of PCa following RP.

Materials and Methods

Design

This is a systematic review of peer-reviewed literature published in English. We structured the protocol following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [23]. The protocol is registered with PROSPERO (ID: CRD42022336918).

Study Characteristics

This review focused on peer-reviewed literature written in the English language, irrespective of location, sample size, and test statistics. We included studies in which participants had a RP and were monitored thereafter. Studies were included regardless of tumor stage and Gleason grade.

Intervention

Intervention was not applicable as we considered prospective and retrospective observational studies that examined the association between pre-operative *t*PSA and PCa survivorship after surgery. Studies were included regardless of whether or not a control group was utilized to explore the subject at hand.

Outcomes

The strength of the association between pre-operative PSA BCR and mortality was assessed using hazard ratio (HR). In this study, we preferred estimate of association, namely, HR obtained from multivariate analysis controlling for putative confounds. Furthermore, for descriptive, we reported odds ratio (OR) irrespective of whether univariate of multivariate. Where OR was not reported, we obtained OR from the study data or converted the reported equivalent estimate of association following Lenhard and Lenhard [24], Bronstein et al. [25], Nweke et al. 2022 [26], and Nwagha and

Nweke, 2023 [27]. We collected information on sample size, study design, setting, and definition of BCR to investigate their potential roles in the association between pre-operative PSA and BCR.

Inclusion Criteria

We included (i) peer-reviewed articles that reported the association between pre-operative *t*PSA and survivorship of PCa and (ii) studies in which PCa participants had RP and were monitored thereafter.

Exclusion Criteria

We excluded (i) studies in which the association of pre-operative PSA with survivorship of PCa was not examined and (ii) peer-reviewed articles in which it is difficult to discern the independent association between pre-operative *t*PSA with survivorship of PCa.

Information Sources and Search Strategy

Searches were undertaken in five databases: PubMed, MEDLINE, Cochrane Library, CINAHL, and Academic Search Complete using medical subject headings (MeSH) and keywords discovered in the title, abstract, and/or text of the publications. Databases were searched from inception to June 2022. The study took place between May 2022 and March 2023. The pilot search includes MeSH terms as well as keywords/free text terms found in key articles. After several permutations of these search terms, the most sensitive terms were chosen and reported. The search terms were adjusted to meet the syntax and subject headers of the remaining databases (MEDLINE, CINAHL, Cochrane Library, and Academic Search Complete) (online suppl. Appendix 1; for all online suppl. material, see https://doi.org/10.1159/000535965). A reference list of selected articles and reviews was examined for any relevant studies.

Study Records and Data Management

The results of the literature search were directly exported to EndNote 8, where they were de-duplicated. We used EndNote 8 to screen all bibliographic entries after removing duplicates, and then choose articles that match the inclusion criteria. To aid in the screening process, we employed a piloted and refined screening form with eligibility questions.

Selection Process and Data Extraction

Two independent reviewers O.C.J. and N.M. carried out a preliminary assessment of the titles and abstracts to identify studies which fulfilled the inclusion criteria. Any conflicts were addressed by MN. Full-text versions of selected articles were downloaded by a competent research assistant. The full-text screening was undertaken by O.C.J. and M.I.A. The flow of studies throughout the selection process is depicted using a PRISMA diagram (Fig. 1).

Quality Appraisal and Assessment of Risk of Bias

To improve the review rigor, we assessed the quality of the included studies. This was necessary because when it comes to the therapeutic use of pre-operative *t*PSA as a prognostic indicator, stakeholders and health-information consumers should apply their best judgment. The mixed-method appraisal tool (MMAT) Version 2011 was utilized [28]. The MMAT evaluates the study's relevance, adequacy, and methodology, as well as its design, participant enrollment, collection of data, data analysis, findings presentation, and authors' discussions and conclusions. We used section 4 which is for descriptive studies. The quality of each study was computed and assessed according to the MMAT principles [28]. Two authors (I.A.M and E.A.E) independently assessed the risk of bias, with conflict resolved in consultation with MN.

Data Items

Indices of the association between pre-operative *t*PSA and PCa survivorship constitute the primary data. The independent variable is pre-operative *t*PSA, while the dependent variable is survivorship. As a result, studies were considered if one or more of the dependent variables were linked to pre-operative *t*PSA.

Data Synthesis and Assessment of Heterogeneity

To summarize the association between pre-operative PSA and each BCR and post-prostatectomy mortality, we fitted a random-effect model of meta-analysis. Measures of heterogeneity (I^2) were computed as per Higgins et al. [29] and interpreted according to the pattern outlined in the Cochrane Handbook for Systematic Reviews of Intervention: low heterogeneity is defined as 0–40%, moderate heterogeneity is 30–60%, substantial heterogeneity is 50–90%, and considerable heterogeneity is 75–100%.

Data Analysis

The putative indicators of heterogeneity and the review outcomes are depicted in Table 1. Although we were able to compute the OR for most of the included studies using information provided in the result table, only a few were derived from multivariate analysis. Hence, to be eligible for inclusion in the meta-analysis study, we had to report adjusted HR and their corresponding 95% confidence intervals derived from multivariate regression models. The association between pre-operative *t*PSA and each of BCR and mortality were estimated using adjusted HR. Egger's test was conducted to assess publication bias [30]. The Statistical Package for Social Sciences (SPSS) version 22 was utilized, and the significance level was set at 0.05.

Results

Study Selection and Characteristics

We identified 5,937 records. Fifty-seven duplicates were identified and de-duplicated accordingly. Following title and abstract screening, all the titles and abstracts, we excluded 5,830 irrelevant records, leaving 107 records for full-text review. Of the 107 full texts, 56 publications were excluded. Ultimately, our review included 51 articles involving 50,737 participants from fifteen countries (Fig. 1). Twenty-four of the studies were conducted in North America, fifteen in Asia, and twelve in Europe, with the USA (46%), and Japan (19%) achieving the highest number of publications. The included studies were published between 1999 and 2022. We conducted two meta-analyses, namely, a meta-analysis estimating the association between pre-operative PSA and BCR post-prostatectomy, and a meta-analysis estimating the

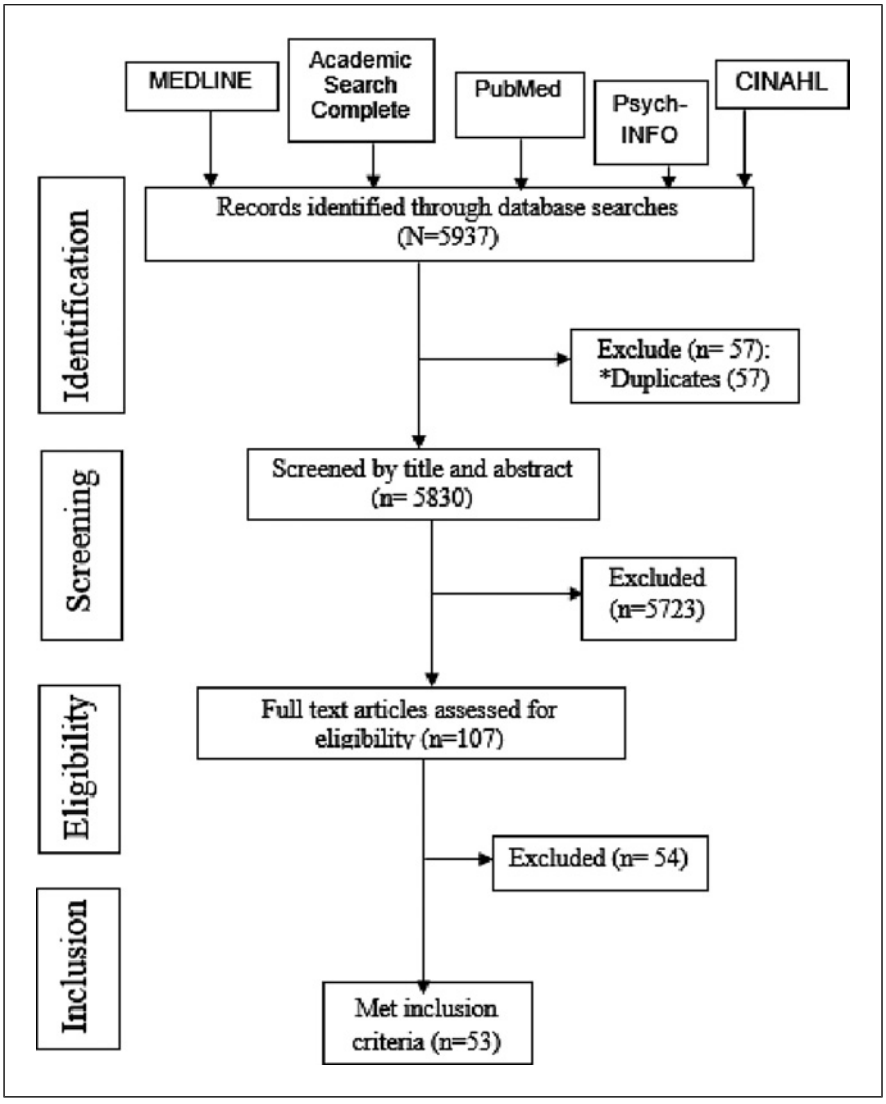

Fig. 1. PRISMA flow diagram of the systematic review of the association between pre-operative total PSA and survivorship of PCa following RP (1999–2022).

association of pre-operative PSA with mortality post-prostatectomy. Fifty-one studies were involved in the meta-analysis. Precisely, 50 studies were involved in estimating the association between pre-operative PSA and BCR post-prostatectomy, while 4 were involved in estimating the association between pre-operative PSA and mortality post-prostatectomy. Only one study (Mithal et al. 2015) [31], appeared in each of the meta-analyses (Fig. 2, 3).

Association of Pre-Operative PSA with Post-Operative BCR and Mortality in Patients with PCa

We observed a weak positive association between pre-operative PSA and BCR [HR = 1.074 (95% CI = 1.042–1.106)]. With a median rise in PSA (≥2 ng/mL), the likelihood for BCR increased by approximately 7.4%. We observed a substantial heterogeneity (I^2 = 90.71) and publication bias (Egger's t = 5.664; p < 0.001). We found no statistically significant association between PSA and mortality [HR = 1.222 (95% CI: 0.917–1.630)]. We observed a substantial heterogeneity (I^2 = 97.467) and publication bias (Egger's t = 5.058; p < 0.001). More than half of the studies (64.5%) defined BCR in terms of ≥0.2 ng/mL, while four studies (19.4%) defined BCR in terms of ≥0.4 ng/mL (Table 1). Assessment of risk of bias revealed that most of the studies involved in this review possessed medium to low risk of bias (online suppl. Appendix 2). We sampled selected factors, namely, sample size, study design, definition of BCR, and setting (country) to assess the sources of heterogeneity. The result shows that only variation in sample size contributed to the heterogeneity in the association of pre-operative PSA and BCR (Table 2).

Table 1. Study characteristics and summary statistics of studies examining the association of pre-operative PSA with BCR and post-prostatectomy mortality

ID	*p* value	Odds ratio	Sample size	Design	Definition of BCR	Country
Association of pre-operative PSA with BCR post-prostatectomy						
Abdel-Raheem et al. 2018	0.0001	2.366	359	Prosp	>0.2 ng/mL after 4 weeks	South Korea
Anastasiou et al. 2011	0.129	1.05	69	Prosp	>0.2 ng/mL, first value after surgery	Greece
Aoun et al. 2017	0.005	1.4	910	Retrosp	>0.2 ng/mL	Belgium
Berger et al. 2006	0.093	1.85	102	Retrosp	>0.2 ng/mL, first value after surgery	Austria
Blanchard et al. 2015	0.13	0.62	136	Retrosp	>0.4 ng/mL	USA
Brureau et al. 2018	0.018	1.37	964	Retrosp	–	France
Bulut et al. 2010	<0.05	9.7	75	Retrosp	>0.2 ng/mL	Turkey
Chung et al. 2022	0.156	1.14	1,483	Retrosp	–	Korea
Eggener et al. 2009	0.100	1.22	881	Retrosp	>0.2 ng/mL confirmed by a subsequent rising value	USA
Freedland et al. 2004	0.001	1.75	459	Retrosp & Prosp	>0.2 ng/mL or 2 values of 0.2 ng/mL	USA
Friedersdorff et al. 2020	<0.001	2.14	330	Retrosp	2 consecutive PSA values ≥0.2	USA
Gasinska et al. 2020	0.003	2.63	130	Retrosp	>0.2 ng/mL	USA
Garcia-Barreras et al. 2018	>0.05	1.022	6,195	Prosp	≥0.2 ng/dL	France
Grossfeld et al. 2003	0.002	1.010	547	Retrosp	2 consecutive PSA ≥0.2	USA
Hamada et al. 2016	0.002	2.12	195	Retrosp	≥0.2 ng/mL	Japan
Hashimoto et al. 2015	<0.001	1.66	784	Retrosp	≥0.2 ng/mL	Japan
Hashimoto et al. 2014	0.001	1.84	389	Retrosp	2 consecutive PSA ≥0.2	Japan
Haukaas et al. 2006	0.006	2.01	211	Retrosp	≥0.5 ng/mL	Norway
Hayashi et al. 2007	0.0018	0.5	268	Retrosp	2 consecutive PSA ≥0.1	Japan
Hisashi et al. 2017	0.0029	1.64	488	Retrosp	>2 consecutive PSA ≥0.2	USA
Ho et al. 2016	0.01	1.63	370	Prosp	≥0.2 ng/mL	USA
Itami et al. 2018	0.0001	2.35	365	Retrosp	–	Japan
Inoue et al. 2015	0.773	1.08	174	Retrosp	0.2 ng/mL	Japan
Jhaveri et al. 1999	0.98	1.00	1,132	Retrosp	≥0.2 ng/mL	USA
Jones et al. 2006	0.027	1.04	348	Retrosp	≥0.1 ng/mL	USA
Kanehira et al. 2019	0.006	1.74	331	Prosp	2 consecutive PSA >0.2 ng/mL	Japan
Koca et al. 2016	0.01	2.42	238	Retrosp	≥0.2 ng/mL	Turkey
Kim et al. 2011	0.520	1.21	149	Prosp	≥0.2 ng/mL	Germany
MacDonald et al. 2008	0.800	0.99	4,563	Retrosp	>0.2 ng/mL	USA
Magheli et al. 2008	<0.001	1.03	13,434	Retrosp	≥0.2 ng/mL	USA
Mithal et al. 2015	0.0001	1.36	2,735	Retrosp	>0.2 ng/mL or 2 values of 0.2 ng/mL	USA
Moul et al. 2001	0.0001	1.76	812	Retrosp	≥0.4 ng/mL	USA

Table 1 (continued)

ID	*p* value	Odds ratio	Sample size	Design	Definition of BCR	Country
Murata et al. 2018	0.0148	1.91	191	Retrosp	≥0.2 ng/mL	Japan
Naselli et al. 2009	0.4738	1.16	318	Prosp	>0.1 ng/mL 6 weeks and repeated within 1 month for confirmation	Italy
Negishi et al. 2017	0.0001	2.11	478	Retrosp	≥0.2 ng/mL or post-surgery	Japan
Okegawa et al. 1999	0.13	2.49	40	Prosp	≥0.4 ng/mL	Japan
Ou et al. 2002	0.0406	2.85	55	Prosp	>0.2 ng/mL	Taiwan
Park et al. 2016	0.127	1.56	158	Retrosp	2 consecutive PSA ≥0.2	Korea
Pavlovich et al. 2008	0.024	1.44	508	Prosp	2 consecutive PSA ≥0.2	USA
Ritch et al. 2012	0.02	1.47	483	Retrosp	>0.2 ng/mL	USA and Jamaica
Secin et al. 2006	0.0001	1.27	4,441	Prosp	2 PSA values 0.2 ng/mL or initiation of therapy for a PSA rise after radiation therapy	USA
Shen et al. 2005	<0.001	1.685	906	Prosp	2 consecutive PSA ≥0.1	USA
Sengupta et al. 2005	0.0001	1.4	2,290	Retrosp	≥0.4 ng/mL	USA
Simforoosh et al. 2020	0.029	1.29	959	Retrosp	2 consecutive PSA ≥0.2	Iran
Simon et al. 2006	0.1555	1.18	936	Retrosp	≥0.4 ng/mL	USA
Sofer et al. 2003	0.0001	1.76	812	Retrosp	≥0.4 ng/mL	USA
Svatek et al. 2008	0.112	1.33	414	Prosp	2 or more PSA >0.2 ng/mL	USA
Tanimoto et al. 2015	0.036	1.44	439	Retrosp	2 PSA values >0.2 ng/mL or initiation of salvage therapy for a PSA rise	USA
Tombal et al. 2002	0.18	1.3	343	Prosp	0.2 ng/mL	Belgium
Wiegel et al. 2009	0.031	1.86	165	Retrosp	0.03–0.1 ng/mL	Germany
Association of Pre-operative PSA with Mortality Post-prostatectomy						
D'Amico et al. 2004	0.01	0.75	1,095	Retrosp		USA
Inman et al. 2008	–	–	236	Retrosp		USA
Mendhiratta et al. 2015	0.595	1.04	1,864	Prosp		USA
Mithal et al. 2015	0.0001	1.36	2,735	Retrosp		USA
Schiavina et al. 2016	0.205	0.063	411	Retrosp		Europe

Discussion

RP remains the primary treatment for localized PCa and has been performed for many years with excellent oncologic control [20]. Despite excellent cancer control with the treatment of localized PCa, some men will experience a recurrence of the disease [32]. PSA has been the pivotal tool for recurrence diagnosis, but there is no consensus about the best PSA threshold to define BCR until this moment [20]. Although the actual history of BCR after prostatectomy is highly variable and has been reported with inconsistency, it is important to determine the nature of the association between BCR as well as mortality to enhance pre-operative m decisions. In this study, a weak positive association was found between pre-operative PSA and BCR (OR = 1.45). With a median rise in PSA (≥2 ng/mL), the likelihood of BCR increased by approximately 1.5 times. This implies that the higher the pre-operative PSA the greater the risk for BCR. This is consistent with an earlier report that men with

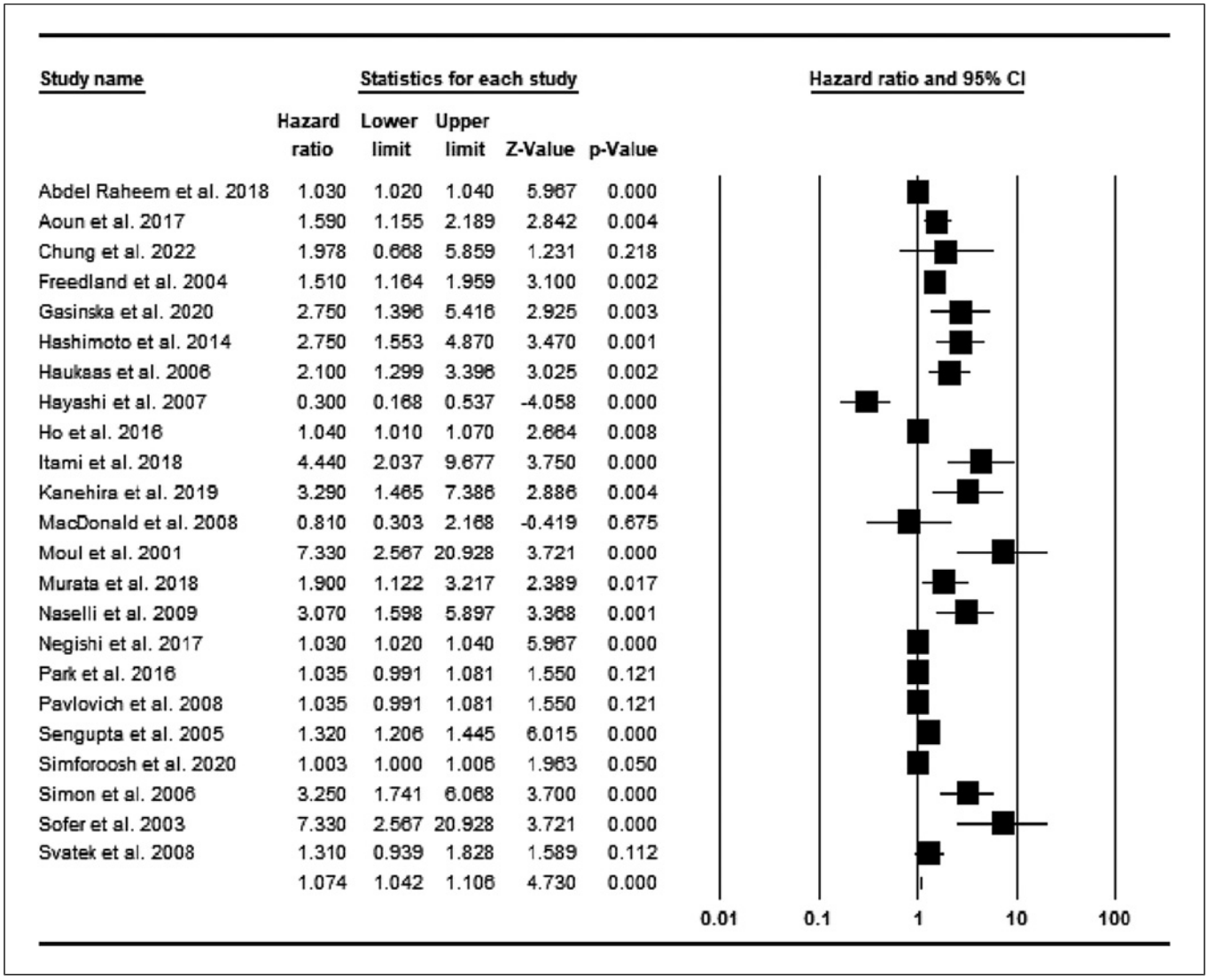

Fig. 2. Forest plot displaying the meta-analysis of the relationship between PSA and BCR after RP.

pre-operative PSA ≥20 ng/mL present a BCR risk 3.7-fold greater than those men with PSA <6 ng/mL [12, 20, 33, 34]. However, the disparity, in terms of strength of association, between the previous study [20] and ours shows that the association between pre-operative PSA and BCR gets stronger with an increasing PSA cutoff value. There are compelling reasons to use a higher cutoff PSA, which better correlates with BCR, however, it possesses low sensitivity as recurrence has been reported among patients with lower pre-operative PSA [35]. This suggests that the sole use of pre-operative PSA in predicting BCR does not connote sound clinical practice and should be discouraged. This is consistent with the D'Amico classification system which is a widely used risk classification system for PCa. The D'Amico classification system comprises a three-point scale for recurrence and metastasis: low risk, medium risk, and high risk, based on the known prognostic factors: PSA level, biopsy Gleason score, and 1992 American Joint Commission on Cancer Staging (AJCC) T stage. High-risk PCa is defined as a PSA level >20 ng/mL, a Gleason score of 8–10, or a clinical stage ≥ T2c [36, 37]. However, the inclusion of a very high PSA criteria (>20 ng/mL) in the D'Amico classification system should be queried as the chance of missing patients who experience BCR at a low PSA threshold is high [38]. However, the inter-method bias between PSA assays is an important consideration as this may impact the correct risk stratification of the patients. Disparate TPSA

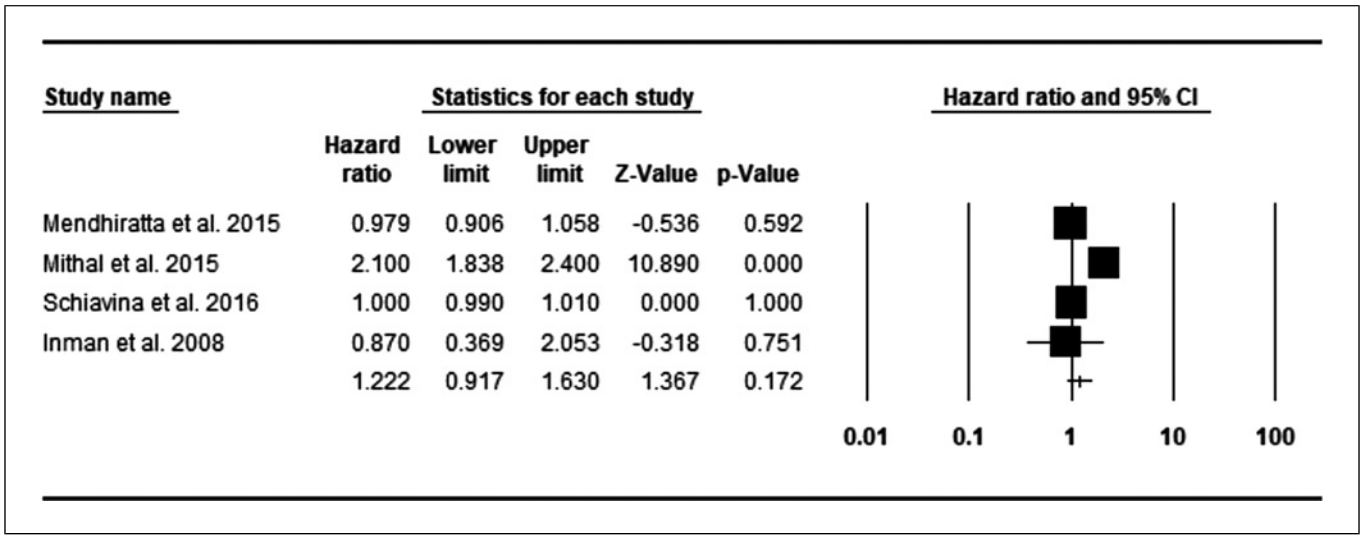

Fig. 3. Forest plot displaying the meta-analysis of the relationship between PSA and Mortality after RP.

Table 2. Assessment of factors contributing to heterogeneity in the relationship of pre-operative PSA and BCR as measured by correlation coefficient (*r*)

Factor	Effect size (*r*)	
Sample size	$r = -0.369$	$p = 0.041$*
Study design	$F = 0.836$	$p = 0.444$
Definition of BCR	$F = 1.925$	$p = 0.151$
Country	$F = 1.903$	$p = 0.108$

results obtained from different laboratories with different assay methods and suboptimal harmonization with inherent inter-method bias may pose difficulty for the clinician in decision-making [39].

The variation in the association between pre-operative PSA and BCR based on sample size is consistent with Suresh and Chandrashekara [40]. Precise and accurate estimation is based on sample size adequacy, research with larger sample sizes typically estimated a smaller effect size (r) than studies with small sample sizes. As an important source of heterogeneity, attention should be paid to the correct estimation of sample size when investigating the association between pre-operative PSA and BCR. Furthermore, the heterogeneity in the estimation of total PSA in the region may be explained by the fact that there exists an inter-method bias between PSA assays [39]. Hence, we recommend that a correction factor should be devised to account for variations in sample sizes and methods of PSA assays when aggregating total PSA in meta-analysis.

Regarding the association between pre-operative PSA and mortality, the result shows there was no association between PSA and mortality after prostatectomy. This may imply that pre-operative PSA value does not determine or contribute to post-prostatectomy mortality. Although no previous systematic review exists on this subject, the study finding is consistent with Inman et al. (2008) [41], in which pre-operative PSA value as high as >100 ng/mL was not found to be a significant risk factor for death. Therefore, pre-operative PSA may not be a useful biomarker for predicting post-prostatectomy mortality.

Strength and Limitations

The cumulative confidence in this review as revealed by the strength of evidence seems high as the included studies possessed a low to medium risk of bias. The presence of possible publication bias by authors may constitute a limitation to this study; however, we have made recommendations on how to handle these limitations. Also, the use of OR obtained from both multivariate and univariate analyses may have contributed to the heterogeneity and hence constitutes a limitation to study findings.

Conclusions

BCR is associated with pre-operative PSA. However, the association between pre-operative PSA and BCR is highly variable. Hence, the sole use of pre-operative PSA in estimating post-prostatectomy is seemingly a bad practice and

should be discouraged. We recommend that further review be conducted using the evidence-synthesis approach first described by Nweke et al. [26], to build a cost-effective multifactorial model for screening BCR following RP.

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Statement of Ethics

Not applicable.

Conflict of Interest Statement

The authors have no conflicts of interest to disclose.

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Author Contributions

Conceptualization of the study was done by Chika Juliet Okwor and Martin Nweke. The study design was by Martin Nweke with inputs from Chika Juliet Okwor and Ijeoma Angela Meka. Screening and extraction of data were done by Chika Juliet Okwor and Ijeoma Angela Meka whereas data analysis was done by Martin Nweke. The initial draft of the manuscript was written by Martin Nweke. All authors contributed to the revision and final approval.

Data Availability Statement

Data used for this study will be available on request from the corresponding author.

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