Prostate-specific antigen velocity in diagnosis and prognosis of prostate cancer - a systematic review

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Abstract

Prostate-specific antigen velocity (PSAV) is widely used to detect PC and predict its progression. In this study, we qualitatively synthesized the currently available evidence from published studies regarding the PSAV role in PC. Electronic databases were searched to find relevant articles published until January 2019. Inclusion and exclusion criteria were applied to identify related papers. Eventually, data extraction followed by evidence synthesis was conducted. Full-text screening resulted in 42 included studies. Multiple definitions and intervals were used for PSAV calculation across studies. Results from the included studies were conflicting regarding the role of PSAV in detecting PC and predicting progression in active surveillance cases. However, there is evidence that PSAV may have a predictive role in post-treated men. There is no clear-cut evidence from the published literature to support the use of PSAV in clinical practice.

Introduction

Prostate cancer (PC) is one of the most common malignancies and leading causes of cancer death in men worldwide.[1,2] In 2010, PC resulted in 256,000 deaths globally.[1] The American Cancer Society has estimated that 16% of American men will develop PC during their lifetime, with 3.4% at risk of death eventually.[3] Prostate-specific antigen (PSA) is a commonly used test for early detection of PC. Since the introduction of PSA in clinical practice, the mortality rate was reduced by about 30%.[4] However, Thompson *et al.*[5] reported that 15% of men with a PSA value less than 4.0 ng/mL, the cutoff value for potential biopsy, were found to have cancer. To increase the accuracy and prediction, PSA kinetics, including PSA velocity (PSAV), have been proposed.

Carter *et al.*[6] introduced PSAV as the change in PSA levels over time, given as nanograms per milliliter per year (ng/mL/y). Their study, which included 16 control patients, 20 patients with benign prostatic hypertrophy (BPH), 14 with local or regional PC, and four with metastatic PC, analyzed stored serum samples for several PSA values over a median range of 14.3 to 17.4 years. Finally, they could differentiate between those having BPH and PC based on the average rate of change in PSA of 0.75 ng/mL/y or more.[6]

Some studies speculated that PSAV could increase the predictive accuracy of cancer growth and predict prognosis. However, other studies provided contradictory evidence.[7] Furthermore, there are variable definitions and calculations for PSAV used across the literature. In a study by O'Brien *et al.*,[8] they found over 20 different definitions of PSAV in the literature with articles including only 2 PSA values drawn over the one-year interval to calculate PSAV, which may have affected the results. Therefore, we conducted this systematic review to build concrete evidence from studies investigating PSAV as a diagnostic and/or prognostic method for PC.

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Materials and Methods

Search strategy

This study was conducted in adherence to the recommendations of preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement.[9] Four electronic search engines/databases were systematically searched for relevant publications, including PubMed, Scopus, Web of Science, and Cochrane Central Register for controlled clinical trials (CENTRAL) for studies in English-language published in peer-reviewed journals till January 2019. Our search terms included different composites of these keywords: prostate cancer, screening, diagnosis, prognosis, surveillance, prostatectomy, prostate-specific antigen velocity, and PSAV. Additionally, we conducted a manual search via reviewing the citations of the publications included in our study, together with reviewing the related references presented in PubMed and related journals.

Selection criteria and screening for inclusion

Search results from the four aforementioned search databases were imported into Endnote X8 (Thompson Reuter, CA, USA) for automatic duplicates deletion. Three reviewers independently screened the references using the predetermined inclusion criteria. We included studies if they assessed PSAV as a diagnostic and/or prognostic method for PC, including cases before and after treat-

ment. No restrictions were done on publication year, country, or age. Studies with unreliable data were excluded. Additionally, we excluded book chapters, conference papers, reviews, theses, posters, abstract-only articles, and editorials. Consultation from the senior reviewer was acquired if necessary. The full-text screening was conducted to identify the most relevant references for data extraction.

Data extraction

We used a data extraction form to extract relevant data from our included studies. Two independent authors then extracted the data into the form. Extracted data included authors' details, year, sample size and characteristics, type of cohort, calculation of the PSAV, and authors' conclusion. We further extracted any measures of predictive accuracy for either the univariate or multivariate model, including sensitivity, specificity, the area under the curve (AUC), and negative or positive predictive values.

Evidence synthesis

We qualitatively synthesized evidence from published data of retrospective and prospective studies, in addition to data from randomized trials. Our main focus was on the endpoint, which is the predictive role of PSAV in pre-treated cases, patients on active surveillance, and surgically- or radiotherapy-treated patients.

Results

Selection and characteristics of the included studies

The databases search resulted in 1540 publications. After removing 522 duplicates by the referencing software, 1018 records were eligible for screening. Title and abstract screening excluded 918 records, and we further excluded 58 articles after the full-text screening. We finally included 42 papers for our study (Figure 1). Some studies were based on data from a large cohort and randomized clinical trials. For studies assessing the predictive role of patients undergoing screening or active surveillance and undergoing biopsies, we summarized the main characteristics like the design, number of included cases for each study, number of events, endpoints for each study, and main results in Table 1.[10-42] For studies assessing the prognostic role of PSAV mainly after surgery and radiotherapy, Table 2[43-51] was constructed to summarize the main characteristics.

The diagnostic value of prostate-specific antigen velocity in detecting prostate cancer

The included studies showed conflicting evidence regarding the predictive accuracy of PSAV for diagnosis of PC. Overall, the evidence tends to show PSAV as a predictive parameter for detecting PC but with no additive value to PSA alone (Table 1). In a ret-

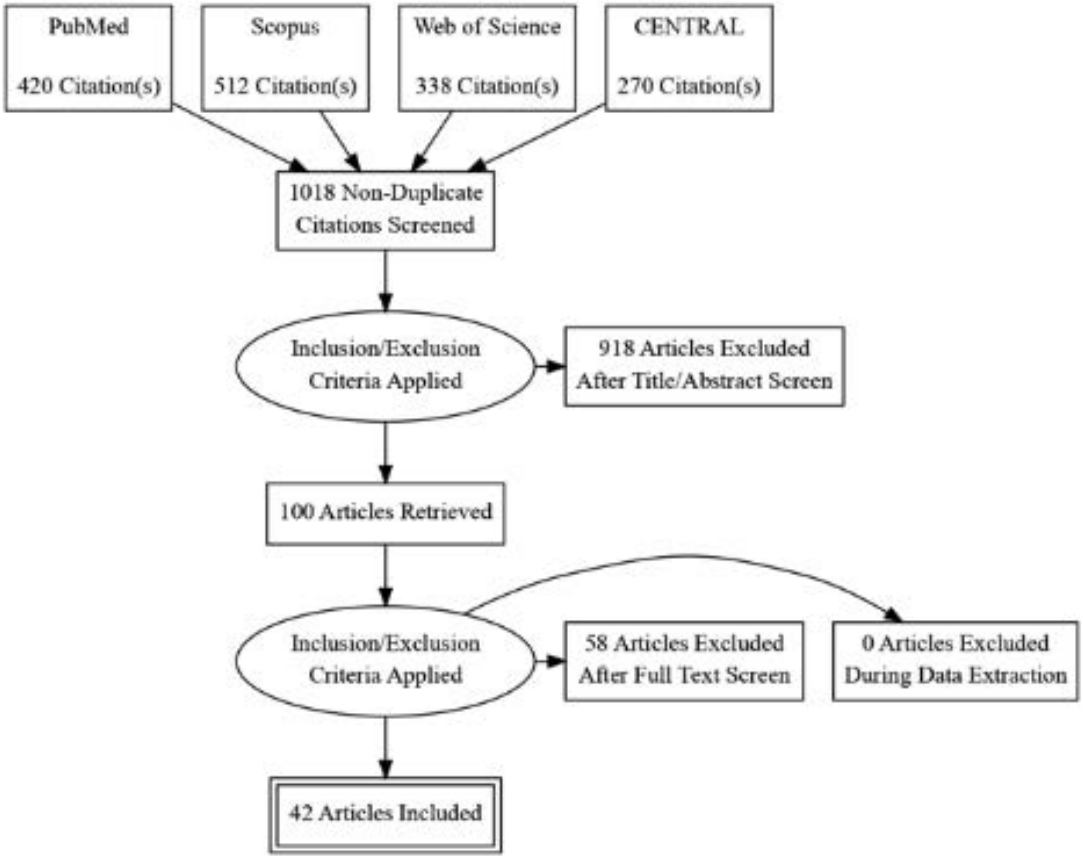

Figure 1. PRISMA flow diagram explaining the cascade of searching several databases, removal of duplicates, screening steps, and reviewing processes.

Table 1. Characteristics and main results of the included studies on prostate-specific antigen velocity for prediction of diagnosis and progression on active surveillance.

Study	Design type	Sample size	Study events	Study endpoint	Main results related to PSAV
Ukimura *et al.*[10]	Retrospective cohort	193	54	Repeat biopsy findings when the initial one is negative for PC	AUC for PSAV is greater than PSA. Additionally, PC incidence is significantly higher in men with a PSAV of more than 0.75 ng/m/yr. PSAV had a good PPV (42%) with lower sensitivity (57%) compared to either volume-referenced PSA or PSA
Djavan *et al.*[11]	Prospective cohort	559	217	Biopsy findings	AUC is greater for PSA than PSAV
Dajvan *et al.*[12]	Prospective cohort	273	66	Biopsy findings	AUC is greater for PSA than PSAV
Lynn *et al.*[13]	Prospective cohort	197	38	Biopsy findings	AUC is greater for PSA than PSAV
Carter *et al.*[14]	Prospective cohort	980	20	PC death before diagnosis from samples	AUC for PSAV is greater than for PSA (0.75 *vs.* 0.74)
Thompson *et al.*[15]	RCT	5519	1211	Biopsy findings	PSAV AUC was slightly greater compared to standard predictors alone (0.709 vs 0.702) and did not improve detection of high-grade cancer (0.792 reduced to 0.791)
Loeb *et al.*[16]	Prospective cohort	6,844	346	Diagnosis of PC during screening	PSAV AUC model is greater compared to PSA alone model (0.83 *vs.* 0.81)
Berger *et al.*[17]	Prospective cohort	4800	528	Diagnosis of PC during screening	AUC is greater for PSAV than PSA (0.87 vs. 0.65)
Sun *et al.*[18]	Retrospective cohort	12087	1622	Diagnosis of PC during screening	AUC for PSA is greater than PSAV.
Ostrted *et al.*[19]	Prospective cohort	4383	170	Detection during follow-up and death	The age-adjusted hazard ratio (HR) for PC detection increased from 2.7 to 5.3 and PC-related death from 2.3 to 3.4 with PSAV
Wallener *et al.*[20]	Retrospective cohort	219,388	-	Biopsy findings	PSAV predicted the presence of PC (AUC = 0.963) and the presence of aggressive disease (AUC = 0.955) with more than a single measurement of PSA alone (AUC = 0.727)
Auprich *et al.*[21]	Retrospective cohort	127	44	Repeat biopsy finding	At second repeat biopsy, PSAV was identified as statistically significant univariable PCa risk factors, with an AUC of 0.72
Benecchi[22]	Prospective cohort	312	67	Biopsy findings	PSAV was significantly higher in patients with PC. PSA slope was better than than PSA velocity (AUC 0.743 *vs.* AUC 0.663 for PSAV)
Benchi *et al.*[23]	Prospective cohort	325	74	Biopsy findings	PSAV was significantly higher in patients with PC. lnPSA slope (AUC 0.793) was better results than PSA (AUC, 0.585), PSAV(AUC, 0.734), PSA slope (AUC, 0.752), and PSADT (AUC, 0.516).
Berger *et al.*[24]	Retrospective cohort	2815	353	Biopsy findings	PSA velocity was significantly associated with Gleason scores and pathologic stage.
Bittner *et al.*[25]	Prospective cohort	217	97	Biopsy findings	PSAV did not predict PC diagnosis, Gleason score, percentage of positive cores, or tumor location.
Gorday *et al.*26	Retrospective cohort	4622	2410	Biopsy findings	PSAV with PSA AUC = 0.570–0.712 was non statistically significant compared to PSA alone (AUC = 0.572–0.699).
Barak *et al.*[27]	Prospective cohort	273	75	Biopsy findings	PSAV had slightly lower sensitivity but much higher specificity than PSA
Fang *et al.*[28]	Prospective cohort	89	21	Biopsy findings	The relative risk (RR) of CaP was 6.53 when the PSAV was 0.1 ng/ml/y or more compared with a PSAV of less than 0.1 ng/ml/y (P = 0.0029). After10 years, the probability of being PC free was 97.1% and 35.2% when the PSAV was less than and greater than 0.1 ng/ml/y, respectively.
Roobol *et al.*[29]	Randomized study	774	149	Biopsy findings	PSAV was significantly higher in men with PC than in men with a negative biopsy (0.62 *vs* 0.46 ng/mL/year) but PSAV did not independently predict cancer after adjusting for PSA level.
Ciatto *et al.*[30]	Prospective cohort	87	13	Biopsy findings	AUC was higher for PSAV than PSA (0.74 *vs.* 0.67). The PPV for a cancer biopsy was 2.7% (1/36), 28.5% (2/7), and 22.7% (10/44) for PSAV values of <0.1, 0.1–0.19, and >0.19 ng/mL/yr

Continued on next page.

rospective study by Ukimura *et al.,*[10] they assessed PSA, PSAV, PSA density, age-referenced PSA, and volume-referenced PSA for predicting the occurrence of cancer. The main endpoint was repeated biopsy results when the initial findings for biopsy were negative for PC. The study found that AUC is greater for PSAV than PSA. However, there was no significant merit for any of the indices, including PSAV over PSA alone in determining patients who should be considered for a repeat biopsy. Moreover, Djavan *et al.*[11] conducted two studies with different PSA levels counting on the biopsy results as their endpoint. The first study evaluated multiple PSA parameters, including PSA density of the whole prostate and of the transition zone, PSAV, percent free PSA to test the ability for prostate cancer detection and hence decrease unnecessary biopsies in men with serum PSA levels of 4.0 to 10.0 ng/mL. They prospectively included 559 patients and showed that AUC was greater for PSA than PSAV. The second study prospectively included 273 men with serum PSA of 2.5 to 4.0 ng/mL referred to showed that AUC was greater for PSA than PSAV.[12] Similarly, Lynn *et al.*[13] included 158 and showed that the AUC was greater for PSA than PSAV, with biopsy as the endpoint of the study. In this study, a statistically significant difference was found between the short-term PSAV of patients with benign prostate and those with PC. The AUC for PSAV was 0.612, which is less than PSA alone. Carter *et al.*[14] study based on the Baltimore Longitudinal Study of Aging (BLSA) cohort included 980 men. Of them, 104 with prostate cancer but surviving or died of another cause, and 20 who died of PC. AUC for PSAV was almost the same as PSA (0.75 *vs*. 0.74) at PSA cutoff value of 4 ng/mL. Men with PSA velocity above 0.35 ng/mL per year had a 4.7 higher risk ration (RR) of PC death than men with PSAV of 0.35 ng/mL per year or less. Thompson *et al.*[15] further reported 5519 cases from the Prostate Cancer Prevention Trial (PCPT) counting on biopsy results as their endpoint. The study mentioned that PSAV did not add much to the AUC of standard predictors alone (0.709 *vs*. 0.702) with no improvement in the detection of high-grade cancer (0.792 reduced to 0.791). Loeb *et al.*[16] reported data from the BLSA in which they included 6844 participants. PC diagnosis in men undergoing PSA screening was the endpoint. The AUC was slightly greater for a model that included both PSAV and PSA compared with a model that included PSA alone (0.83 *vs*. 0.81). Berger *et al.*[17] studied 4800 cases with and without PC. PC diagnosis in men undergoing screening was the endpoint. AUC was significantly greater for PSAV than PSA (0.87 *vs*. 0.65). Sun *et al.*[18] study included 12,087 men undergoing PSA screening. The AUC was greater for PSA than PSA velocity. Ostrted *et al.*[19] included 4383 in the prospective Copenhagen City Heart Study. In 28 years of follow up, 170 men developed PC while 94 men died from CP. With PSAV, the age-adjusted hazard ratio (HR) for PC detection increased from 2.7 to 5.3 and PC-related death from 2.3 to 3.4. Wallener *et al.*[20] in a retrospective study of 219,388 men, showed that PSAV could more be accurate for predicting PC (AUC = 0.963) than PSA alone (AUC = 0.727). Auprich *et al.*[21] aimed to compare PSA, percentage free PSA (%fPSA), PSAV, and urinary prostate cancer gene 3 (PCA3) at first, second, and ≥ third repeat biopsy session. They included 127 with overall PC detection of 34.6%. At second repeat biopsy, including 40 patients, PSAV (P=0.04) was among the predictors for PC. Benecchi[22] aimed to compare PSA velocity and PSA slope on 312 participants. At the ROC analysis, the PSA slope showed

Table 1. Continued from previous page.

Study	Design type	Sample size	Study events	Study endpoint	Main results related to PSAV
Schroeder *et al.*[32]	Randomized study	588	167	Biopsy findings	PSAV cut-off points was not helpful for PC prediction
Ulmert *et al.*[33]	Preventive medicine study	4907	433	Diagnosis during screening	There is a strong correlation between PSAV and PSA level (r = 0.93) and PSAV did not add much to PSA prediction.
Vickers *et al.*[34]	Randomized study	2742	710	Biopsy findings	PSAV improved the predictive accuracy of total PSA slightly (AUC 0.57 *vs* 0.53)
Vicker *et al.*[35]	Randomized study	2579	363	Biopsy findings	PSAV is statistically associated with PC but with low predictive accuracy (AUC 0.55)
Ito *et al.*[36]	Prospective cohort	504	-	Biopsy findings	PSAV before the PSA increase was not significantly different between those with and without PC
Whitson *et al.*[37]	Prospective cohort	241	55	Biopsy findings of progression on AS	PSAV was not statistically significant in predicting progression on AS
Ng *et al.*[38]	Prospective cohort	199	53	Biopsy findings of progression on AS	AUC for predicting adverse histology of patients on AS was 0.70 and 0.63 for PSAV and PSADT, respectively.
Ross *et al.*[39]	Prospective cohort	290	102	Biopsy findings of progression on AS	PSAV was not correlated with subsequent adverse biopsy findings significantly
Kotb *et al.*[40]	Prospective cohort	102	-	Biopsy findings of progression on AS	PSAV was correlated (0.3) with progression
Iremashvili *et al.*[41]	Prospective cohort	250	64	Biopsy findings of progression on AS	PSAV predicted tumor progression in certain subgroups as men undergoing their fourth biopsy significantly but no significant increase in the predictive accuracy was showed on the overall population compared with PSA alone.
Iremashvili *et al.*[42]	Prospective cohort	137	37	Biopsy findings of progression on AS	Prediagnostic PSAV of more than 2 ng/mL/year and 3 ng/mL/year was associated with the risk of future biopsy progression but this was not significant after adjustment for baseline PSA density

PSA, prostate-specific antigen; AUC, area under the curve; AS, active surveillance, PPV, positive predictive value, NPV, negative predictive value.

better results than PSAV (AUC 0.743 *vs*. 0.663).

Benchi *et al.*[23] aimed to compare prostate biopsy, PSAV, PSA slope, the natural logarithm of PSA slope (ln PSA slope), and PSA doubling time (PSADT) on 325 male patients. PSAV AUC was significant and equaled 0.734. Berger *et al.*[24] study assessed PSA changes over ten years in patients with and without prostate cancer. PSAV was found to be associated with Gleason scores and pathologic stage. Bittner *et al.*[25] evaluated 217 patients undergoing biopsy. The PSAV was not showed to be a predictor for PC diagnosis, Gleason score, tumor volume, and cancer location. Gorday *et al.*[26] included 4622 men. PSAV with PSA AUC = 0.570-0.712 was non-statistically significant compared to PSA alone (AUC = 0.572-0.699). Barak *et al.*[27] included 147 patients who were eligible for biopsy, with 72 found to have a benign prostatic disease, while 75 had primary prostate cancer. They showed that PSAV had a slightly lower sensitivity but much higher specificity than PSA. Fang *et al.*[28] evaluated 89 men from the BLSA with PSA levels between 2.0 and 4.0 ng/mL for at least 18 months. They reported that the sensitivity and specificity of PSAV of 0.1 ng/mL/y was 81% and 50%, respectively. The RR of PC was 6.53 when the PSAV was 0.1 ng/mL/y or more compared with a PSAV of less than 0.1 ng/mL/y which was statistically significant. After 10 years, the probability of being PC free was 97.1% and 35.2% when the PSAV was less than and greater than 0.1 ng/mL/y, respectively. In a study conducted among 774 men with PSA below 4.0 ng/mL who had their first biopsies during the European Randomized Study of Screening for Prostate Cancer (ERSPC), 149 were found to have cancer. The study reported that PSAV only did not differentiate between men with and without PC diagnosed by biopsies (0.62 *versus* 0.46 ng/mL/year). Furthermore, the sensitivity of a PSAV cutoff of 0.3 ng/mL/year was only 39%.[29] Ciatto *et al.*[30] evaluated 87 men with initial negative biopsy and repeat biopsies performed for PSA elevation (>4 ng/mL). AUC was higher for PSAV than PSA (0.74 *vs.* 0.67). PSAV was significantly associated with biopsy results. The positive predictive value was 22.7% for PSAV >0.19 ng/mL/yr. In a study by Eggener *et al.*[31] on 995 men, the negative predictive value of PSA velocity was almost the same as PSA (91% *vs* 88%). The main endpoint was the biopsy result in men with the first neg-

Table 2. Characteristics and main results of the included studies on prostate-specific antigen velocity for prediction of prognosis in the treated cases of prostate cancer.

Study	Design	Intervention type	Number of patients	Events	Endpoint	Main results related to PSAV
Freedland *et al.*[43]	Clinical cohort	Radical prostatectomy	331	-	Pathologic features or biochemical recurrence	Preoperative PSAV was not predictive of positive surgical margins, capsular penetration, or seminal vesicle invasion and it was not predictor of bi chemical recurrence.
D'Amico e *et al.*[44]	Clinical cohort	Radical prostatectomy	1095	27	Death due to PC	Annual PSAV of more than 2.0 ng/ml was associated with a shorter time to death from PC
D'Amico *et al.*[45]	Clinical cohort	Radiotherapy	358	28	Death due to PC	Annual PSAV of more than 2.0 ng/ml was associated with a shorter time to death from PC
Sengupta *et al*[46]	Clinical cohort	Radical prostatectomy	2290	Biochemical progression, clinical progression and death from PC in 583, 156 and 42 patients	Biochemical progression, clinical progression and death from PC	PSAAV was a significant predictor for biochemical progression, clinical progression, and death specific PC
Patel *et al.*[47]	Clinical cohort	Radical prostatectomy	202	31	Relapse	Preoperative PSAV of greater than 2 ng/ml/y predicted surgical stage, positive margins, pathologic grade, and relapse-free survival.
Berger *et al.*[48]	Clinical cohort	Radical prostatectomy	102	-	Biochemical progression	PSAV were found to be correlated significantly with tumor volume, but not prostate volume
Palma *et al.*[49]	Clinical cohort	-	202	-	Biochemical disease-free survival	PSAV greater than 2.0 ng/mL/year is associated with reduced biochemical disease-free survival.
Datan *et al.*[50]	Clinical cohort	Radical prostatectomy	239	60	Positive bone scan	In univariate and multivariate analysis, preoperative PSAV predicted a positive bone scan with OR of 0.93.
Helfand *et al.*[51]	Retrospective cohort	Transurethral resection of the prostate, holmium laser resection of the prostate, or open prostatectomy	465	-	Incidental PC	Patients with PC had a significantly high postoperative PSAV compared with patients without PC

PSA, prostate-specific antigen; PC, prostate cancer.

ative biopsy. In another study by Schroeder *et al.*,[32] PSAV was applied to the data of 588 men from ERSPC who presented at their first screening with PSA of 4.0 ng/mL. Their results showed no value of PSAV cutoff values for improving the positive predictive value of the PSA cutoff of 4.0 ng/mL. However, the rate of aggressive cancers seemed to increase with increasing PSAV. Ulmert *et al.*[33] questioned if PSAV improved the accuracy of a model using the PSA level to predict long-term risk of PC diagnosis. They included 4907 participants and found that PSAV was highly correlated with PSA level (r = 0.93), which means no value of adding PSAV to predict PC. Vickers *et al.*[34] included 2742 men with PSA <3 ng/mL from ERSPC. PSAV added a little to the predictive accuracy (AUC 0.569 *vs* 0.531). In addition, Vicker *et al.*[35] also reported that PSAV was of no additive value in men with prior negative biopsies. Ito *et al.*[36] carried out a study on 504 men with baseline PSA of 4.0 ng/mL or less who had a PSA increase greater than 4.0 ng/mL on the following screening. The results showed that PSAV was not significantly different between those with and without PC.

Prostate-specific antigen velocity predictive role for progression on active surveillance

Several studies have investigated the role of PSAV during surveillance. However, the evidence is not consistent across them. For instance, Whitson *et al.*[37] included 241 men undergoing active surveillance (AS). In 55 of them, biopsy progression took place over a 24-month period. The study found no statistically significant role for PSAV in predicting progression. Ng *et al.*[38] aimed to compare PSAV *vs*. PSADT in 199 patients with PC on active surveillance. Using univariate analysis, PSAV was associated with adverse histology with AUC of 0.70. In a study by Ross *et al.*[39] for patients on active surveillance, the rate of disease progression was 35% on repeat biopsy, and PSAV was not a significant predictor of progression on univariate analysis. Kotb *et al.*[40] evaluated 102 patients with localized PC on active surveillance. They found that PSAV correlated with tumor progressing on subsequent biopsies (P=0.03). Iremashvili *et al.*[41] Showed that PSAV significantly predicted tumor progression in specific subgroups as men undergoing their fourth biopsy, but no significant increase in the predictive accuracy was shown in the overall population compared with PSA alone. Additionally, another study included 137 patients on active surveillance. They showed that Pre-diagnostic PSAV of more than 2 ng/mL/year and 3 ng/mL/year was associated with the risk of future biopsy progression, but this was not significant after adjustment for baseline PSA density.[42]

Prostate-specific antigen velocity predictive role after surgical and radiotherapy treatment

PSAV was of a good predictive value in treated cases. Yet, the difference in the predictive model with and without PSAV is still unclear (Table 2). Freedland *et al.*[43] evaluated 331 men who underwent radical retro-pubic prostatectomy for PC. They found that preoperative PSAV was not predictive of positive surgical margins, capsular penetration, or seminal vesicle invasion, and it was not a predictor of biochemical recurrence. D'Amico *et al.*[44] assessed 1095 patients undergoing radical prostatectomy. They found that PSAV above 2.0 ng/mL/y before surgery had a significantly shorter time to recurrence, death from PC. Similarly, D'Amico *et al.*[45] reported a cohort of 358 men who underwent external beam radiation. They estimated that 7-year PSA recurrence was 78% *vs*. 54% for patients with PSAV more than and less than 2.0 ng/mL/y, respectively. For mortality due to PC, the estimates were 19% vs. 0%. Sengupta *et al.*[46] included 2290 patients who underwent radical retro-pubic prostatectomy. PSAV was a significant predictor of biochemical progression, clinical progression, and death specific PC. In addition, Patel *et al.*[47] further studied 202 men performing radical prostatectomy. They reported that preoperative PSAV of greater than 2 ng/mL/y predicted surgical stage, positive margins, pathologic grade, and relapse-free survival. Berger *et al.*[48] evaluated 102 patients having a radical retro-pubic prostatectomy. The PSAV was significantly correlated with tumor volume, but not prostate volume. The median PSAV in the year before diagnosis in men with and without relapse was 1.98 *vs*. 1.05 ng/mL/y. Palma *et al.*[49] reported on 473 patients with PC treated with external beam radiation therapy. Men with a PSAV greater than 2.0 ng/mL/year had a shorter biochemical disease-free survival compared with men with PSAV of 2.0 ng/mL/y. However, on multivariate analysis, PSAV was no longer a significant predictor of biochemical disease-free survival in the entire cohort (p=0.09). PSAV was an independent predictor of biochemical recurrence in high-risk patients only. However, it does not predict survival outcomes. Datan *et al.*[50] built a predictive model for a positive scan. In univariate and multivariate analysis, preoperative PSAV predicted a positive bone scan with an odds ratio of 0.93. Helfand *et al.*[51] performed a review of cases undergoing transurethral resection of the prostate, holmium laser resection of the prostate, or open prostatectomy. Patients with PC had a significantly higher postoperative PSAV compared with patients without PC.

Discussion

Since Carter *et al.*[6] introduced PSAV, there have been many studies trying to connect the dots for its diagnostic and prognostic value. In our study, the qualitative synthesis showed big controversial results regarding the PSAV prediction value. However, the available evidence suggests a better value of PSAV in post-treated compared to pre-treated patients.

Across the studies, several ways of calculating PSAV with different durations and intervals were proposed, which may have affected the results. For instance, D'Amico *et al.*[44] calculated PSAV over one year based on only two values. Moreover, Critical reviews discussed the effect of the mode of PC detection on PSAV.[52,53] For instance, cancers detected by screening may tend to have lower PSA and PSAV compared to clinically detected cancers, which may lead to bias.[53] In addition, some studies showed significant co-linearity of both PSA and PSAV.[15] That's why some authors criticized the real value that PSAV can add with all these complicated calculations and definitions.[54] Verification bias was encountered as a big issue that may affect some of our included studies.[18]

Some of our included studies were based on PCPT data, but D'Amico reported that the PCPT data had no quality assurance for PSA tests, which might affect the accuracy of the results.[55] In that context, Carter *et al.*[56] introduced the concept of PSAV risk count assessment as a concept that could aid in the long-term prediction of potentially killing PC. They built it on the hypothesis that men with dangerous advanced disease may have consistent increases in PSA compared with others. Adding to the conflicting results and sever methodological variability, applying the PSAV calculation using the accurate interval and standard methods may be hard in real clinical practice for urologists. Our systematic review has its limitations due to the variability of comparisons and reporting of studies assessing the utility of PSAV.

Conclusions

To summarize, our study did not find clear-cut evidence to support the use of PSAV as a diagnostic predictive tool to indicate the need for biopsy or in AS. Furthermore, the PSAV role is not fully clear in the prognosis of treated cases. Therefore, we highly encourage more future well designed prospective studies employing the standard definition and calculation of PSAV. In addition, studies comparing both PSAV and PSA and PSA alone are warranted.

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