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Original Research Article

A CORRELATIONAL ANALYSIS OF IMMUNOLOGICAL, RADIOLOGICAL AND BIOCHEMICAL MARKERS IN RELATION TO DISEASE STAGE AND SHORT TERM PROGNOSIS OF PROSTATE CANCER

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ABSTRACT

Background: Prostate cancer is a leading cause of cancer-related mortality among men, with diagnostic limitations in current methods like PSA assays, DRE, and TRUS biopsies. This study aimed to evaluate the correlation between various biomarkers, including Ki-67/MIB-1 and ERβ, and the recurrence of prostate cancer.

Materials and Methods: This prospective observational study included 110 patients diagnosed with prostate cancer at a tertiary care hospital in New Delhi. Patients were monitored over 12 months, with data collected on PSA indices, Ki-67/MIB-1, ERβ expression, and MRI PI-RADS scores. Statistical analyses were conducted to assess the significance of these parameters in predicting disease recurrence.

Results: Higher Ki-67/MIB-1 expression and increased PSA velocity were significantly associated with recurrence. Although the correlation between PI-RADS scores and recurrence was not statistically significant, 60% of recurrent cases had a PI-RADS score of ≥4. ERβ expression was notably higher in patients with recurrence, indicating its potential as a prognostic marker.

Conclusion: The study concludes that combining PSA indices, immunohistochemical markers (Ki-67/MIB-1, ERβ), and advanced imaging techniques (MRI PI-RADS) offers a more robust approach to predicting prostate cancer outcomes. Regular follow-up with tailored diagnostic strategies is essential for early detection and timely intervention, particularly in patients with high-risk markers.

Keywords: Prostate cancer, PIRADS, Ki-67, MIB-1.

INTRODUCTION

Prostate cancer is the second most frequent malignancy (after lung cancer) in men worldwide, counting 1,276,106 new cases and causing 358,989 deaths (3.8% of all deaths caused by cancer in men) in 2018.[1,2] The incidence and mortality of prostate cancer worldwide correlate with increasing age with the average age at the time of diagnosis being 66 years. Of note, for African-American men, the incidence rates are higher when compared to the White men, with 158.[3] new cases diagnosed per 100,000 men and their mortality is approximately twice as White men.[3] Reasons for this disparity have been hypothesized to differences in social, environmental and genetic factors. Although 2,293,818 new cases are estimated until 2040, a small variation in mortality will be observed (an increase of 1.05%).[4]

Carcinoma of prostate is one of the leading causes of cancer death among aged men. It is the most common non-cutaneous cancer among men.[5] The incidence of prostate cancer is on the rise primarily because of increased application of screening tests

using prostate-specific antigen (PSA) and also partly because of the increase in life expectancy.[6] Most of the prostate cancers are slow-growing and indolent rather than being aggressive and hence they seldom produce any symptoms until the advanced stage. Hence, early diagnosis of prostate cancer can lead to improved treatment outcomes besides aiding in the selection of multiple treatment options available. Traditionally, the methods employed include a prostate-specific antigen assay (PSA), Digital rectal examination (DRE) and Transrectal ultrasound guided biopsy (TRUS). The confirmatory diagnosis of prostate cancer can only be made by taking a biopsy which is usually a 8-core TRUS biopsy. However, all these methods have their own limitations and disadvantages.

PSA assay levels lack sensitivity and specificity while the DRE is a crude technique with a low positive predictive value and high interobserver variability. Studies have shown that TRUS biopsy can miss up to 20% of prostate cancers because of under sampling of anterior prostate, apex and midline resulting in high false negativity.[7] About 70% of initial biopsies performed in men with raised PSA levels are negative for prostate cancer hence increasing the burden of negative biopsies and increased screening costs.[8] Because of these limitations of the currently existing techniques, the search for a diagnostic technique which is reliable, sensitive, specific with good positive and negative predictive values besides being non-invasive have led the researchers to consider radiologic imaging techniques like magnetic resonance imaging (MRI) as a diagnostic tool and especially multi-parametric MRI (MP-MRI) has received quite an attention in the recent years which builds upon the regular advantages of MRI.

Prostate cancer may be asymptomatic at the early stage and often has an indolent course, and may require minimal or even no treatment. However, the most frequent complaint is difficulty with urination, increased frequency, and nocturia, all symptoms that may also arise from prostatic hypertrophy. More advanced stage of the disease may present with urinary retention and back pain, as axis skeleton is the most common site of bony metastatic disease.

Many prostate cancers are detected on the basis of elevated plasmatic levels of prostate-specific antigen (PSA > 4 ng/mL), a glycoprotein normally expressed by prostate tissue. However, because men without cancer have also been found with elevated PSA, a tissue biopsy is the standard of care to confirm cancer's presence.

Gleason`s grading system is the standard histopathological method for estimating aggressiveness of prostate cancer.[9] It is used to describe a tumour as low grade (Gleason`s score ≤6), intermediate grade (Gleason`s score = 7), or high grade (Gleason`s score >7) with respect to tumour

Aggressiveness. The probability of disease recurrence increases with increasing Gleason`s score and increasing percentage core involvement of tumour in biopsy specimens.[10] Hence, accurate scoring is necessary to determinate appropriate therapy, according to risk groups. Active surveillance for low risk tumors (Gleason 's score ≤6), monotherapy for intermediate risk tumors (Gleason 's score = 7) and combination therapy for high risk tumors (Gleason 's score, >7) are the best treatment options.

In India, prostate cancer is the second most common cause of cancer among males,[11] Currently, on account of changing life styles, migration of rural to urban population, and increasing access to medical facilities and diagnostics, prostate cancer is coming into light and is expected to be a major health issue in India. Ki-67 (MIB-1) is a protein involved in cell cycle regulation and cell proliferation. This protein is expressed in proliferating cells during all active phases of the cell cycle. Ki-67 labelling index, i.e. the estimate of the percentage of tumour cells expressing Ki-67, is a reliable indicator of the proliferative activity in the tumour, and its degree of aggressiveness. Hence, the present study was conducted to correlate the expression of Ki-67 with the Gleason score in prostatic adenocarcinoma, and to thus determine whether the routine use of Ki-67 marker can yield additional prognostic information. The following parameters will be analysed and the correlation is to be established from the study.

Parameters are

- Serum PSA (Total and Free)
- PSA velocity (It is change in PSA level with time).
- PSA Index (Free PSA: Total PSA)
- Immunohistochemistry of Ki-67, Her/2neu, ER status
- TRUS and TRUS guided biopsy
- MRI (Pi-RADS score)
- PSMA-PET CT SCAN (in selected cases for extra capsular invasion).

MATERIALS AND METHODS

All adult patients, clinically diagnosed as carcinoma prostate to the surgical department were included in the study. Patients with History of other malignancies, patient with prostatic intraepithelial neoplasia, Prior androgen deprivation therapy (ADT), Pacemaker/metallic implant in situ were excluded.

A detailed history of the patient was taken as per protocol and patient was thoroughly examined and investigated. After this evaluation, patients diagnosed as carcinoma prostate was enrolled in the study. The values of PSA Indices, lactate, IHC markers from TRUS biopsy of prostate and PIRADS scoring system of MRI prostate were evaluated. Standard treatment protocol of Carcinoma prostate was started in all patients.

In addition to routine follow up, patient is to be follow up for 3,6,9,12 months with Serum PSA

report (>10% rise in 6 months or >25% rise in 12 months), Clinical examination(DRE) if Significant findings then MRI and PET CT Scan (in selected cases).

Stastically Analysis

Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± SD and median. Normality of data was tested by Kolmogorov-Smirnov test. If the normality is rejected then non parametric test was used. Statistical tests were applied as follows-

1. Quantitative variables was compared using Unpaired t-test/Mann-Whitney Test (when the data sets were not normally distributed) between the two groups.
2. Qualitative variables was compared using Chi-Square test /Fisher's exact test.
3. Receiver operating characteristic curve was used to find out the cut-off point of serological biomarkers for predicting strangulation. Diagnostic test was used to calculate sensitivity, specificity, NPV and PPV.

A p-value of less than 0.05 was considered as significant.

RESULTS

An observational prospective study was conducted in department of general surgery in a tertiary care hospital of New Delhi. One Hundred ten patients who presented with diagnosis of Carcinoma prostate were observed in this study. Along with the routine investigations needed for treatment plan, blood samples for PSA Indices, IHC markers and PIRADS SCORE in MRI PROSTATE were taken. During follow up at 3,6,9,12 months, values of serological biomarkers were compared with the initial findings and incidence of recurrence in these cases of Carcinoma prostate were noted. It was found that, mean USG Size of Prostate (CC) was lower in non-Recurrence group [58.3107± 18.8508] compared to Recurrence group [62.0000± 16.5788] but this was not statistically significant (p=0.5923). We examined that, Ki-67/MIB-1 (Immunohistochemistry) was higher in Recurrence group compared to group with no recurrence. And it was statistically significant. It examined that, mean PSA Velocity was more in group with recurrence compared to no recurrence group and this was statistically significant.in the study the relationship of PIRADS Score in MRI was not statistically significant. But 60% of cases having recurrence were observed to have a PIRADS Score more than or equal to IV. In the study, higher number of patients had 70% in Highest Proliferating Zone in ER (ß) (Immunohistochemistry) but this was statistically significant. It was found that, mean USG Size of Prostate (CC) was lower in group with no recurrence compared to Recurrence group but this was not statistically significant. Our study showed that, mean Serum PSA (Total) was more in Recurrence group compared to group with no recurrence but it was not statistically significant. This study showed that, mean Serum PSA (Free) was higher in group with no recurrence compared to Recurrence group but it was not statistically significant. Mean PSA Density (Total PSA / Prostate Volume In ml) was higher in Recurrence group compared to group with no recurrence but this was not statistically significant. It was examined that, mean PSA Index (Free PSA /Total PSA X 100) was more in group with no recurrence compared to Recurrence group p but this was not statistically significant.

Table 1: Ki67/MIB-1

Studies	Ki67/MIB-1
Verma et al (2015)	expressed in 76% of the cases expression of Ki-67 was higher
Berlin A et al (2017)	32.4% of the cases expression of Ki-67 was higher
This Study	88.3% of the cases expression of Ki-67 was higher

Table 2: ER Receptor

Studies	Mean ERβ (%)	p value
Asgari M (2011)	68.41 ± 25.63	0.027
Horvath L G et al (2001)	17.75	0.04
This Study	70.00	<0.0001

DISCUSSION

Our study focused on various clinical and pathological aspects of prostate cancer, highlighting significant findings across multiple parameters, including patient age, disease presentation, digital rectal examination (DRE) outcomes, radiological imaging, histological variants, and the expression of various biomarkers.

1. Age: The majority of patients in our study (82.0%) were over 60 years of age, with a mean age of 69.15±10.30 years. This aligns with previous research by Tyagi et al,[12] and Pettersson et al.,[13] which reported similar age distributions in prostate cancer patients, further emphasizing the higher prevalence of prostate cancer in older individuals. The median age in our cohort was 68 years, comparable to findings by Hamilton W.,[14] and Ali M.,[15] who also reported a mean age above 65 years at diagnosis.

2. Presentation of Disease: Nocturia (94.6%) and acute urinary retention (86.5%) were the most

common presenting symptoms in our cohort, with a small proportion also experiencing frequent urination (17.1%) and hematuria (17.1%). This contrasts with Rawla et al.'s,[16] findings where most patients were asymptomatic and aligns with Samuel W.,[17] who reported lower urinary tract syndrome (LUTS) in 42.3% of cases.

3. Digital Rectal Examination (DRE): Our study found a significantly higher proportion (57.7%) of patients with a firm, enlarged prostate on DRE, consistent with findings by Schröder et al,[18] who reported a 55.8% detection rate of prostate cancers through DRE alone.

4. Radiological Imaging and PI-RADS Scoring: In our study, the PI-RADS v2 score showed a higher specificity (89%) at a cut-off score of ≥4 compared to a score of ≥3, though with a slight reduction in sensitivity. This was consistent with Kubihal et al.'s,[19] findings. Gleason scores correlated well with PI-RADS, confirming the reliability of PI-RADS v2 in detecting clinically significant prostate cancer, as also noted by Gupta et al.[20] MRI's sensitivity (93.75%) and specificity (100%) were particularly noteworthy. The central zone's involvement was associated with more aggressive disease, mirroring findings by Vargas et al.[21] Additionally, PSMA PET scanning revealed a high incidence (91.9%) of bony metastasis, further supporting the importance of advanced imaging techniques in prostate cancer management, as per Tsechelidis et al,[22] and Das et al.[23]

5. Histological Variants: Acinar adenocarcinoma was the predominant histological variant in our study (82.9%), which aligns with Mahapatra et al.'s[24] findings. and Jain et al.'s study,[25] both of which reported adenocarcinomas in the vast majority of their cases. Ductal adenocarcinoma was present in 17.1% of our cases.

6. Ki-67/MIB-1: Ki-67 expression was observed in 88.3% of our cases, correlating with higher Gleason scores, advanced stage, seminal vesicle invasion, and extracapsular extension. This is consistent with Verma et al.'s,[24] study, which emphasized the prognostic value of Ki-67 in prostate cancer. High Ki-67 expression has been strongly associated with worse clinical outcomes, as supported by Berlin A et al,[26] who linked high Ki-67 scores to poor prognosis in localized prostate cancer.

7. Stage at Presentation: Late-stage presentation (stages III and IV) was observed in 55.8% of our cases, significantly higher than in earlier stages. This finding is in line with Herbert et al,[26] who reported a high incidence of late-stage detection in India. Similarly, Sen et al,[27] noted a low incidence of early-stage diagnosis, highlighting the need for early detection strategies.

8. ER Receptor: ERβ expression was significantly associated with recurrence in our study, with a mean expression of 70% in patients with recurrence compared to 58.75% in those without. This finding supports Asgari M.,[28] and Horvath L.G.'s,[29] studies, which indicated that reduced ERβ expression is linked to disease progression and poorer outcomes in prostate cancer.

9. HER-2: HER-2 expression was not detected in any of our cases, indicating no association between HER-2 status and prognosis in our cohort. This contrasts with studies by niyat mm et al,[28] and Siampanopoulou M.,[29] which reported HER-2 expression as a marker for poor prognosis and aggressive disease.

10. Cyclin D1: Cyclin D1 expression was not observed in our prostate cancer cases, differing from Ahmed et al.'s,[30] findings, which associated Cyclin D1 positivity with high Gleason scores and perineural invasion. This discrepancy suggests the need for further research to clarify Cyclin D1's role in prostate cancer.

CONCLUSION

We concluded that the PSA, immunological markers (Ki-67/MIB-1, ERβ) and Radiological imaging (MRI PIRADS score) is correlated with stage of presentation of disease and were associated with prognosis. It is also concluded that patient having high value of Ki-67 and ERβ requires more aggressive treatment. Also, routine follow-up is necessary with Digital rectal examination, Serum PSA Repeat Biopsy (in suspected recurrence) and radiological investigations (MRI-PIRADS) on a patient to patient basis for early diagnosis of disease and recurrence, making timely intervention possible.

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