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Original Article

Circulating Long Non-Coding RNA HOX Transcript Antisense RNA (HOTAIR) as a diagnostic and prognostic Biomarker in Prostate Cancer

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Abstract

Background: Prostate cancer (PCa) is considered the most prevalent non-skin cancer affecting males and remains controversial owing to the limited specificity of Prostate Specific Antigen (PSA) testing. HOX transcript antisense RNA (HOTAIR), as a long non-coding RNA, could serve as a significant biomarker for prognosis and prediction in cancer. This work aimed to evaluate the role of circulating LncRNA HOTAIR in cancer prostate detection and prediction of metastasis.

Methods: This case-control study enrolled 60 male patients (20 cases with begin prostatic hyperplasia (BPH) as control group, 20 cases with localized prostate cancer and 20 cases with metastatic prostate cancer). Circulating LncRNA HOTAIR was assessed in plasma by quantitative real-time polymerase chain reaction.

Results: Among patients with PSA levels in the 4–10 ng/mL gray zone, HOTAIR was significantly lower in benign cases (1.05 ± 0.15) than in localized cancer (3.32 ± 0.43, $p = 0.006$). Circulating HOTAIR levels were substantially higher in both localized (median: 3.7) and metastatic cancer (median: 14.38) compared to benign prostatic hyperplasia (BPH) (median: 1.0), and also significantly higher in metastatic versus localized cases ($p < 0.001$). Among patients with PSA levels in the 4–10 ng/mL gray zone, HOTAIR was significantly lower in benign cases (1.05 ± 1.15) than in localized cancer (3.32 ± 1.43, $p = 0.006$). HOTAIR levels positively correlated with total PSA, tumor grade, and Gleason score (all $p < 0.001$), and negatively with prostate volume and free/total PSA ratio (both $p < 0.001$). ROC analysis revealed combined HOTAIR and PSA achieved high accuracy for differentiating cancer (AUC = 0.997, sensitivity = 100%, specificity = 95%) and detecting metastasis (AUC = 0.994, sensitivity = 100%).

Conclusions: Plasma HOTAIR expression achieved good diagnostic accuracy in discrimination of metastatic PCa from localized PCa and benign conditions suggesting that plasma HOTAIR could act as a novel diagnostic as well as prognostic biomarker for PCa. HOTAIR combined with PSA showed a greater ability to discriminate between the presence and absence of cancer.

Keywords: Biomarker, HOTAIR, Metastasis, Prostate cancer.

INTRODUCTION

Prostate cancer (PCa) is one of the most prevalent cancers affecting males urinary and reproductive organs. As per the 2020 Global Cancer Statistical Report by the WHO International Agency for Research on Cancer, there were a lot of new prostate cancer cases worldwide in 2020, making up about 7.3% of all cancers. It's the third most common after breast and lung cancer [1]. The thing is, early symptoms are usually mild or hidden, so most cases end up getting diagnosed only after the cancer has already spread to other places [2]. And even though there have been a lot of advances in prostate cancer treatments, it still doesn't really improve the outcome for patients whose cancer has already spread [3].

As a malignancy marker for prostate cancer, prostate-specific antigen has its limitations. While PSA is useful for detecting prostate cancer early, it's not specific to the disease, meaning higher PSA levels can also occur due to benign conditions like begin prostatic hyperplasia (BPH) and prostatitis, leading to false positives and unnecessary biopsies. Therefore, research is focused on identifying new biomarkers that can improve cancer detection [4].

Research showed that long noncoding RNAs (lncRNAs) was linked with how tumors start and their spread. In prostate cancer, some lncRNAs have unusual expression levels, and researchers have found them in both cancer cell lines and patient samples. These lncRNAs might have important roles in how prostate cancer develops and spreads [5].

The HOX transcript antisense RNA (HOTAIR) is a type of long noncoding RNA found between genes, and it's pretty much linked to cancer spreading and a higher chance of the cancer coming back. HOTAIR works by acting on other genes, it can control how genes are turned on and off. It usually shuts down gene expression by bringing in stuff that changes the chromatin [6]. Overexpression of HOTAIR has a role in pathogenesis of many human diseases such as osteoarthritis, liver fibrosis, Parkinson disease, preeclampsia and cardiovascular diseases [7]. In most human cancers, HOTAIR is actually important for predicting how things might go for a patient and can even be used as a marker in the blood. This is seen a lot in cancers like breast, lung, cervical, prostate, liver, and even stomach cancer [8].

Li et al. [3] reported that HOTAIR can enhance the spread of prostate cancer by interacting with hepacam, a cell adhesion molecule that resembles immunoglobulins. Transmembrane glycoprotein, hepacam regulates cell adhesion and migration via its extracellular area.

We hypothesized that plasma HOTAIR expression could distinguish between metastatic and localized prostate cancer. Based on previous evidence indicating that HOTAIR is overexpressed in various cancers and is associated with tumor progression and metastasis, so circulating LncRNA HOTAIR may have roles in early detection, risk stratification, and prediction of prostate cancer progression. So, this work aimed to assess the role of circulating LncRNA HOTAIR in cancer prostate detection and prediction of metastasis.

METHODS

We conducted this case-control study on 60 patients who were selected from the General Surgery Department, Zagazig University Hospitals, Faculty of Human Medicine from April 2022 to November 2023. The study was approved by Zagazig university local ethics commission (ZU-IRB # 10256). From all patients participating in this study an informed consent was obtained. The sample size was calculated by assuming the mean of lncRNA HOTAIR was 1±0.2 vs 1.6±0.9 in PCa patient vs control. At 80% power and 95 % CI, the estimated sample was 60

subjects. The study follows the Helsinki Declaration, which is the World Medical Association's guideline of ethics for research involving human subjects.

This study enrolled 60 male patients who classified into three age-matched groups: 20 patients with BPH, 20 patients with localized prostate cancer, and 20 patients with metastatic prostate cancer. PCa was diagnosed by histopathological examination of biopsy samples and magnetic resonance imaging (MRI).

Individuals who underwent chemotherapy, radiotherapy or hormonal therapy prior to sample collection were not included in the study. Additionally, we excluded patients with other malignancies, patients have osteoarthritis, Parkinson disease or cardiovascular diseases.

All patients underwent thorough history taking and clinical assessment, including digital rectal examination and ultrasonography. Tumor staging was carried out following the American Joint Committee on Cancer (AJCC) criteria, utilizing the tumor, node, and metastasis (TNM) classification system [9]. Tissue samples, obtained either by needle biopsy or prostatectomy, were then graded using the Gleason Grading System, which assigns scores from 1 to 5 based on histological patterns [10].

Sample collection: Approximately four mL of venous blood were aseptically collected from all subjects by venipuncture and allocated as follows: two ml were delivered into a sterile tube containing gel separator for free and total PSA. Other two mL were delivered into an ethylene diamine tetra acetic acid (EDTA) vacutainer for extraction of lncRNA HOTAIR. Samples were processed within an hour from collection. The follow-up duration for the patients was 30 months.

PSA methodology: Total and free PSA determination was performed using the Electro Chemiluminescence method with the automated analyzer Cobas 6000-e602 (Roche Diagnostics, Germany). Assessment of PSA density was estimated as total PSA (ng/mL) divided by prostatic volume (mL) [11].

LncRNA HOTAIR expression assessment: Extraction of RNA: Total RNA was extracted from plasma samples utilizing “miRNeasy Mini kit” (Qiagen, Germany), complied with the instructions provided by the manufacturer.

Reverse transcription reaction (RT): RT was conducted utilizing “High-capacity cDNA Reverse Transcriptase Kit” (ThermoFisher scientific, USA) by implementing the protocols outlined by the manufacturer to produce cDNA.

Quantitative Real Time PCR: To amplify the cDNA, Applied Biosystems' qPCR SYBR® Green PCR Master Mix (Life Technologies, USA) was utilized. A real-time PCR plate was used for each reaction, which had a volume of 25 µL. The volume of each reaction included 12.5 µL of qPCR Green Master, 1 µL of forward and reverse primers, 9 µL of template cDNA, and 1.5 µL of PCR-grade water. This real-time polymerase chain reaction (PCR) was carried out on a US-based Applied Biosystems apparatus according to the following cycling protocol: a 10-minute activation step at 95°C, 40 cycles of denaturation for 15 seconds and annealing/extension for 1 minute. One cycle was conducted for the melting (dissociation) curve, beginning with 95ºC for 1 minute, followed by 60ºC for 30 seconds, and finally 95ºC for 30 seconds. Melting curve analysis was evaluated to confirm specificity. The 2-ŸΔΔCT technique was used to determine the relative expression levels of LncRNA HOTAIR [3].

The primers specific for LncRNA HOTAIR gene and housekeeping gene (GAPDH) were purchased as lyophilized reagents

(Invitrogen, Thermo Fisher Scientific, USA) (Table 1). The Nanodrop 2000 spectrophotometer (Thermo Fisher, Waltham, MA, USA) was used to measure both the quantity and quality of the RNA.

Statistical analysis

We used SPSS, an IBM Company, version 21, to do the statistical analysis on the data. The Chi-squared test assesses relationships between categorical variables. The Kruskal-Walli's test compares multiple groups when data are not normally distributed. ANOVA evaluates differences in group means. Post-hoc tests were applied for multiple comparisons (Dunn's test and Tukey HSD, respectively). ROC curves analyze diagnostic test performance. Kaplan–Meier curves estimate survival over time, with the log-rank test comparing groups. For all the above-mentioned statistical tests done, the threshold of significance was deemed when p value<0.05.

RESULTS

Age, smoking status, and lower urinary tract symptoms didn't differ significantly between the groups. While prostate volume, total PSA, and free/total PSA ratio showed significant differences among the groups (all $p < 0.001$). Circulating lncRNA HOTAIR levels, differed significantly between the groups ($p < 0.001$) (Table 2).

HOTAIR expression was substantially higher in localized cancer compared to BPH ($P1 < 0.001$), metastatic cancer compared to BPH ($P3 < 0.001$), and metastatic compared to localized cancer ($P2 < 0.001$) (Table 2).The mean lncRNA HOTAIR level in patients with PSA levels between 4 and 10 ng/mL (the gray zone) was significantly lower in benign cases (1.05 ± 1.15) compared to cases with localized prostate cancer (3.32 ± 1.43). Localized tumor group (n=6) and Benign group (n=4) ($p = 0.006$). (Table 2).

A significant positive correlation was revealed between plasma HOTAIR levels and total PSA ($r = 0.858$, $p < 0.001$), tumor grade ($r = 0.923$, $p < 0.001$), and Gleason score ($r = 0.882$, $p < 0.001$). On the other hand, plasma HOTAIR showed a significant negative correlation with prostate volume ($r = -0.585$, $p < 0.001$) and the free/total PSA ratio ($r = -0.638$, $p < 0.001$). Non-significant correlations were revealed between plasma HOTAIR and age ($r = 0.131$, $p = 0.319$) (Table 3).

Table 4, Figures 1, 2 show that for distinguishing prostate cancer from benign conditions, PSA (≥8.5 ng/mL) showed an AUC of 0.975, 95% sensitivity, and 85% specificity. HOTAIR (≥1.43 fold-change) had an AUC of 0.982, 100% sensitivity, and 90% specificity. Combined, they achieved an AUC of 0.997, with 100% sensitivity and NPV, 95% specificity, and 98.3% accuracy. For detecting metastatic prostate cancer, PSA (≥19.95 ng/mL) achieved an AUC of 0.938, with 90% sensitivity and 80% specificity. HOTAIR (≥5.07 fold-change) yielded an AUC of 0.975, with 90% sensitivity and specificity. Combining both reached an AUC of 0.994, with 100% sensitivity and NPV, 95% specificity, and 97.5% accuracy. Patients with low HOTAIR level (<5.07 fold-change) showed a better survival rate (100%) compared with (40%) for patients who had high lncRNA HOTAIR level (≥5.07 fold-change), with statistically significant difference ($p<0.001$) (Figure 3).

Table 1: Primer sequence for studied markers

Target	Forward primer	Reverse primer
LncRNA HOTAIR	5′GGCAAATGTCAGAGGGTT -3′	5′-GTGTAACAGGCAGGTGGA -3′
GAPDH	5′- CACCAGGGCTGCTTTTAACTC -3′	5′- GACAAGCTTCCCGTTCTCAG -3′

Table 2: Clinico-pathologic characteristics of studied patients (n=60).

Parameter	BPH N=20	Localized Cancer N=20	Metastatic cancer N=20	Test	P
Age (Years)	68.6±8.702	71.7±6.814	70.80±7.459	0.858	0.429
Smoking	10 (50.0%)	8 (40.0%)	11 (55.0%)	0.934	0.627
LUTS	18 (90.0%)	18 (90.0%)	17 (85.0%)	0.323	0.851
Prostate volume (cc)	58 [44-70]	32 [27-40]	34 [28-42]	40.33	<0.001*
P1<0.001*, P2=0.305, P3<0.001*					
Grading					
Grade 1	---	2 (10.0%)	0 (0.0%)	21.33	<0.001*
Grade 2	---	4 (20.0%)	0 (0.0%)		
Grade 3	---	6 (30.0%)	3 (15.0%)		
Grade 4	---	8 (40.0%)	4 (20.0%)		
Grade 5	---	0 (0.0%)	13 (65.0%)		
Gleason scores					
6(3+3)	---	7 (35.0%)	0 (0.0%)	105.75	<0.001*
7(3+4)	---	7 (35.0%)	1 (5.0%)		
7(4+3)	---	6 (30.0%)	2 (10.0%)		
8(4+4)	---	0 (0.0%)	2 (10.0%)		
8(5+3)	---	0 (0.0%)	2 (10.0%)		
9(4+5)	---	0 (0.0%)	1 (5.0%)		
9(5+4)	---	0 (0.0%)	12 (60.0%)		
Total PSA (ng/mL)	3.16 [1.1-10]	18 [8-20.5]	285 [18-1969]	46.77	<0.001*
P1<0.001*, P2<0.001*, P3<0.001*					
Free/total PSA ratio	30 [25-49]	10 [2-20]	9.5 [1-21]	39.55	<0.001*
P1<0.001*, P2=0.957, P3<0.001*					
HOTAIR (Fold change)	1 [0.82-1.2]	3.7 [1.7-5.3]	14.4 [4.3-19.6]	49.43	<0.001*
P1<0.001*, P2<0.001*, P3<0.001*					

Data was expressed as number (percentage), or mean ±SD, or Median [range].

LUTS lower urinary tract symptoms, PSA: Prostate specific antigen, HOTAIR: HOX antisense intergenic RNA.P_1 difference between groups BPH and localized; P_2 difference between groups localized and metastatic; P_3 difference between groups BPH and metastatic; *: Significant

Table 3: Correlation between plasma HOTAIR and the studied parameters in PCa patients (n=40).

Parameters	r	P
Age	0.131	0.319
Prostate volume	-0.585	<0.001*
Total PSA	0.858	<0.001*
Free/Total PSA ratio	-0.638	<0.001*
Grade	0.923	<0.001*
Gleason score	0.882	<0.001*

r: Spearman rank correlation coefficient, PSA: Prostate specific antigen, *: significant

Table 4: Performance of studied markers among the studied patients (n=60).

Cutoff	AUC	Sensitivity	Specificity	PPV	NPV	Accuracy
Differentiating prostate cancer from benign conditions						
PSA ≥8.5 ng/mL	0.975	95%	85%	92.7%	89.5%	91.7%
HOTAIR ≥1.43 fold-change	0.982	100%	90%	95.23%	100%	96.7%
Combined	0.997	100 %	95 %	97.6 %	100 %	98.3 %
Detection of Metastatic prostate cancer						
Total PSA ≥19.95 ng/mL	0.938	90%	80%	81.8%	88.9%	85%
HOTAIR ≥5.07 fold-change	0.975	90%	90%	90%	90%	90%
Combined	0.994	100%	95%	95.2%	100%	97.5%

AUC: area under curve, PPV: positive predictive value, NPV: negative predictive value, PSA: Prostate specific antigen, HOTAIR: HOX antisense intergenic RNA.

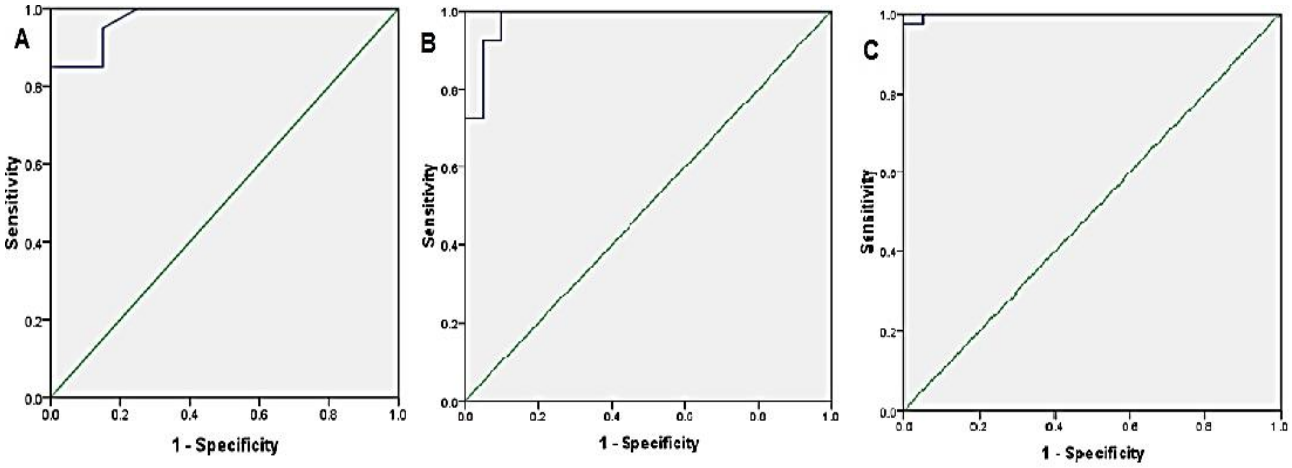

Figure 1: ROC curves of markers in Differentiating prostate cancer from benign conditions (A): Total PSA, (B): HOTAIR, (C): Combined

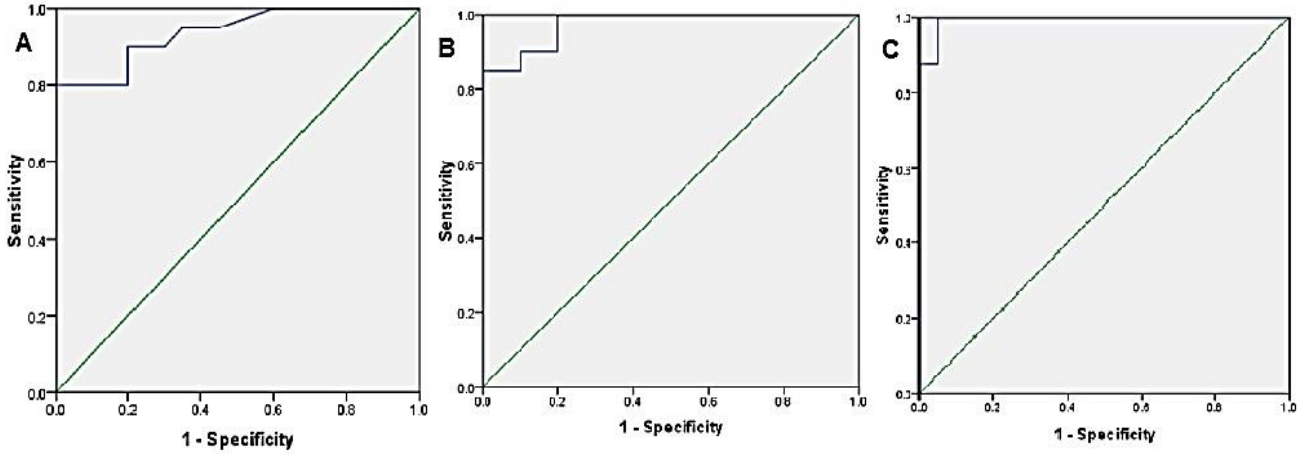

Figure 2: ROC curves of markers in detection of Metastatic prostate cancer. (A): Total PSA, (B): HOTAIR, (C): Combined

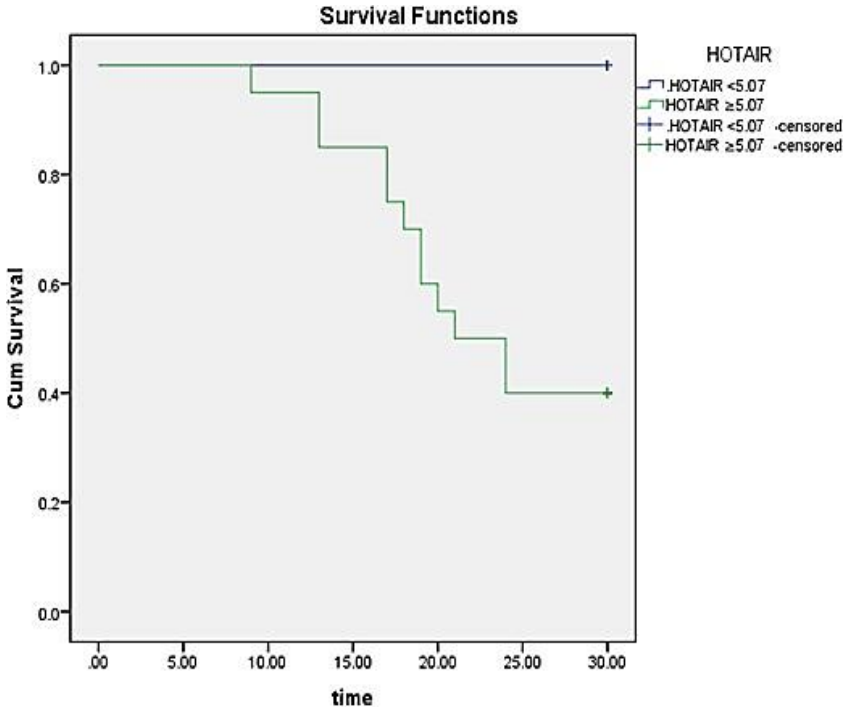

Figure 3: The Kaplan-Meier curve shows the survival rate of patients with different lncRNA HOTAIR levels.

DISCUSSION

Prostate cancer (PCa) remains the second most common malignancy among men worldwide, accounting for over 396,000 deaths and 1.46 million new cases in 2022. The incidence is projected to increase by approximately 79.1% by 2040. Regional variations exist, with the Middle East reporting an incidence of 10.50 per 100,000 person-years in 2020, but the rates in the Middle East and North Africa are steadily rising, possibly due to lifestyle and cultural changes [12].

The limited specificity of the PSA test has driven efforts to develop more accurate diagnostic tools. Recent advances include novel biomarkers that improve not only detection but also staging, assessment of tumor aggressiveness, and guiding therapy. These molecular diagnostics are incorporated into diagnostic algorithms, enhancing prostate cancer management throughout various stages [13].

The HOTAIR, a long non-coding RNA involved in chromatin remodeling and transcription regulation, has garnered attention due to its overexpression in multiple cancer types, including prostate cancer. It is a polyadenylated RNA composed of 2158 nucleotides with six exons, and its elevated expression has been linked to tumor progression and metastasis [14].

The primary aim of this work was to evaluate the diagnostic as well as the prognostic significance of plasma HOTAIR levels among prostate cancer patients. By analyzing its gene expression and correlating it with clinical and laboratory

findings, the study sought to determine the utility of HOTAIR as a biomarker.

The demographic data revealed no significant age differences among the groups, with mean ages around 68–71 years, aligning with previous studies indicating similar age distributions among prostate cancer patients [15-17].

Regarding tumor grading, most patients presented with high-grade tumors or late-stage disease, with Gleason scores predominantly between 6 and 9. The distribution indicated a tendency toward advanced disease, consistent with other reports showing late-stage presentations are common in similar cohorts [17]. Prostate volume was significantly larger in benign cases compared to cancer patients, corroborating with previous findings that prostate size tends to decrease as malignancy advances [15].

Serum PSA levels were markedly higher in prostate cancer patients, especially those with metastatic disease, while the free/total PSA ratio was significantly lower in malignant cases. These findings support the role of PSA parameters in differentiating prostate cancer from benign conditions, aligning with prior studies that report similar trends [17, 18]. ROC curve analysis identified a PSA cutoff of ≥8.5 ng/mL for prostate cancer diagnosis, demonstrating high sensitivity and specificity, which aligns with established thresholds used clinically. For detecting metastatic disease, a PSA level of ≥19.95 ng/mL was optimal, providing high diagnostic accuracy. These thresholds are comparable to those suggested by other studies, confirming PSA's utility in clinical staging.

This study revealed that HOTAIR expression was significantly higher in prostate cancer tissues, particularly in metastatic cases, compared to benign and localized tumors. These results agree with prior research indicating that HOTAIR is upregulated in metastatic prostate cancer and associated with poor clinical outcomes [19, 20]**.** Elevated HOTAIR levels have also been linked to tumor invasion, migration, and prognosis, likely through epigenetic mechanisms that promote metastasis [3, 21].

In this study, plasma HOTAIR levels positively correlated with PSA, tumor grade, and Gleason score, and negatively with prostate volume and free/total PSA ratio, indicating its potential as a biomarker reflecting tumor burden and aggressiveness. ROC analysis demonstrated that plasma HOTAIR had excellent diagnostic performance, with a cutoff of ≥1.43 yielding near-perfect sensitivity and high specificity for prostate cancer detection. For metastatic disease, a cutoff of ≥5.07 also achieved high accuracy. When combined with PSA levels, the diagnostic accuracy further improved, reaching near-perfect sensitivity and specificity, supporting the combined use of these markers for reliable detection. Meta-analyses of existing literature support these findings, showing that HOTAIR alone and in combination with other biomarkers have strong diagnostic capabilities, with combined approaches offering superior accuracy over individual tests [22].

Notably, in patients with PSA levels in the gray zone (4–10 ng/mL), HOTAIR demonstrated better discrimination between benign and malignant conditions, highlighting its potential in resolving ambiguous cases.

Further research involving a larger patient cohort is necessary to validate the role of HOTAIR as a diagnostic as well as a prognostic biomarker for prostate cancer, particularly in ambiguous or gray-zone cases. Additional studies should focus on

elucidating the relationship between HOTAIR expression in tumor cells and other prognostic factors. Exploring different molecular techniques, such as Western blot, restriction fragment length polymorphism, and tissue microarrays, could enhance the understanding and detection of HOTAIR. Moreover, comparative analyses between HOTAIR levels in blood and tumor tissues, as well as evaluations of HOTAIR alongside other molecular markers, are essential to establish its clinical utility and improve diagnostic accuracy in prostate cancer management.

This study has a few limitations that should be mentioned. First, the sample size was relatively small, and all patients were recruited from a single center, which may limit how well the findings can be applied to other populations. Also, the study included only male patients from one geographical area, so results might not be the same in different regions or more diverse groups. Another point is that we didn't include healthy controls—just patients with BPH, localized, or metastatic prostate cancer—so it's unclear how HOTAIR levels would compare in healthy individuals. Because the study was cross-sectional, we couldn't track changes in HOTAIR levels over time or see how they might relate to long-term outcomes or response to treatment.

Currently, our research does not account for variables such as comorbidities, medication use, or other factors that could influence circulating HOTAIR levels. Conditions like inflammatory diseases, metabolic disorders, or cardiovascular illnesses may alter HOTAIR. Additionally, medications such as anti-inflammatory agents or hormonal therapies particularly androgen deprivation therapy used in prostate cancer could impact HOTAIR expression, thereby affecting plasma levels independently of disease status. Finally, we only used one method (qPCR) for measuring HOTAIR and didn't compare it with other molecular techniques, which could add more reliability or new insights.

CONCLUSIONS

Plasma HOTAIR expression achieved good diagnostic accuracy in discrimination of metastatic PCa from localized PCa and benign conditions suggesting that plasma HOTAIR could act as a novel diagnostic as well as prognostic biomarker for PCa. HOTAIR combined with PSA showed a greater ability to discriminate between the presence and absence of cancer.

Conflict of Interest or financial disclosure: No potential conflict of interest to be reported by the authors.

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Figure legend

Figure 1: ROC curves of markers in Differentiating prostate cancer from benign conditions (A): Total PSA, (B): HOTAIR, (C): Combined.

Figure 2: ROC curves of markers in detection of Metastatic prostate cancer. (A): Total PSA, (B): HOTAIR, (C): Combined.

Figure 3: The Kaplan-Meier curve shows the survival rate of patients with different lncRNA HOTAIRlevels.

Citation

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