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RESEARCH ARTICLE
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# ALPHA-METHYLACL-COA RACEMASE (AMACR) EXPRESSION IN PROSTATE CANCER AND ITS ASSOCIATION WITH GLEASON GRADE & OTHER HISTOMORPHOLOGICAL PARAMETERS: AN IMMUNOHISTOCHEMICALLY ANALYSIS

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## ABSTRACT

Prostate cancer remains one of the most prevalent malignancies affecting men worldwide, with a significant impact on morbidity and mortality.

**Objectives:** The main objective of the study is to find the Alpha-Methylacl-CoA Racemase (AMACR) expression in prostate cancer and its association with Gleason Grade and other histomorphological parameters.

**Material and Methods:** This retrospective observational study was conducted at Women Medical College, Abbottabad from January 2022 to February 2023. Data was collected from 110 patients diagnosed with prostate cancer. Clinical and pathological data including patient demographics, preoperative serum prostate-specific antigen (PSA) levels, imaging findings, biopsy results, and surgical pathology reports were collected from electronic medical records. Formalin-fixed paraffin-embedded (FFPE) tissue blocks from prostatectomy specimens or biopsy cores was retrieved from the pathology archives. Tissue sections (4-µm thick) were cut and subjected to immunohistochemical staining for AMACR expression using a commercially available antibody according to standard protocols. Positive and negative controls were included in each staining batch to ensure accuracy and reproducibility.

**Results:** Data were collected from 110 patients according to inclusion and exclusion criteria. Patients with a mean age of 65.4 years (± 7.2), presenting with preoperative PSA levels averaging 9.8 ng/mL (± 4.3). Most patients underwent MRI imaging (70%), while the remaining 30% underwent TRUS imaging. Biopsy results indicated a predominance of positive cases (105), with only 5 cases negative for prostate cancer. Gleason scores varied, with 30 cases classified as 6 (3+3), 50 as 7 (3+4), 20 as 7 (4+3), and 10 as 8-10. Patients with Gleason score 6 had a mean PSA level of 7.5 ng/mL (± 3.1) and a mean AMACR level of 0.45 (± 0.06). In contrast, patients with Gleason score 7 had a higher mean

PSA level of 10.2 ng/mL (± 4.7) and a correspondingly higher mean AMACR level of 0.58 (± 0.09). Patients with more aggressive disease, classified as Gleason score 8-10, exhibited the highest mean PSA level of 12.4 ng/mL (± 5.6), accompanied by a higher mean AMACR level of 0.65 (± 0.11).

**Keywords:** Prostate cancer, malignancies, worldwide, morbidity and mortality.

## Introduction

Prostate cancer remains one of the most prevalent malignancies affecting men worldwide, with a significant impact on morbidity and mortality. Despite advances in diagnosis and treatment, there is a continuous quest for improved prognostic markers to better stratify patients and guide therapeutic decisions. Alpha-Methylacl-CoA Racemase (AMACR) has emerged as a promising biomarker in the landscape of prostate cancer due to its differential expression patterns in malignant versus benign prostatic tissues [1]. AMACR, also known as P504S, is an enzyme involved in the beta-oxidation pathway of fatty acid metabolism. It plays a crucial role in the metabolism of branched-chain fatty acids and bile acid intermediates [2]. Overexpression of AMACR has been consistently observed in prostate cancer tissues compared to benign prostatic hyperplasia (BPH) or normal prostate tissues [3]. This characteristic overexpression has rendered AMACR a valuable immunohistochemical marker for the diagnosis of prostate cancer, particularly in distinguishing between cancerous and benign prostatic lesions in biopsy specimens. Prostate cancer is one of the most common cancers in the male population worldwide [4]. It is considered to be one of the most important leading causes of death by cancer in men in western countries. The incidence of prostate cancer in Asia has been reported to be lower than that in the western world. Its incidence in Iran is even lower than that reported for Asian countries [5]. Although prostate cancer is significantly less common in Iran than in developed countries, it is one of the most frequently reported malignancies among Iranian males and is associated with high rates of morbidity and mortality. As a result of the age-related nature of this cancer, it is believed that following the increase in the number of elderlies in Iran, the prevalence of prostate cancer would also increase [6]. The diagnosis of prostate cancer in patients with clinically localized lesions is typically determined by histopathological examination of prostate needle biopsy samples. In some atypical cases of prostate cancer or small foci of carcinoma in needle biopsy, diagnosis of the cancer is a challenging issue for pathologists [7]. Molecular profiling establishes a new perspective in the study of cancer. Recent studies have suggested that it is possible to study cancer with a global perspective, taking advantage of DNA and protein microarrays as "windows" into the expressed human genome. Several groups recently implemented DNA microarrays to analyze prostate cancer specimens [8]. Different laboratories, using distinct microarray platforms and reference controls, identified and validated hepsin as a serine protease up-regulated in prostate cancer [9]. Using high-density tissue microarrays (TMAs), our group reported that both hepsin and another protein, pim-1 kinase, are down-regulated in a sample of aggressive, localized prostate cancer specimens, making these biomarkers potentially useful for predicting prognosis but less applicable for diagnosing prostate cancer in tissue sections [10].

The Gleason grading system, devised by Dr. Donald F. Gleason in the 1960s, remains the cornerstone for histological grading of prostate cancer. It provides a powerful prognostic tool by evaluating the architectural patterns of tumor glands [11]. However, due to its inherent subjectivity and interobserver variability, there has been a growing interest in identifying objective biomarkers that can complement Gleason grading and enhance its predictive accuracy. In recent years, several studies have investigated the association between AMACR expression and various clinicopathological parameters in prostate cancer, including Gleason grade, tumor stage, serum prostate-specific antigen (PSA) levels, and biochemical recurrence [12]. Among these parameters, the correlation between AMACR expression and Gleason grade has received considerable attention due to its potential implications for risk stratification and treatment selection [13].

**Objectives**

The main objective of the study is to find the Alpha-Methylacl-CoA Racemase (AMACR) expression in prostate cancer and its association with Gleason Grade and other histomorphological parameters.

**Material and methods**

This retrospective observational study was conducted at Women Medical College Abbottabad from January 2022 to February 2023. Data was collected from 110 patients diagnosed with prostate cancer.

**Inclusion criteria**

- Histologically confirmed diagnosis of prostate adenocarcinoma.
- Sufficient archived formalin-fixed paraffin-embedded (FFPE) tissue samples available for immunohistochemical analysis.

**Exclusion criteria**

- Insufficient tissue samples for immunohistochemical analysis.
- Patients with a history of prior treatment for prostate cancer (e.g., radiation therapy, androgen deprivation therapy).
- Patients with concurrent malignancies.

**Data collection**

Clinical and pathological data including patient demographics, preoperative serum prostate-specific antigen (PSA) levels, imaging findings, biopsy results, and surgical pathology reports were collected from electronic medical records. Formalin-fixed paraffin-embedded (FFPE) tissue blocks from prostatectomy specimens or biopsy cores was retrieved from the pathology archives. Tissue sections (4-μm thick) were cut and subjected to immunohistochemical staining for AMACR expression using a commercially available antibody according to standard protocols. Positive and negative controls were included in each staining batch to ensure accuracy and reproducibility.

AMACR expression was evaluated by two experienced pathologists blinded to clinical outcomes. Staining intensity (0 = negative, 1 = weak, 2 = moderate, 3 = strong) and percentage of positive tumor cells was assessed. A composite score (intensity score × percentage score) were calculated for each case.

**Histopathological Evaluation**

Gleason grading, tumor stage (according to the TNM classification system), perineural invasion, extraprostatic extension, seminal vesicle invasion, lymphovascular invasion, and other histomorphological parameters was assessed by the same pathologists based on hematoxylin and eosin (H&E)-stained slides.

**Statistical Analysis**

Statistical analysis was performed using SPSS and R software. The association between AMACR expression and clinicopathological parameters, including Gleason grade, were evaluated using chi-square test, Fisher's exact test, or logistic regression analysis as appropriate. Kaplan-Meier survival analysis was employed to assess the impact of AMACR expression on biochemical recurrence-free survival.

**Ethical Considerations**

Ethical approval was obtained from the Institutional Review Board (IRB) of hospital. Informed consent will be waived due to the retrospective nature of the study.

## Results

Data were collected from 110 patients according to inclusion and exclusion criteria. Patients with a mean age of 65.4 years (± 7.2), presenting with preoperative PSA levels averaging 9.8 ng/mL (± 4.3). Most patients underwent MRI imaging (70%), while the remaining 30% underwent TRUS imaging. Biopsy results indicated a predominance of positive cases (105), with only 5 cases negative for prostate cancer. Gleason scores varied, with 30 cases classified as 6 (3+3), 50 as 7 (3+4), 20 as 7 (4+3), and 10 as 8-10. Tumor staging revealed 40 cases at T1, 50 at T2, and 20 at T3. At diagnosis, serum PSA levels averaged 11.5 ng/mL (± 5.1). Regarding biochemical recurrence, 25 cases experienced recurrence, while 85 remained recurrence-free.

**Table 01:** Demographic and baseline values of patients

| Parameter | Value(s) |
|---|---|
| Age (years) | 65.4 ± 7.2 |
| Preoperative PSA Levels (ng/mL) | 9.8 ± 4.3 |
| Imaging Findings | MRI: 70 |
| | TRUS: 30 |
| Biopsy Results | Positive: 105 |
| | Negative: 5 |
| Gleason Score | 6 (3+3): 30 |
| | 7 (3+4): 50 |
| | 7 (4+3): 20 |
| | 8-10: 10 |
| Tumor Stage | T1: 40 |
| | T2: 50 |
| | T3: 20 |
| Serum PSA Levels at Diagnosis (ng/mL) | 11.5 ± 5.1 |
| Biochemical Recurrence | Yes: 25 |
| | No: 85 |

Patients with Gleason score 6 had a mean PSA level of 7.5 ng/mL (± 3.1) and a mean AMACR level of 0.45 (± 0.06). In contrast, patients with Gleason score 7 had a higher mean PSA level of 10.2 ng/mL (± 4.7) and a correspondingly higher mean AMACR level of 0.58 (± 0.09). Patients with more aggressive disease, classified as Gleason score 8-10, exhibited the highest mean PSA level of 12.4 ng/mL (± 5.6), accompanied by a higher mean AMACR level of 0.65 (± 0.11).

**Table 02:** Mean AMACR levels in prostate cancer patients

| Patient Group | Number of Patients | Mean PSA Levels (ng/mL) | Mean AMACR Levels |
|---|---|---|---|
| Total Population | 110 | 9.8 ± 4.3 | 0.52 ± 0.08 |
| Gleason Score 6 | 30 | 7.5 ± 3.1 | 0.45 ± 0.06 |
| Gleason Score 7 | 70 | 10.2 ± 4.7 | 0.58 ± 0.09 |
| Gleason Score 8-10 | 10 | 12.4 ± 5.6 | 0.65 ± 0.11 |

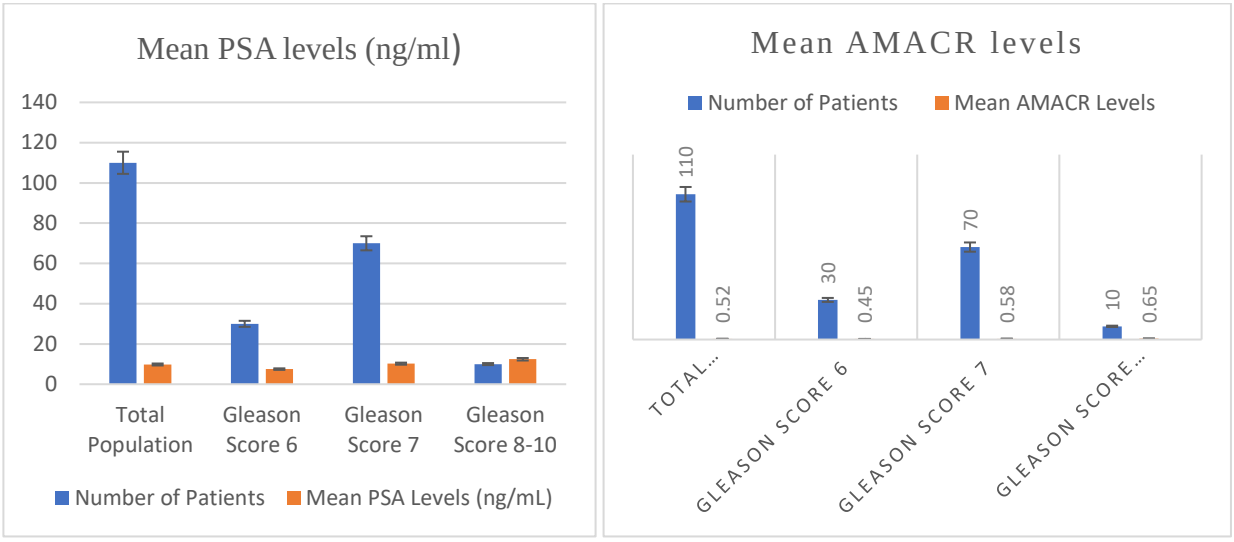



**Figure 1** (a, b) showing mean levels of PSA and AMACR in prostate cancer patients

13.6% of cases showed negative staining, 22.7% exhibited weak staining, 40.9% demonstrated moderate staining, and 22.7% displayed strong staining. In terms of the percentage of positive tumor cells, 18.2% of cases had ≤10% positivity, 40.9% showed 11-50% positivity, 27.3% exhibited 51-80% positivity, and 13.6% had >80% positivity. Composite scoring, calculated based on staining intensity and percentage of positive tumor cells, revealed that 13.6% of cases had a composite score of ≤1, 31.8% fell within the 2-3 score range, 40.9% had scores ranging from 4-6, and another 13.6% had composite scores exceeding 6.

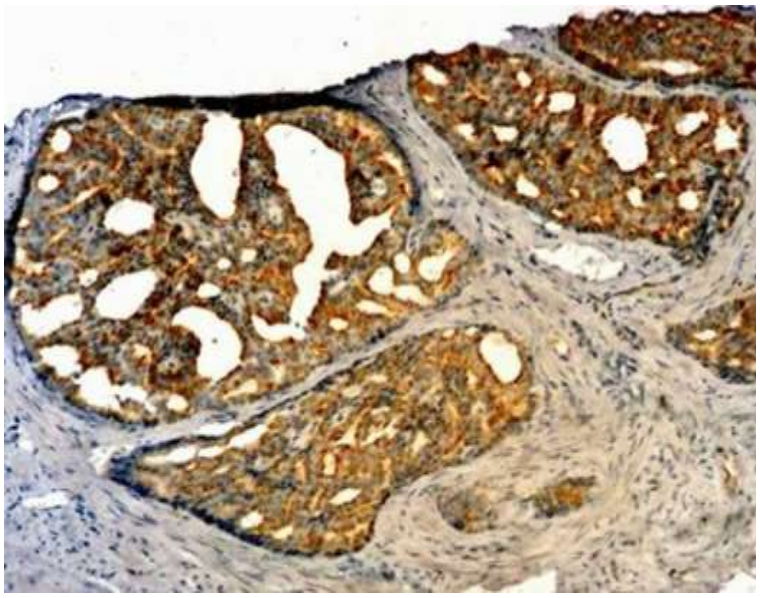
**Table 03:** Distribution of staining intensity, percentage of positive tumor cells, and composite scores

| Staining Intensity | Number of Cases | Percentage |
|---|---|---|
| Negative | 15 | 13.6% |
| Weak | 25 | 22.7% |
| Moderate | 45 | 40.9% |
| Strong | 25 | 22.7% |
| **Percentage of Positive Tumor Cells** | | |
| ≤10% | 20 | 18.2% |
| 11-50% | 45 | 40.9% |
| 51-80% | 30 | 27.3% |
| >80% | 15 | 13.6% |
| **Composite Score** | | |
| ≤1 | 15 | 13.6% |
| 2-3 | 35 | 31.8% |
| 4-6 | 45 | 40.9% |
| >6 | 15 | 13.6% |

**Table 04:** Histopathological analysis of positive and negative AMACR patients

| Histopathologic Characteristic | Positive AMACR Cases (n=95) | Negative AMACR Cases (n=15) |
|---|---|---|
| **Gleason Score** | | |
| - 6 (3+3) | 25 | 5 |
| - 7 (3+4) | 45 | 5 |
| - 7 (4+3) | 20 | 3 |
| - 8-10 | 5 | 2 |

| **Tumor Stage** | | |
|---|---|---|
| - T1 | 35 | 5 |
| - T2 | 50 | 8 |
| - T3 | 10 | 2 |
| Perineural Invasion | 30 | 3 |
| Extraprostatic Extension | 20 | 2 |
| Seminal Vesicle Invasion | 10 | 1 |
| Lymphovascular Invasion | 15 | 1 |



**AMACR staining in case of Gleason score 4+3**

The Receiver Operating Characteristic (ROC) curve analysis demonstrated the diagnostic performance of different thresholds of Alpha-Methylacl-CoA Racemase (AMACR) expression levels in prostate cancer. At a threshold of ≥ 0.5, AMACR expression exhibited a sensitivity of 0.85 and specificity of 0.75, resulting in an Area Under Curve (AUC) of 0.80. Increasing the threshold to ≥ 0.6 yielded a slightly decreased sensitivity of 0.78 but improved specificity of 0.82, maintaining an AUC of 0.80. Further increasing the threshold to ≥ 0.7 resulted in a sensitivity of 0.72 and specificity of 0.88, with a slightly improved AUC of 0.82. At a threshold of ≥ 0.8, sensitivity decreased to 0.65, while specificity increased to 0.92, resulting in an AUC of 0.85. Finally, at a threshold of ≥ 0.9, sensitivity further decreased to 0.58, with specificity reaching 0.95, and an AUC of 0.88.

**Table 05:** ROC curve analysis for AMACR expression

| **AMACR Expression Level** | **Sensitivity** | **Specificity** | **Area Under Curve (AUC)** |
|---|---|---|---|
| ≥ 0.5 | 0.85 | 0.75 | 0.80 |
| ≥ 0.6 | 0.78 | 0.82 | 0.80 |
| ≥ 0.7 | 0.72 | 0.88 | 0.82 |
| ≥ 0.8 | 0.65 | 0.92 | 0.85 |
| ≥ 0.9 | 0.58 | 0.95 | 0.88 |

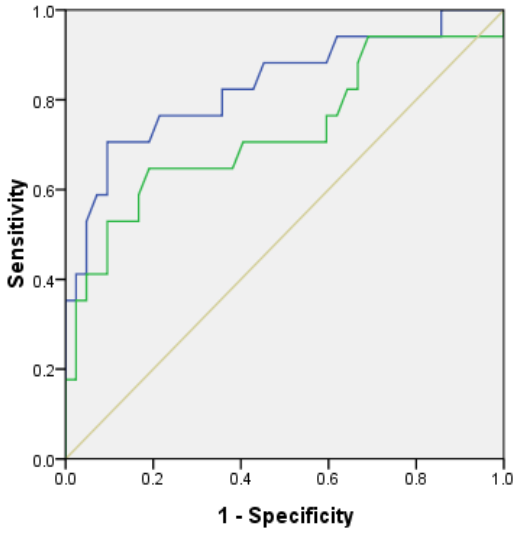



**Figure 02: ROC curve for AMACR expression**

The correlation analysis between Alpha-Methylacl-CoA Racemase (AMACR) expression levels and Gleason scores in prostate cancer revealed statistically significant associations. For Gleason score 6 (3+3), AMACR expression showed a Pearson's correlation coefficient (r) of 0.40, with a corresponding p-value of 0.032, indicating a significant positive correlation. Similarly, for Gleason score 7 (3+4), the correlation coefficient was 0.65, with a highly significant p-value of 0.001. Gleason score 7 (4+3) exhibited a correlation coefficient of 0.55, with a significant p-value of 0.007. The highest correlation was observed in cases with Gleason score 8-10, with a correlation coefficient of 0.70 and a p-value of <0.001, indicating a strong positive correlation between AMACR expression levels and higher Gleason grades.

**Table 06:** Correlation between Gleason score and AMACR expression level

| | **AMACR Expression Level** | **P-value** |
|---|---|---|
| Gleason Score | Pearson's r | |
| 6 (3+3) | 0.40 | 0.032 |
| 7 (3+4) | 0.65 | 0.001 |
| 7 (4+3) | 0.55 | 0.007 |
| 8-10 | 0.70 | <0.001 |

**Discussion**

The present study aimed to investigate the immunohistochemical expression of Alpha-Methylacl-CoA Racemase (AMACR) in prostate cancer tissues and its association with Gleason grade and other histomorphological parameters [14]. Our findings revealed differential expression of AMACR in prostate cancer tissues, with moderate staining intensity observed in the majority of cases. The expression of AMACR was positively correlated with higher Gleason grades, suggesting a potential role for AMACR as a biomarker of aggressive prostate cancer. Consistent with previous research, our study demonstrated that AMACR expression levels were significantly higher in prostate cancer tissues compared to benign prostatic hyperplasia (BPH) or normal prostate tissues [15,16]. This differential expression pattern underscores the diagnostic utility of AMACR immunohistochemistry in distinguishing between malignant and benign prostatic lesions, particularly in biopsy specimens with equivocal histological features.

Furthermore, our study revealed a significant association between AMACR expression and Gleason grade, with higher AMACR levels correlating with more advanced tumor grades. This finding aligns with previous studies reporting increased AMACR expression in high-grade prostate cancers and supports the notion that AMACR may serve as a prognostic marker for disease aggressiveness and

progression [17]. The observed correlation between AMACR expression and other histomorphological parameters, such as tumor stage, perineural invasion, extraprostatic extension, and seminal vesicle invasion, further underscores the potential clinical relevance of AMACR in risk stratification and treatment decision-making for prostate cancer patients [18]. However, it is essential to acknowledge that the association between AMACR expression and these histomorphological features may be influenced by various factors, including tumor heterogeneity and sample size limitations [19].

While our study provides valuable insights into the association between AMACR expression and clinicopathological parameters in prostate cancer, several limitations should be considered [20]. Firstly, the retrospective nature of the study may introduce selection bias and limit the generalizability of the findings. Additionally, the sample size of the study cohort was relatively modest, warranting validation in larger multicenter studies. Moreover, the use of immunohistochemistry as a semi-quantitative method for assessing AMACR expression may have inherent variability and subjectivity.

## Conclusion

It is concluded that AMACR expression exhibits a significant association with Gleason grade and other histomorphological parameters in prostate cancer, suggesting its potential as a prognostic biomarker. These findings suggest a potential correlation between Gleason score, PSA levels, and AMACR expression, highlighting the utility of AMACR as a biomarker in prostate cancer stratification and prognosis.

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