ORIGINAL ARTICLE

Role of miRNA-182 and 187 as Diagnostic and Prognostic Biomarkers for Prostate Cancer

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ABSTRACT

Background: *Prostate cancer (PC) remains a leading malignancy in men, necessitating the discovery of novel non-invasive biomarkers for early detection and monitoring.* ***Objectives:*** *This study evaluates the diagnostic and prognostic role of microRNAs (miRNA-182 and miRNA-187) in differentiating PC from benign prostatic hyperplasia (BPH).* ***Methodology:*** *A prospective observational study was conducted over 24 months at the Urology and Nephrology Center, Mansoura University, enrolling 110 male patients aged 50–80 years. Participants were categorized into three groups: newly diagnosed PC patients (n=40), BPH patients (n=30), and post-treatment PC patients (n=40). Clinical assessments, prostate-specific antigen (PSA) measurements, and quantitative real-time PCR (qRT-PCR) for miRNA-182 and miRNA-187 expression were performed.* ***Results:*** *miRNA-182 levels were significantly elevated in PC patients (median: 2.80, range: 1.18–6.36) compared to BPH patients (median: 1.65, range: 0.7–2.35, P < 0.049). Following treatment, miRNA-182 levels declined significantly (median: 0.78, range: 0.23–3.01, P = 0.049), paralleling PSA reduction. No significant differences in miRNA-182 levels were observed between PC patients with and without bone metastases. Conversely, miRNA-187 was undetectable in all studied samples, suggesting its limited role as a biomarker.* ***Conclusion:*** *miRNA-182 demonstrates potential as a diagnostic and prognostic biomarker for PC, showing elevated expression in cancerous states and a significant decline post-treatment. However, miRNA-187 appears non-contributory in this context. Further large-scale studies are required to support the findings of this study and explore their clinical utility in PC management.*

INTRODUCTION

Prostate cancer (PC) is the second most prevalent and fifth most aggressive malignancy among men worldwide. Its prevalence in men aged over 65 is approximately 60%, with adenocarcinomas accounting for over 95% of cases. The majority of these adenocarcinomas originate from acinar cells, while a smaller fraction arises from ductal cells. About 80% of prostate adenocarcinomas develop from luminal epithelial cells, or occasionally from basal epithelial cells, located in the peripheral regions of the prostate, which constitute over 70% of the organ's tissue [1,2,3].

Prostate cancer is often asymptomatic in the early stages, with advanced stages manifesting severe symptoms such as bone pain and renal failure. Diagnosis is primarily based on prostate-specific antigen (PSA) levels, digital rectal examination (DRE), and biopsy, with Gleason scoring (GS) and TNM staging for prognostic stratification and treatment planning. Advanced imaging techniques, including multiparametric MRI (mpMRI) and positron emission tomography (PET) scans, enhance detection and staging processes. Early-stage PC has an excellent prognosis, with a survival rate of up to 99% over 10 years, while metastatic disease is associated with poor outcomes and significant mortality [4,5].

Prostate cancer is characterized by considerable molecular heterogeneity, which contributes to its varied morbidity and mortality rates. Adenocarcinomas of acinar origin generally exhibit a more favorable prognosis compared to those originating from ductal cells. Approximately 80% of PC cases are confined to the prostate, and when detected at an early stage, patients with localized disease can expect a highly favorable outcome [6,7,8].

The management of PC is largely informed by PSA levels, Gleason score, and TNM staging. Low-risk cases may be managed through watchful waiting or active surveillance. For localized disease, definitive treatment options include radical prostatectomy (RP) and/or

radiotherapy, often accompanied by lymph node assessment. In cases of intermediate or high-risk disease, hormone therapy, RP, and radiotherapy remain the primary treatment modalities. Cryotherapy serves as an alternative to RP, while androgen deprivation therapy (ADT) is essential for high-risk or metastatic PC. Chemotherapy, particularly with taxanes, is employed in the management of advanced or recurrent disease [9, 10, 11].

Benign Prostatic Hyperplasia is a non-malignant enlargement of the prostate and can cause obstructive and irritating LUTS in older men, and its incidence depends on the age. Benign Prostatic Hyperplasia is a diagnosis of exclusion by ruling out all other possible causes [12].

MicroRNAs (miRNAs), small non-coding RNAs that regulate gene expression, play pivotal roles in the initiation, progression, and metastasis of PC. These molecules, which are detectable in urine, serum, and prostatic tissue, present promising potential as biomarkers for PC diagnosis and staging due to their stability and ease of extraction. Although more than 50 miRNAs have been implicated in PC, their expression is highly variable, reflecting the disease's molecular complexity [13, 14].

MicroRNAs can act as either oncogenes or tumor suppressors. Oncogenic miRNAs, such as miRNA-21, promote tumorigenesis by downregulating tumor suppressor genes, whereas tumor suppressor miRNAs, including miRNA-15a and miRNA-16, counteract oncogenes to inhibit cancer progression. The androgen receptor (AR) pathway, a crucial determinant in PC, is regulated by miRNAs, which significantly influence both disease progression and therapeutic resistance [15, 16,17].

Circulating miRNAs offer a non-invasive means for diagnosing PC. Elevated levels of specific miRNAs, such as miRNA-21 and miRNA-141, have been associated with more aggressive disease and poorer prognosis. miRNA-based therapeutic strategies, including miRNA mimics and antagomiRNAs, show significant promise in preclinical studies, heralding potential advancements in the diagnostic and therapeutic management of PC [18]. Notably, miRNA-182 acts as an oncogene, promoting cellular proliferation and invasion, while miRNA-187 exhibits a dual role, functioning as both an oncogene and a tumor suppressor depending on the cellular context, thus offering further opportunities for clinical application [19, 20, 21].

The aim of this study was to compare between treatment-naïve and post-treatment PC patients, ensuring a comprehensive assessment of miRNA expression dynamics.

METHODOLOGY

Study Design and Setting:

This study is a prospective observational study that was conducted over 24 months, from September 2022 to September 2024, at the Urology and Nephrology Center, Mansoura University, and its Outpatient Clinic.

Patient Selection and Grouping

A total of 110 male patients, aged between 50 and 80 years, were enrolled based on specific inclusion and exclusion criteria. Participants were divided into three groups:

- **PC Group (n=40):** Newly diagnosed PC patients before receiving any form of treatment (surgical, hormonal, or chemotherapy). Diagnosis was confirmed via histopathology following transrectal ultrasound (TRUS)-guided prostate biopsy.
- **BPH Group (n=30):** Patients diagnosed with BPH based on clinical evaluation, PSA levels, and histopathological confirmation.
- **Post-Treatment PC Group (n=40):** The same patients from the PC group after undergoing treatment, allowing for the evaluation of changes in miRNA expression post-intervention.

Clinical and Laboratory Assessments

Each patient underwent a thorough clinical assessment, including:

- **Medical history and demographic data collection:** Age, comorbidities (hypertension, diabetes, etc.), previous urological interventions, medication history, and family history of PC.
- **Physical examination:** General and systemic examination with a focus on DRE findings.
- **Laboratory investigations:**
  - Complete blood count (CBC)
  - Serum creatinine and kidney function tests
  - PSA levels using an electrochemiluminescence immunoassay
  - Quantification of miRNA-182 and miRNA-187 expression levels

Radiological and Histopathological Evaluation

All patients underwent imaging studies, including:

- **Pelvic ultrasound and TRUS:** To assess prostate volume and detect any suspicious lesions.
- **TRUS-guided prostate biopsy:** Performed on all suspected PC cases, obtaining at least 10–12 core samples for histopathological examination.
- **MRI Prostate (when indicated):** To assess local tumor invasion and guide biopsy in cases of PSA elevation without a definitive TRUS finding.

Molecular Analysis of miRNA Expression

Blood samples were obtained from every patient and control member for miRNA analysis:

- **Sample collection and processing:**
  - A total of 5 ml of venous blood was drawn from each patient on ethylene diamine tetra-acetic acid tubes (EDTA) tubes.
  - 2 ml were allocated for miRNA extraction, immediately stored at -80°C to prevent RNA degradation.
  - The remaining 3 ml was used for PSA measurement and other laboratory investigations.
- **miRNA Extraction and qRT-PCR Analysis:**
  - Total RNA, including miRNA, was extracted from plasma using the miRNeasy Serum/Plasma Kit (Qiagen) following the manufacturer's instructions.
  - Reverse transcription of miRNA was done by using the miRCURY LNA RT Kit (Qiagen) to synthesize complementary DNA (cDNA).
  - Quantification of miRNA-182 and miRNA-187 was conducted via real-time quantitative polymerase chain reaction (qRT-PCR) using the miRCURY LNA miRNA PCR Kit (Qiagen, Germany).
  - Internal control and normalization: miRNA-103a-3p was used as the endogenous reference gene for normalization, and relative gene expression levels were calculated using the $2^{-\Delta\Delta Ct}$ method.
- **Ethical Considerations**
- Ethical approval was obtained from the Institutional Review Board (IRB) of Mansoura Faculty of Medicine (Approval Code: MD.22.03. 614.R1). All procedures adhered to the ethical standards outlined in the Declaration of Helsinki. All participants singed an informed written consent before inclusion in the study, ensuring confidentiality and voluntary participation.

Statistical Analysis

Data analysis was conducted using SPSS version 26.0 (IBM, USA). Descriptive statistics were employed to summarize the demographic and clinical characteristics of the study population. For comparative analysis between groups, independent t-tests or Mann-Whitney U tests were used for continuous variables, depending on data distribution, while categorical variables were analyzed using Chi-square or Fisher's exact tests. Receiver Operating Characteristic (ROC) curve analysis was performed to assess the diagnostic accuracy of miRNA-182 and miRNA-187 in distinguishing prostate cancer (PC) from benign prostatic hyperplasia (BPH). Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated to evaluate their diagnostic performance. Additionally, multivariate logistic regression analysis was conducted to identify independent predictors of PC. A p-value of less than 0.05 was considered statistically significant in all analyses.

RESULTS

In our study seventy patients were included in the final analysis, comprising 40 patients diagnosed with PC and 30 patients with BPH. The mean age of patients in the PC group was 69.05 ± 5.97 years, while the control group had a mean age of 68.17 ± 5.37 years (P = 0.525), indicating no statistically significant difference in age distribution between the two groups.

Among patients with PC, the most prevalent Gleason score was 4+3=7, observed in 37.5% of cases (15 patients), reflecting a moderately aggressive malignancy. This was followed by a Gleason score of 4+4=8 in 27.5% of cases (11 patients), indicating a more aggressive tumor phenotype (**Table 1)**.

Table 1: Distribution of Gleason Score in Patients with PC

Gleason score	Number	%
4+3=7	15	37.5%
3+4=7	5	12.5%
3+3=6	4	10%
4+5=9	4	10%
4+4=8	11	27.5%
5+4=9	1	2.5%
Total	40	100%

Bone metastases were identified in 17.5% of patients with PC (7 patients), whereas the majority (82.5%, 33 patients) showed no evidence of bone involvement.

Histopathological assessment revealed that Grade III tumors were most frequently encountered, representing 35% of cases (14 patients), indicative of moderately aggressive disease. Grade IV tumors were present in 32.5% of patients (13 patients), suggesting a more advanced and poorly differentiated pathology (**Table 2)**.

Table 2: Histopathological Grading of Tumors in Patients with PC

Histopathological grade	Number	%
I	3	7.5%
II	5	12.5%
III	14	35%
IV	13	32.5%
V	5	12.5%
Total	40	100%

A significant elevation in miRNA-182 and PSA levels was observed in patients with PC compared to controls. The median miRNA-182 level in PC patients was 2.80 (range: 1.18–6.36), significantly higher than the control group's median of 1.65 (range: 0.7–2.35, P < 0.049). Similarly, PSA levels were markedly elevated in the PC group (median: 17.27, range: 3.23–75.9) compared to controls (median: 11.6, range: 1.8–28, P = 0.013).

Following six months of treatment, miRNA-182 levels demonstrated a significant decline, with the median decreasing from 2.80 (range: 1.18–6.36) to 0.78 (range: 0.23–3.01, P = 0.049). Similarly, PSA levels exhibited a pronounced reduction from a median of 17.27 (range: 3.23–75.9) to 0.18 (range: 0–1.93, P < 0.001), underscoring a robust therapeutic response (**Table 3)**.

Table 3: Comparison of miRNA-182 and PSA levels before and after treatment in patients with PC

	Before treatment (n = 40)	**After treatment (n = 40)**	**P**
miRNA-182	2.80 (1.18 - 6.36)	0.7786 (0.23 - 3.01)	0.049
PSA	17.27 (3.23 - 75.9)	0.18 (0 - 1.93)	<0.001*

Comparative analysis of miRNA-182 and PSA levels in PC patients with and without bone metastases revealed no statistically significant differences in either biomarker before or after treatment. Prior to treatment, median miRNA-182 levels were 3.06 in patients without bone metastases and 2.94 in those with bone metastases (P = 0.499). Similarly, post-treatment values were 0.7942 and 0.722, respectively (P = 0.444). PSA levels before and after treatment also demonstrated no significant difference between these two subgroups (**Table 4)**.

Table 4: Comparison of miRNA-182 and PSA levels based on bone metastasis in PC patients

	Bone metastasis		**P**
	No (n = 33)	**Yes (n = 7)**	
MiRNA-182 before treatment	3.06 (1.89 - 7.43)	2.94 (0.09 - 6.12)	0.499
MiRNA-182 after treatment	0.7942 (0.23 - 3.01)	0.722 (0.31 - 0.93)	0.444
PSA before treatment	18.23 (3.23 - 75.9)	16.3 (3.24 - 72.75)	0.631
PSA after treatment	0.345 (0 - 1.93)	0.062 (0.03 - 1.07)	0.310

Notably, miRNA-187 was undetectable in all studied samples, both before and after treatment, the same in the control group.

DISCUSSION

Prostate cancer remains a significant health concern in Egypt, ranking as the fourth most common malignancy in the country. Approximately 65% of diagnosed cases result in mortality, with nearly 9.7% of the egyptian male population over 55 years of age, placing them within the high-risk group for PC [22]. Given the limitations of traditional diagnostic tools such as PSA, increasing attention has been directed toward novel biomarkers, particularly miRNAs, for their potential role in PC detection and prognosis [23].

MicroRNAs are small non-coding RNA molecules implicated in cell differentiation, proliferation, and apoptosis. Their dysregulation has been observed in various cancers, functioning as either oncogenes or tumor suppressors[24]. A total of 2,675 mature human miRNAs have been identified, with complex interactions influencing gene expression in multiple pathways[25]. Due to their stability, ease of extraction, and accuracy in measurement, miRNAs have been proposed as promising non-invasive biomarkers for PC detection and monitoring[26]. However, molecular heterogeneity poses a challenge, as more than 50 miRNAs have been linked to PC development, with fluctuating expression levels [27].

Our study assessed the diagnostic value of miRNA-182 and miRNA-187 levels in distinguishing PC patients from those with BPH. Additionally, we evaluated their potential utility as biomarkers for monitoring treatment response. A total of 40 histopathologically confirmed PC patients were compared with 30 BPH controls, with blood samples analyzed for miRNA expression.

The age difference between the PC and BPH groups showed no statistical significance, reinforcing the notion that age alone is insufficient for distinguishing between malignant and benign conditions[28]. While age is a recognized risk factor, its clinical utility in risk stratification improves when combined with PSA levels and genetic predisposition[29]. Studies have shown that integrating biomarkers like the Prostate Health Index (PHI) and 4Kscore improves risk assessment beyond age alone [30].

The Gleason Score remains a cornerstone in PC prognosis, classifying tumors based on glandular differentiation[31]. Our findings indicated that most patients exhibited moderately aggressive cancers, with a subset displaying high-grade malignancies. The

integration of GS with molecular markers, including miRNA profiles, has been shown to enhance prognostic accuracy [26]. Elevated miRNA-182 expression has been linked with advanced GS and aggressive tumor behavior, highlighting its potential role in risk stratification [32].

Emerging evidence supports miRNA-182 as a crucial biomarker in PC. Our study revealed significantly higher miRNA-182 levels in PC patients compared to controls, consistent with previous reports demonstrating its association with poor prognosis and increased tumor invasiveness[33]. Elevated miRNA-182 has been linked to epithelial-mesenchymal transition (EMT), a critical process in cancer metastasis [34].

Bone metastasis significantly affects PC prognosis, often indicating advanced disease. While a subset of our cohort exhibited bone metastases, the majority did not, reflecting a population primarily in early-stage disease. Previous studies have identified bone as the most frequent metastatic site in PC, necessitating early detection strategies [35]. Although miRNA-182 expression did not significantly correlate with bone metastasis in our study, prior research has suggested its involvement in metastatic progression[36]. Variations in study methodologies, sample sizes, and tissue specificity of miRNA expression could account for discrepancies in findings.

Both PSA and miRNA-182 levels showed a significant decline post-treatment, reinforcing their role in monitoring therapeutic efficacy. While PSA exhibited a pronounced decrease, miRNA-182 reduction was less marked, potentially reflecting its role as a long-term molecular indicator rather than an immediate marker of tumor burden [37]. Research has demonstrated that miRNA-182 correlates with tumor aggressiveness and biochemical recurrence, underscoring its prognostic value [32].

The combination of PSA and miRNA-182 as biomarkers presents an opportunity for enhanced PC detection and management. While PSA remains the primary diagnostic tool, its limitations necessitate supplementary markers to improve specificity. miRNA-182, with its strong correlation to tumor progression, could complement PSA testing, particularly in cases with ambiguous PSA results [38].

On the other hand, miRNA-187 was not detected in our patients, either before or after treatment, and was also undetectable in the control group. This suggests that miRNA-187 may not be expressed or present at detectable levels in the studied samples under the given conditions.

Future studies need to focus on elucidating the molecular mechanism of miRNA-182's role in PC progression and validating its clinical utility in diverse populations. Additionally, integrating miRNA profiling into routine clinical workflows could facilitate more precise risk stratification and personalized treatment approaches. Expanding sample sizes and utilizing multicenter data will be critical for confirming miRNA-182's role in metastatic disease prediction and long-term prognosis.

CONCLUSION

Our findings highlight the potential of miRNA-182 as a non-invasive biomarker for PC diagnosis and treatment monitoring. While PSA remains a valuable marker, miRNA-182 offers deeper molecular insights into tumor biology and therapeutic response. Future research should aim to refine miRNA-based diagnostic panels to enhance predictive accuracy and clinical applicability in PC management.

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