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An update on the serum and urinary biomarkers in diagnosing prostate cancer

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ABSTRACT

Introduction: In terms of global health issues, prostate cancer ranks high. The prostate cancer diagnosis rate is on the rise in India, where it ranks as the second most frequent malignancy among men. Most of the prostate cancers are not life threatening, but one fifth of them end up with unfavorable outcome [1]. Transrectal prostate biopsy (PBx) is used to diagnose prostate cancer widely nowadays. The results of the digital rectal examination (DRE) and/or increased blood prostate specific antigen (PSA) levels are used to determine whether a PBx is necessary [5]. Both DRE and serum PSA have low positive predictive value. A biomarker with high negative predictive value ensures confidence among the patients and health care providers for delaying undergoing biopsy of the prostate [5]. Our primary objective in doing this research was to compile a detailed inventory of all the diagnostic biomarkers now utilized in clinical practice, together with all of the relevant characteristics for each.

Methodology: All papers published during the last fifteen years were considered, including original and reviews. Molecular markers, fractions of prostate specific antigen (PSA), prostate health index (PHI), microseminoprotein-beta (MSMB), and prostate cancer markers were the keywords used to obtain articles from the Scopus and Pub Med databases.

Conclusion: To prove their usefulness in diagnosing and prognosing prostate cancer, several biomarkers need more evidence. This research gap has to be filled so that unwanted prostate biopsies can be minimized. This helps in achievement of prompt diagnosis and best therapeutic response.

Keywords: *Prostate cancer, Prostate specific antigen, Prostate Health Index, 4K score, Microseminoprotein- beta.*

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1. INTRODUCTION

Prostate cancer is one of the major medical concerns in the world [1]. The Caribbean area has the greatest incidence rates of this disease, and it is the most frequent form of cancer in males globally. In the majority of countries, it is also the primary cause of cancer-related deaths. [1]. In Western countries, mortality from prostate cancer ranks second among male cancers. The prostate cancer diagnosis rate is high in India. This is due to the fact that prostate cancer is the second most common cancer among men. With the present incidence, the occurrence is predicted to be doubled by 2040, with the mortality doubling by then[2]. Most of the prostate cancers are not life threatening, but one fifth of them end up with an unfavorable outcome[1]. It is proven that majority of prostate cancer patients may not exhibit any clinical symptoms and may not be noticed in their lifetime[1]. Factors like life style modification, ageing, genetics affects the occurrence of the disease[1]. Prostate cancer is identified through a digital rectal examination (DRE) and elevated levels of prostate-specific antigen (PSA) and a biopsy of the prostate is performed to confirm the diagnosis [3]. Since fewer cases are recorded and

the data is limited to cancer registries in metropolitan areas, we do not have an accurate picture of the actual incidence of prostate cancer. There are also limitations in the quantity of community-focused research on prostate cancer [2]. To decrease mortality and complications, early diagnosis is needed[4].

Transrectal prostate biopsy (PBx) is used to diagnose prostate cancer widely nowadays. Results from digital rectal examinations (DREs) and/or increased blood prostate specific antigen (PSA) levels are needed for the decision to do prostate biopsy (PBx). Both DRE and serum PSA have low positive predictive value. Clinical research has revealed that only one in four prostate biopsies will be diagnosed with prostate cancer. What is more concerning is that serial biopsy will show positive in up to 35% of the patients with previous negative biopsies. Such findings increase confusion among physicians and patients, which mandates the need for vigorous diagnostic strategies including multiple biopsies. This in turn increases the chances of complications among patients, and indolent prostate cancer patients receiving radical treatment[5].

Diagnostic biomarkers are very important in identifying the disease in patients/ population who are at risk. The biomarker's usefulness as a diagnostic tool depends on the accuracy and pre-test likelihood of illness diagnosis in patients. A biomarker is helpful in the screening of patients when it can accurately determine the low likelihood of the disease which avoids for further testing. A biomarker with high negative predictive value ensures confidence among the patients and health care providers for delaying the biopsy of the prostrate. To be a clinically useful biomarker, it should be able to diagnose the disease early, without any errors [5]. For the purposes of this research, we present here diagnostic biomarker criteria currently used in clinical practice.

2. METHODOLOGY

This inquiry includes the search for biomarkers in blood, tissues, and physiological fluids that may be used to diagnose prostate cancer. All papers published during the last fifteen years were considered, including original research articles and reviews. Molecular markers, fractions of prostate specific antigen (PSA), prostate health index (PHI), microseminoprotein -beta (MSMB), and prostate cancer markers were the keywords used to obtain articles from the Scopus and Pub Med databases. Research that used blood, urine, or tissue samples to diagnose prostate cancer was considered for inclusion. The papers included in the review also contrasted the use of biomarkers in the blood and urine for the diagnosis of prostate cancer. Emerging molecular markers in tissue and urine were also reviewed. Variables considered in this narrative literature review included biomarker, sample type, year of study, analytical variables including sensitivity, specificity, and predictive value, both positive and negative, when available.

Prostate Specific Antigen and its fractions:

Prostate-specific antigen (PSA) is the preferred test for detecting prostate cancer [6]. Prostate-specific antigen, or PSA, is one of the most common proteins in sperm. PSA testing is one method of detecting prostate cancer. It is a serine protein that belongs to the kallikrein protein family. The gene that encodes it is known as KLK3. Both healthy prostate cells and cancerous prostate cells produce this antigen. It is regulated by androgen[7,8]. Because it may be increased in other prostatic disease like benign prostatic hypertrophy(BPH), its specificity increases when combined with digital rectal examination and USG [9,10]. In addition to PSA, the American Urological Association and the American Cancer Society concur that a digital rectal examination is the gold standard for cancer prevention.[11]. Isolated measurement of PSA is commented to have low specificity especially in the range between 4-10 ng/dL[6]. Not only prostate specific antigen, also its fraction, free PSA, has limited specificity in prostate cancer detection especially in clinically significant and curable indolent prostate cancer, which may lead to unnecessary biopsies[12]. To a lesser extent than PSAD and transitional zone PSA density, even free PSA (fPSA), %fPSA (fPSA/total PSA), and PSA density have contributed to PSA specificity [6]. The -2proPSA is a derivative of free PSA that has been shortened; this isoform is seen in higher abundance in prostate cancer cells. In normal individuals, it contributes up to 20% of free PSA. In prostate cancer patients it may rise from 25% to 95%[6]. For predicting aggressive prostate cancer blood biomarkers like PHI and 4Kscore, which, according to the strongest available data, could be useful for prostate cancer treatment [13].

Using PSA density criteria, patients with increased PSA levels who have undergone a normal rectal examination may have benign prostatic hyperplasia (BPH), which may be distinguished from prostate cancer. Men whose PSA levels are normal may benefit from its usage in diagnosing prostate cancer, particularly in cases when a cure is likely. [14].

Screening with PSA has shown decreased mortality, but the same increases the overdiagnosis, in prostate cancer classified as low to moderate risk. Usually prostate cancer is identified using PSA. But it has variable specificity. Therefore, for prostate cancer risk assessment, more targeted approaches are necessary[15].

Prostate health index

The Food and Drug Administration (FDA) has approved the Prostate Health Index (PHI) test for use in males over 50 with PSA values between 4 and 10 ng/mL who have not yet been diagnosed with prostate cancer. The Prostate Health Index (PHI) is derived from three types of prostate-specific antigen: total (tPSA), free (fPSA), and [-2]proPSA. The diagnostic likelihood of prostate cancer rises as the PHI range rises[16]. As increasing PHI values reflect increased prostate cancer risk, PHI is proposed as a patient monitoring tool. PHI may be a more accurate indicator of a person's risk for prostate cancer, especially in men with somewhat elevated PSA values, since those with PHI ≥55 had a five-fold higher chance of a positive biopsy and over 50% chance of a prostate cancer diagnosis. The occurrence of higher Gleason grade (≥7) was associated with higher PHI scores (>55) among prostate cancer patients. PHI did not differ by age and race, suggesting that it can be generalized to a broad spectrum of men. Physicians can recommend biopsies for a patient with PHI more than 55 and suggest surveillance when PHI is less than 25. When patients are reluctant to undergo prostate biopsy, sequential monitoring using PHI might aid in effective follow-up[16].

4K Score

Results from tPSA, iPSA, fPSA, and HK2 were used to compute the 4Kscore. It provides a number between 0 and 100 that indicates the likelihood that a patient may have prostate cancer based on the biopsy [16].On its own, the 4K score is a crucial tool for individualised risk assessment, and subtracting 100% from which yields the NPV [16]. The number of biopsies could be decreased by 50%. But this may miss 12 in every 1000 clinically significant cancers with indication for biopsy[16].

Serum MSMB

Prostate secretes microseminoprotein-beta (MSMB) from its epithelial cells. In the prostate, it prevents the development of cancer. A prospective study has shown that increase in MSMB even by an unit, decreases the likelihood of developing prostate cancer by 2%[17].

Urinary PSA

Prostate cancer will strike many men at some time in their life. Complications might arise as a result of the intrusive procedures used for diagnosis. A greater proportion of negative prostate biopsies are indicated by blood PSA levels that are low in predictive value, particularly between 4 and 10 ng/mL [3].

After a digital rectal examination, those with prostate cancer may have lower levels of prostatic acid phosphatase and prostate-specific antigen. The low urine PSA to serum PSA ratio in these cases indicates that those with PSA levels between 2.5 and 10 ng/ml may have either benign prostatic hyperplasia or prostate cancer. [3].The PSA ratio distinguishes between benign prostatic hypertrophy, prostate cancer, and healthy men because PSA is released by cells of both benign and malignant prostates. By this urinary PSA measurement can be used in diagnosis of prostatic cancer [18].

Urinary MSMB

Microseminoprotein-beta (MSMB) is made up of 94 amino acids. It is used as a diagnostic and prognostic marker for prostate cancer due to the fact that its synthesis decreases in cancer. It could serve as a target in therapy in addition to its use as a biomarker in detection and prognosis. In Caucasian population decreased levels of urinary MSMB is found to be linked to death specifically from prostate cancer. Additionally, decreased urine MSMB levels may be linked to prostate cancer in Asian-Indian populations [3].

Tissue biomarker

Prediction of prostate cancer using tissue biomarkers has been in research for quite some time. A few of them have been able to diagnose metastasis also. Some of the tissue biomarkers include oncotype DX, Prolaris and Decipher. Prolaris and oncotype DX have proven local aggressiveness than distant metastasis. Predicting distant metastases was the goal of Decipher's design. All of the samples utilised in this research were from radical prostatectomy procedures; however, needle biopsy samples were also used more recently [19].

Molecular markers

Molecular biomarkers in the urine like Select mdx and PCA3 showed increased specificity in detecting prostate cancer, even the malignancies which might not be harmful are diagnosed with these biomarkers [1]. Another biomarker transcript of transmembrane protease serine 2 (TMPRSS2)-ERG gene fusion correlates well with prostatic cancer cells. Nearly 50% of the prostate cancer individuals shows positive for this above androgen regulated gene fusion and the specimens without prostate cancer shows negative for the above gene [1]. CD 90 fragments were found in urine of prostatic cancer patients. It was specifically found in PCa patients before prostatectomy when compared to post surgery [1].

3. DISCUSSION

In order to diagnose prostate cancer and assess males at risk for its development, this study analysed a number of biomarkers that are now accessible. Biomarkers that were often employed were PSA levels and its fractions. Age, BPH status, prostatitis, and prostate cancer are among factors that can affect their levels [20,21]. The introduction of molecules carrying prostate-specific antigen (PSA) has improved the accuracy of prostate cancer diagnosis. Additionally, the adoption of the free PSA to total PSA ratio has reduced the number of unnecessary biopsies.[22].

PSA and its fraction levels have been impacted by factors like age, race and ethnicity, so age specific reference interval could be helpful for specific race and ethnicity. Further studies have proven that fractions of PSA, PHI and PHID helps in the decreasing unnecessary biopsies[23]. Studies have proven strong association of decreased urinary PSA and prostatic cancer thus making it an important tool in the diagnosis and prognosis. Reduction in urinary PSA levels have been useful in the differentiating prostate cancer from BPH. Prostate biopsies are supposedly not performed when urinary PSA levels are more than 150 ng/mL.[18,24].

In men without prostate cancer rise in levels of urinary PSA and blood MSMB post DRE was observed, which differentiates normal men from prostate cancer patients in whom these parameters were not increased. Low levels of serum MSMB is indicative of elevated risk of prostate cancer. MSMB is believed to play a protective role against this disease, even though its physiology is not clear. Alerting the levels of MSMB may be used as an option for treatment[3,19,26].

Prediction of prostate cancer using tissue biomarkers have been fruitful, with a few of them able to identify metastasis like the Decipher. Oncotype DX and Prolaris are some tissue biomarkers which help in diagnosis of prostate cancer.

Molecular biomarkers in the urine like Select mdx and PCA3 have shown increased specificity in detecting prostate cancer. The fusion of the transmembrane protease serine 2 (TMPRSS2) gene with the ERG gene is another biomarker that has a strong negative predictive value and a high correlation with prostate cancer cells.

Table 1: Summary of the various biomarkers and their significant observations

S.No	Biomarkers	Author	Observation
1	PSA and its fraction	Punglia RS et al.,	The levels of PSA vary with respect to age, presence or absence of BPH, prostate cancer. The cut off value for PSA may not be fixed and it may vary with respect to the above factors[26].
2	PSA and its fraction	Schaeffer et al.,	Conditions like prostatitis can increase the levels of PSA, which can be decreased by treatment of the same. This in turn can decrease negative biopsies[21].
3	PSA and its fraction	Roddam AW et al.,	Unnecessary biopsies can be cut down by the use of free PSA/total PSA ratio[22].
4	PSA and its fraction	Govinda Raju NL et al.,	Factors like age, race and ethnicity may have an impact on the levels of PSA and its fractions. Age specific reference interval is needed for a specific race and ethnicity[20].
5	PSA and its fraction PHI	J Juan Escudero et al.,	In a prostate biopsy, Gleason score more than seven is best predicted by -2proPSA. A more precise diagnosis of prostate cancer may be made with PHI in men with normal DRE and PSA values ranging from 3 to 10 ng/ml. [6].
6	PSA and its fraction, PHI, PHID	Shih-Ting Chiu et al.,	Fractions of PSA, PHI, PHID had shown better performances, which in turn can decrease most of the unnecessary biopsies[23].
7	Urine PSA	Stephane Bolduc et al.,	Decrease in levels of urinary PSA may be used in differentiating prostate cancer from BPH. Level of PSA>150 ng/mL prevents prostatic biopsies[24].
8	Urine PSA	Sergio Occhiointi et al.,	There was an association between prostate cancer and urinary PSA. Urinary PSA levels are used in prostate cancer diagnosis and prognosis[18].
9	Urine PSA & Urine MSMB	Prashanth Shrivastava et al.,	In men without prostate cancer rise in levels of urinary PSA and MSMB post DRE was observed, which differentiates normal men from prostate cancer patients in whom these parameters were not increased[3].
10	Plasma MSMB	Christopher A et al.,	Those whose plasma MSMB levels were lower had a greater chance of developing prostate cancer.[25].

11	Plasma MSMB	Smith Byrne et al.,	Plasma MSMB may have a protective role in prostate cancer, even though the mechanism is yet to be identified. Research in the area for increasing MSMB levels may be used as a treatment option[17].

4. CONCLUSION

Recent research on the diagnostic and prognostic approach for prostate cancer has involved multiple biomarkers in serum, urine and tissues. However, PSA test and invasive prostrate biopsy have been relied by most physicians in treating patients, even though there exists clear evidence that some of the biomarkers have proven to have good negative predictive value. Many biomarkers need more data for proving their efficacy in the diagnosis, prognosis of prostate cancer. This research gap has to be filled so that unwanted prostate biopsies can be minimized. By this prompt diagnosis and best therapeutic response is achieved.

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