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Diagnosis and Prognosis Utility of microRNA-205 Expression in Prostate Carcinogenesis: Meta-Analysis and Bioinformatics Study

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ABSTRACT **Published Online: March 04, 2024**

Background: Prostate cancer (PCa) is a common disease that affects millions of men worldwide. Precise and non-invasive markers for diagnosing and prognosing PCa are vital to enhance patient management. MicroRNAs have been proposed as non-invasive biomarkers. We performed a meta-analysis and a bioinformatics study of miR-205 to give a full assessment of its diagnostic and prognostic relevance.

Materials and methods: We searched all published papers on miR-205 expression in PCa up to April 30, 2023 using PubMed, sciencedirect, Google Scolar, Web of Science. We used RevMan software to Meta-analyze the included literature. A bioinformatics investigation of genes and pathways that may be targets of the mature miR-205-5p impact was also performed.

Results: The pooled standardized mean difference of miR-205 differential expression in PCa compared to normal tissue, in primary and progressed cancer and hazard ratio were -1.58; $p<0.001$, -0.23; $p=0.06$ and 2.61; $p=0.002$ respectively. Bioinformatics analysis revealed that miR-205-5p may regulate YAP1 and the Hippo signaling pathway.

Conclusion: The current study found that miRNA-205 is downregulated in PCa and have a significant prognostic value. MiRNA-205 may have a role in prostate carcinogenesis via regulating YAP1 through the Hippo signaling pathway.

KEYWORDS: miR-205, prostate, differential expression, meta-analysis, bioinformatics

1. INTRODUCTION

Prostate cancer (PCa) is a common disease that affects millions of men worldwide, with a high incidence rate (1). Despite breakthroughs in early identification and treatment, PCa remains a substantial cause of death and a big challenge for the healthcare system, especially in advanced stages (2). Because PSA lacks specificity, it cannot detect PCa or predict its biochemical recurrence with sufficient accuracy (3,4). As a result, characterization of accurate and non-invasive diagnostic markers is crucial in enhancing patient outcomes by facilitating early detection and prognostic evaluation.

Non-coding microRNAs (miRs) have demonstrated promising results among moleculobiological markers (5).

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MiRs are short RNA molecules that modulate gene expression through binding to mRNA regions and lowering target gene expression post-transcriptionally, either by preventing translation or encouraging RNA breakdown (6). Changes in MiRs expression have been discovered in a range of malignancies, including PCa (5,7–11). MiRs have been proven to act as tumour suppressors or oncogenes based on the regulation of specific target gene (8). Furthermore, miRs expression patterns differentiate cancers based on clones and differentiation level, demonstrating that miRs play a role in cancer progression (8,12).

MiR-205 has been demonstrated to be often down-regulated, and this down-regulation has been linked to a worse prognosis in PCa (13–15). However, the overall utility of miR-205 as a diagnostic and prognostic biomarker for PCa is still unclear.

We conducted a meta-analysis of its differential expression between normal and malignant tissues, expression as the cancer develops, and hazard ratio in 21 PCa studies to give a thorough assessment of miR- 205 's diagnostic and prognostic significance in PCa. Our investigation sought to quantify the extent of differential expression of miR-205 in PCa compared to normal prostate tissue, and in primary versus advanced PCa tissue. Subsequently, we aimed to assess its comprehensive diagnostic utility as a PCa marker and its prognostic value by examining its predictive capacity for disease outcomes. Additionally, a bioinformatics analysis was conducted to explore the potential impact of mature miR-205-5p on genes and pathways.

2. MATERIALS AND METHODS

2.1. Search strategy

The study was performed following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (16). We conducted a comprehensive search for all published papers in both English and French languages pertaining to miR-205 expression in PCa up to April 30, 2023. We used PubMed**,** sciencedirect**,** Google Scolar, Web of Science and the keywords combination including ‘miRNA-205’ OR ‘miR-205’ OR ‘hsa-mir-205*’ OR ‘microRNA-205’ AND ‘prostate neoplasm’ OR ‘prostate tumor’ OR ‘prostate cancer’ OR ‘prostate adenocarcinoma’.

2.2. Selection criteria

The criteria for papers included in the current analysis are: 1) Related to miR-205 expression and PCa or survival analysis, 2) Cases are pathologically confirmed, 3) publications in English and French languages, 4) Studies including humans only, 5) The availability of the mean and standard deviation for miR-205 expression in PCa patients and controls, as well as the hazard ratio (HR) and its 95% confidence intervals (CIs), or enough raw data to compute them. If they were not available, we reached out to the authors and made efforts to acquire the papers. in case the author did not respond to our request, two authors extracted data independently from published graphical representations using the online WebPlotDigitizer tool.
(https://automeris.io/WebPlotDigitizer/) (17), For more precise findings, each extraction was repeated twice.

Certain categories of papers were excluded from the search: 1) studies involving cells or animals, 2) reviews, conference abstracts, expert opinion, case reports, or incomplete data. 3) Articles that were only provided as abstracts and did not include the entire text.

2.3. Data extraction

The information from eligible articles was extracted independently by two authors, and any discrepancies were resolved through consensus. This included details such as the first author's name, publication year, country, sample type, and size, test method, mean and standard deviation (SMD), the cut-off, the survival analysis, hazard ratio (HR) and 95% confidence intervals (CI), follow-up time of the article included in this analysis were collected.

2.4. *Quality assessment*

The standard Newcastle-Ottawa Scale (NOS) (18) was independently appraised by two authors. Discrepancies were resolved through discussion and consensus. This evaluation aimed to assess the quality of the included papers, utilizing three domains for case-control studies: a) Selection: Adequacy of the definition of cases; Representativeness of cases; Selection of controls and definition of controls. b) Comparability: Comparison of cases and controls based on design or analysis. c) Exposure: Ascertainment of exposure; Use of the same method of ascertainment for cases and controls; Non-response rate.

For cohort studies, the assessment covered the following domains: a) Selection: Representativeness of the intervention cohort; Selection of the non-intervention cohort; Ascertainment of intervention and demonstration that the outcome of interest was not present at the start of the study. b) Comparability: Comparison of cohorts based on design or analysis. c) Outcome: Assessment of the outcome; Adequacy of follow-up duration for outcomes to occur; Adequacy of follow-up of cohorts.

2.5. Statistical analysis

To conduct a meta-analysis of the included literature, Review Manager (RevMan) 5.4.1 software was employed. In instances where substantial heterogeneity was identified ($I2 > 50\%$ or $P < 0.05$), the random-effects model was applied; otherwise, the fixed-effects model was utilized. Sensitivity analysis was conducted by systematically removing one study at a time to scrutinize the source of heterogeneity and ensure result stability. Standardized mean difference (SMD) and 95% confidence intervals (CI) were used to evaluate the differential expression of miR-205 and its progression in PCa

considering potential variabilities in samples and measurement instruments across studies.

We utilized the hazard ratio (HR) along with its corresponding 95% confidence interval to evaluate the prognostic significance of miR-205. Additionally, a funnel plot was generated to visually inspect the potential presence of publication bias.

2.6. Bioinformatics analysis

We utilized three databases, namely Targetscan 7.2 (19), miRDB (20), and miRPathDB 2.0 (21), for predicting target genes. Genes present in all three databases were considered as the predicted target genes of miR-205-5p. The Venny 2.1 tool (https://bioinfogp.cnb.csic.es/tools/venny/ (22)) facilitated an intersection analysis. Subsequently, gene ontology (GO), Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichments, and protein-protein interaction (PPI) network analysis were conducted based on these predicted target genes of miR-205-5p to explore potential molecular mechanisms and pathways in prostate cancer (PCa). The GO enrichment (23) covered three categories: biological process (BP), cellular component (CC), and molecular function (MF), while the KEGG pathway (24) analyses were performed using ShinyGO v0.741: Gene Ontology (http://bioinformatics.sdstate.edu/go74/). In addition, the protein-protein interaction (PPI) network (https://string-db.org/) was analyzed for the retrieval of interacting genes. for a PPI network, the highest confidence of minimum required interaction score was of>0.9. The disconnected nodes in the network were hided. the strength of data is indicated by thick lines. Moreover , to extract hub of highly connected genes from the PPI network we used the plug-in of cytoHUBBA app in Cytoscape 3.7.0 software (25). UALCOULD (http://ualcan.path.uab.edu/index.html) (26) was employed to assess the differential expression levels and conduct survival analysis of miR-205-5p target genes in both PCa and non-tumor tissues. Additionally, the LinkedOmics online software (http://www.linkedomics.org/) (27) was utilized to determine Spearman's correlation between the expression levels of miR-205-5p and the potential predicted target genes.

3. RESULTS

3.1. Study Characteristics

The first search yielded 359 articles. Following a review of titles and abstracts, 46 articles were screened, with 12 being considered for meta-analysis. These articles were chosen after removing data that was irrelevant or incomplete. The research included 13 studies that compared miR-205 expression levels between PCa and normal samples, five that compared miR-205 expression levels between primary and progressed PCa, and four that evaluated the prognostic value of miR-205. The studies characteristics are listed in Tables 1 and 2. The search strategy is depicted in Figure 1.

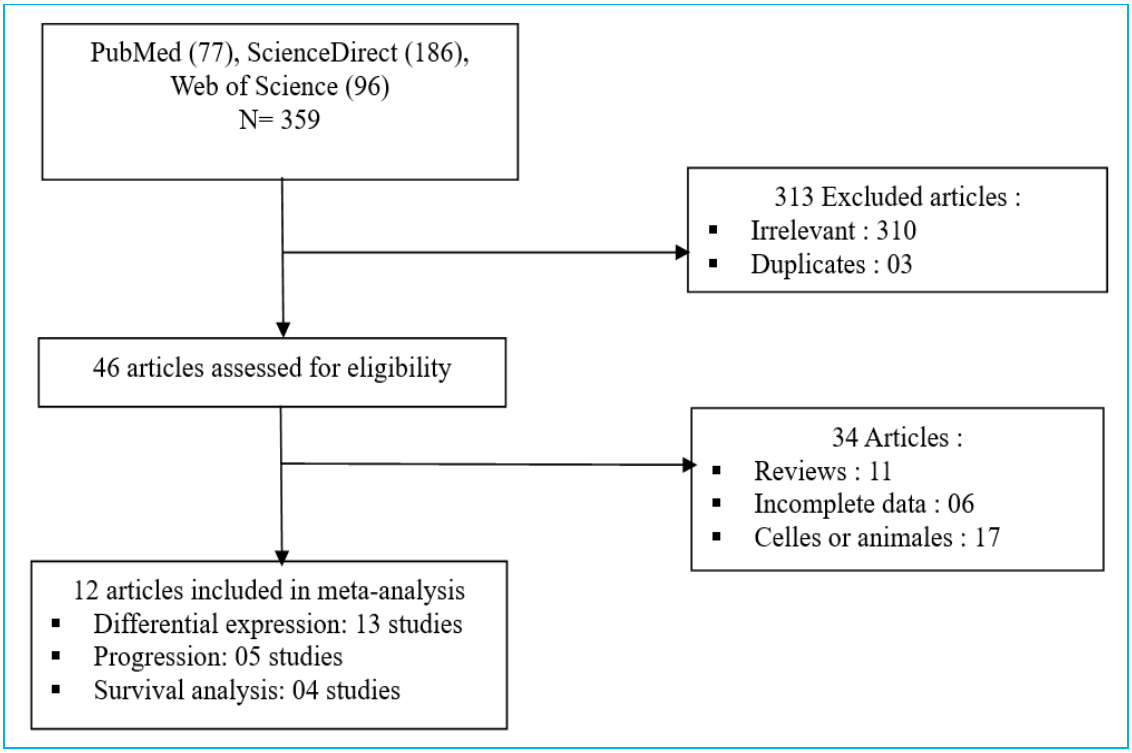

Figure 1. a PRISMA flow diagram of study selection process.

Table 1. Characteristics of studies included in the differential expression and progression meta-analysis.

First author	Year	Country	Sample type	Case/Control	Test method	p-value	Mean Case±SD	Mean Control±SD
Differential expression								
Rönnau 1	2021	Germany	Tissue	20/20	SL-RT-qPCR	p < 0.01	0.89±0.60	1.87±1.29
Rönnau 2	2021	Germany	Tissue	23/20	SL-RT-qPCR	p < 0.01	0.65±0.55	1.87±1.29
Zhang	2019	China	Tissue	30/30	q-PCR	p<0.01	1.92±1.04	5.43±1.51
X. Guo	2018	China	Serum	72/34	qRT-PCR	0.001	0.49±0.32	1.10±0.37
Ghorbanmehr	2019	Iran	Urine	17/28	qPCR	0.01	6.29±2.21	8.42±2.25
Li	2018	China	Tissue	18/18	RT-qPCR	P<0.01	0.28±0.15	0.77±0.23
Kalogirou	2013	Germany	Tissue	105/10	qRT-PCR	P<0.01	0.50±1.68	3.91±0.51
Srivastava	2013	Usa	Tissue	40/40	qRT-PCR	p<0.0001	0.63±0.65	1.85±1.18
Wang	2013	China	Tissue	15/18	qRT-PCR	P<0.01	0.05±0.05	0.22±0.11
Tsuchiyama	2013	Japan	Tissue	65/42	qRT-PCR	P < 0.01	0.028±0.011	1±0.01
Gandellini	2012	Italy	Tissue	18/18	qRT-PCR	P<0.01	0.29±0.44	0.77±0.48
Hagman 1	2013	Sweden	Tissue	22/25	qRT-PCR	P<0.01	1.04±0.63	1.57±0.65
Hagman 2	2013	Sweden	Tissue	14/25	qRT-PCR	p < 0.0001	0.35±0.23	1.57±0.65
					Progression			
X. Guo $_{Stage}$	2018	China	Serum	33/39	qRT-PCR	0.093	0.43±0.29	0.54±0.34
X. Guo $_{met}$	2018	China	Serum	34/38	qRT-PCR	0.012	0.55±0.26	0.44±0.36
X. Guo $_{Grade}$	2018	China	Serum	43/29	qRT-PCR	0.312	0.46±0.31	0.53±0.34
Hagman $_{met}$	2013	Sweden	Tissue	18/17	qRT-PCR	P = 0.004	0.40±0.35	0.90±0.55
Rönnau $_{Grade}$	2021	Germany	Tissue	23/20	SL-RT-qPCR	NA	0.66±0.55	0.90±0.61

SD: standard deviation
SL-RT-qPCR: stem-loop reverse transcriptase polymerase chain reaction
$_{met}$: metastasis

Table 2. Characteristics of studies included in the prognosis meta-analysis

Study	Year	Country	Sample type	Method	Cases high/low	Cut-off	Survival	HR (95% CI)	Analysis	Follow up
Nordby	2017	Norway	Tissue	ISH	245/220	Median	BF	1.70 (1.23–2.35)	Multivariate	192 months
Kalogirou 1	2013	Germany	Tissue	qRT-PCR	105*	Δct=0.75	GSM	6.88 (1.66-28.53)	Multivariate	150 months
Kalogirou 2	2013	Belgium	Tissue	qRT-PCR	78*	Δct=0.75	GSM	6.55 (1.29-33.10)	Multivariate	150 months
Hagman	2013	Sweden	Tissue	qRT-PCR	49*	Median	OS	2.33 (1.11–4.88)	NA	20 years

*High and low not provided separately
ISH : in situ hybridization
NA: not applicable

3.2. Literature quality assessment

The Newcastle–Ottawa Scale was applied to assess the methodological quality of the included studies, categorizing them into differential expression case-control studies, PCa progression case-control studies, and cohort studies (Table 3).

3.2.1. Differential Expression Case-Control Studies:

The NOS scores for these studies was between 6 and 8, with a mean score of 7. This suggests a generally high quality of methodological rigor in the included differential expression case-control studies.

3.2.2. PCa Progression Case-Control Studies:

The NOS scores for PCa progression case-control studies fell within the range of 7-8, with an average score of 7.2. This indicates a satisfactory level of methodological quality in the PCa progression case-control studies.

3.2.3. Cohort Studies:

Cohort studies obtained NOS scores between 6 and 8, resulting in an average score of 6,25. While the overall quality is good, there may be variations within this category.

3.2.4. Overall Quality Assessment Results:

Considering the aforementioned results, the overall quality of the included studies was deemed good. The mean NOS score for all studies, encompassing both case-control and cohort studies, was good. Importantly, all 21 studies were included in the ultimate analysis, indicating a consistent and robust approach to study inclusion.

Table 3: Quality assessment of included studies according to the Newcastle–Ottawa Scale.

Study ID		Selection	Comparability	Outcome or Exposure	Total score
Case-control studies					
Differential expression					
Rönnau_1	2021	***	**	**	7
Rönnau_2	2021	***	**	**	7
Zhang	2019	***	**	***	8
X. Guo	2018	***	**	**	7
Ghorbanmehr	2019	***	**	**	7
Li	2018	***	*	**	6
Kalogirou	2013	***	**	**	7
Srivastava	2013	***	**	***	8
Wang	2013	***	**	**	7
Tsuchiyama	2013	***	*	**	6
Gandellini	2012	***	**	**	7
Hagman 1	2013	***	**	**	7
Hagman 2	2013	***	**	**	7
Progression					
X. Guo $_{Stage}$	2018	***	**	**	7
X. Guo $_{met}$	2018	***	**	**	7
X. Guo $_{Grade}$	2018	***	**	**	7
Hagman $_{met}$	2013	***	**	***	8
Rönnau Grade	2021	***	**	**	7
Cohort studies					
Nordby	2017	***	**	**	7
Kalogirou 1	2013	***	*	**	6
Kalogirou 2	2013	***	*	**	6
Hagman	2013	***	*	**	6

3.3. Meta-Analysis

3.3.1. The differential expression of miR-205

Based on the expression level of miR-205, 12 studies from 10 article published from 2012 to 2021 with 680 patients were included in the meta-analysis (14,28–37). This latter revealed a SMD = -1.58 IC 95% = [-1.92, -1.23] p=0,00003, random-effects model (Figure 2).

Due to the significant heterogeneity that was observed, we performed a subgroup analysis based on both sample type and ethnicity. Mir-205 was found to be downregulated in all ethnic subgroups: Asian -1.92 95% CI = [-2.52, -1.33]; Caucasian -1.35 95% CI = [-1.82, -0.89] all p= 0.00001. It was also significantly underexpressed in tissues subgroup: -1.62 95% CI = [-2.03, -1.21] p≤0.00001 (Table 4).

This indicates a notable downregulation of miR-205 in PCa in comparison to normal prostate tissue. These findings provide support for the potential utility of miR-205 as a diagnostic biomarker in PCa.

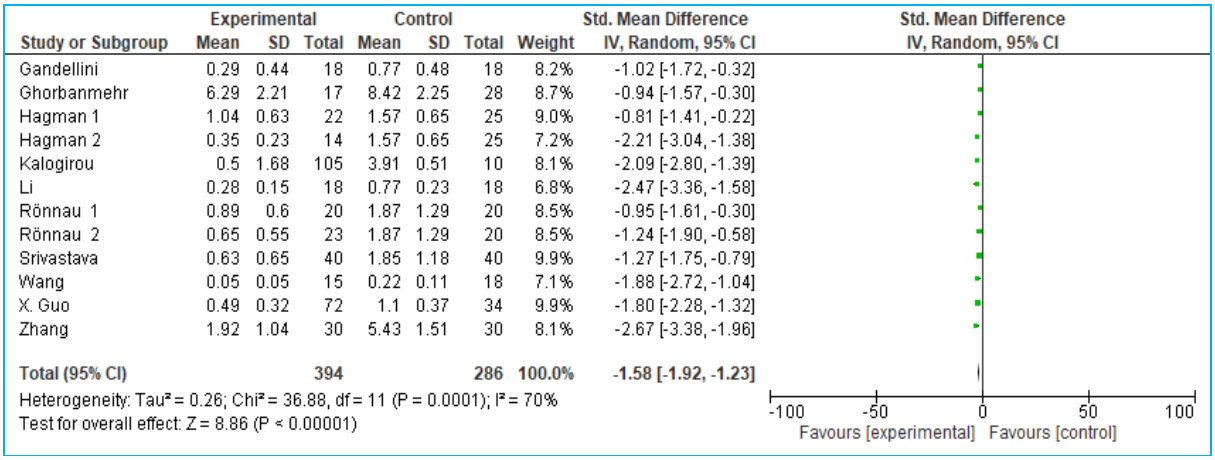

Figure 2. Random-effects SMD for the association of miR-205 expression level and PCa.

3.3.2. Progression of PCa

Based on the differential expression of miR-205 between naive localized primary cases, and aggressive metastasized cases, five studies from three articles published from 2013 to 2021 with 288 patients were included in this meta-analysis (14,28,30). The latter revealed a raw SMD of -0.23 95% CI = [-0.46, 0.01] p=0.06, random effects model (Figure 3). Stratified analysis showed that miR-205 is significantly underexpressed only when the disease progresses by grade -0.47 95% CI = [-0.81, -0.13] p=0.007.

This suggests that the lowering of miR-205 expression is not significant during progression from primary CaP to more advanced states but is significant only when considering disease grade (Table 4).

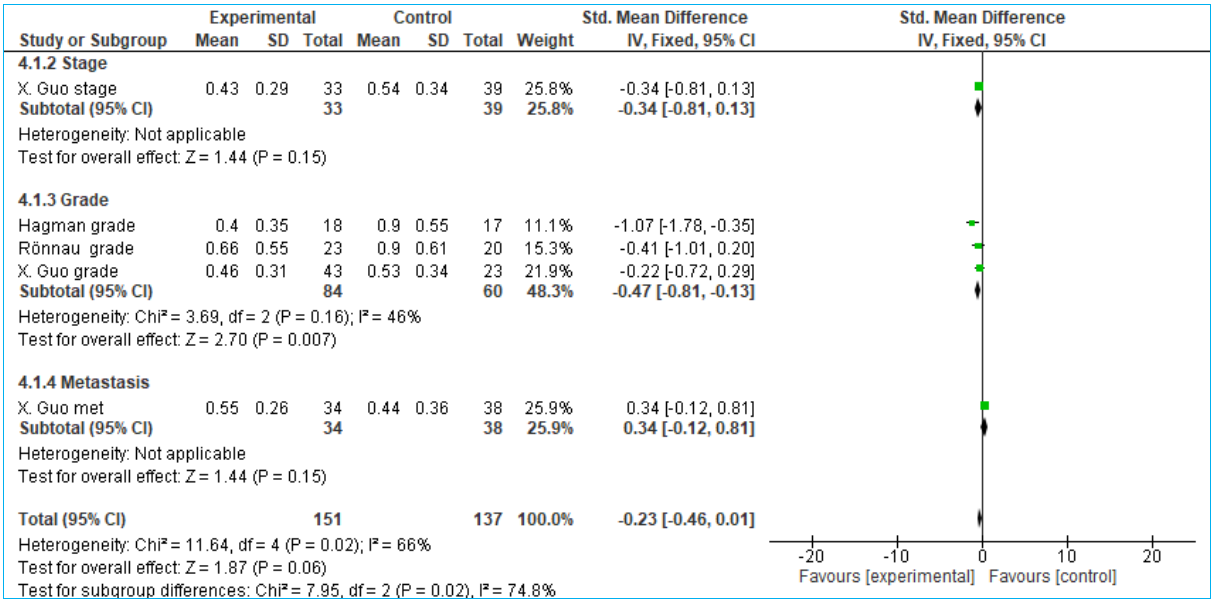

Figure 3. the SMD for the association of miR-205 expression level and PCa progression as per the Random-effects.

3.3.3. Prognosis value of miR-205

The miR-205 prognostic value was assessed using hazard ratio (HR) analysis in four studies from three articles from 2013 to 2017 (14,33,38). The random effect model was utilized to estimate the HR and 95% CI. There was a strong statistically significant association between the expression level of miR-205 and overall survival outcome HR = 2.61 95% CI = [1.43, 4.76] p = 0.002 (Figure 4 and Table 4).

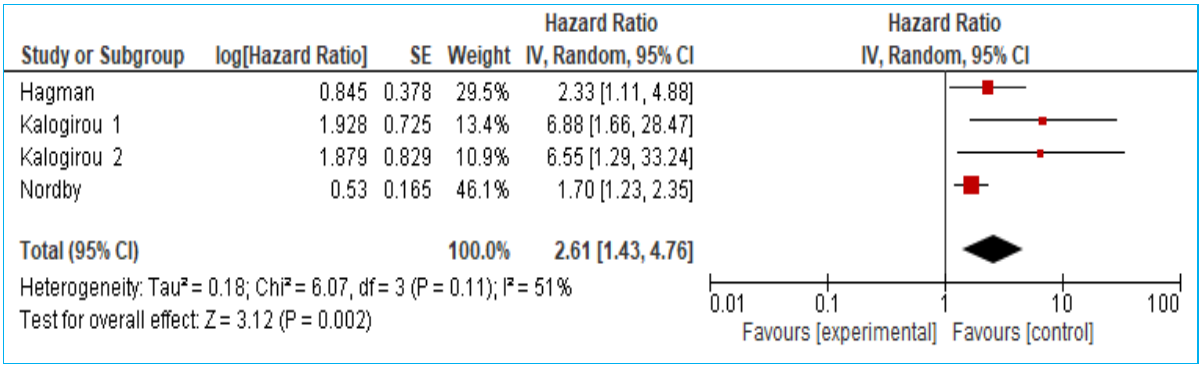

Figure 4. the forest plot of the relationship between miR-205 levels and survival outcomes in PCa.

Table 4. Results of the meta-analysis

					Hétérogénéité	
Comparaisons	**Groupes**	**OR/HR**	**95% CI**	**P value[a]**	**I^2(%)**	**P value**
Type d'échantillon	Globale	-1.58^{R}	[-1.92, -1.23]	0.00001	70	0.0001
	Sang	-1.80^{F}	[-2.28, -1.32]	0.00001	NA	NA
	Tissue	-1.62^{R}	[-2.03, -1.21]	0.00001	72	0.0002
	Urine	-0.94^{F}	[-1.57, -0.30]	0.004	NA	NA
Ethnicité	Globale	-1.58^{R}	[-1.92, -1.23]	0.00001	70	0.0001
	Asiatique	-1.92^{R}	[-2.52, -1.33]	0.00001	73	0.005
	Caucasien	-1.35^{R}	[-1.82, -0.89]	0.00001	63	0.02
	Africain américain	-1.27^{F}	[-1.75, -0.79]	0.00001	NA	NA
Progression	Globale	-0.23^{R}	[-0.46, 0.01]	0.06	66	0.02
	Stage	-0.34^{F}	[-0.81, 0.13]	0.15	NA	NA
	Grade	-0.47^{F}	[-0.81, -0.13]	0.007	46	0.16
	Métastase	0.34^{F}	[-0.12, 0.81]	0.15	NA	NA
Pronostic (HR)	Globale	2.61^{R}	[1.43, 4.76]	0.002	51	0.11

a: Z-test
OR$^{F/R}$: Odds Ratio$^{F: \text{ fixed effects model / R: random effects model}}$
HR: Hazard Ratio
NA: not applicable

3.4. Sensitivity and publication bias

The robustness of the results was assessed by conducting a sensitivity analysis, systematically excluding individual studies in a stepwise manner. This analysis revealed that the study conducted by Tsuchiyama (36) significantly impacted the stability of the results. Consequently, it was excluded from all subsequent analyses.

Furthermore, visual inspection of funnel plots revealed a symmetrical distribution, indicating the absence of significant publication bias in any of the performed meta-analyses. (Figure 5, Supplementary)

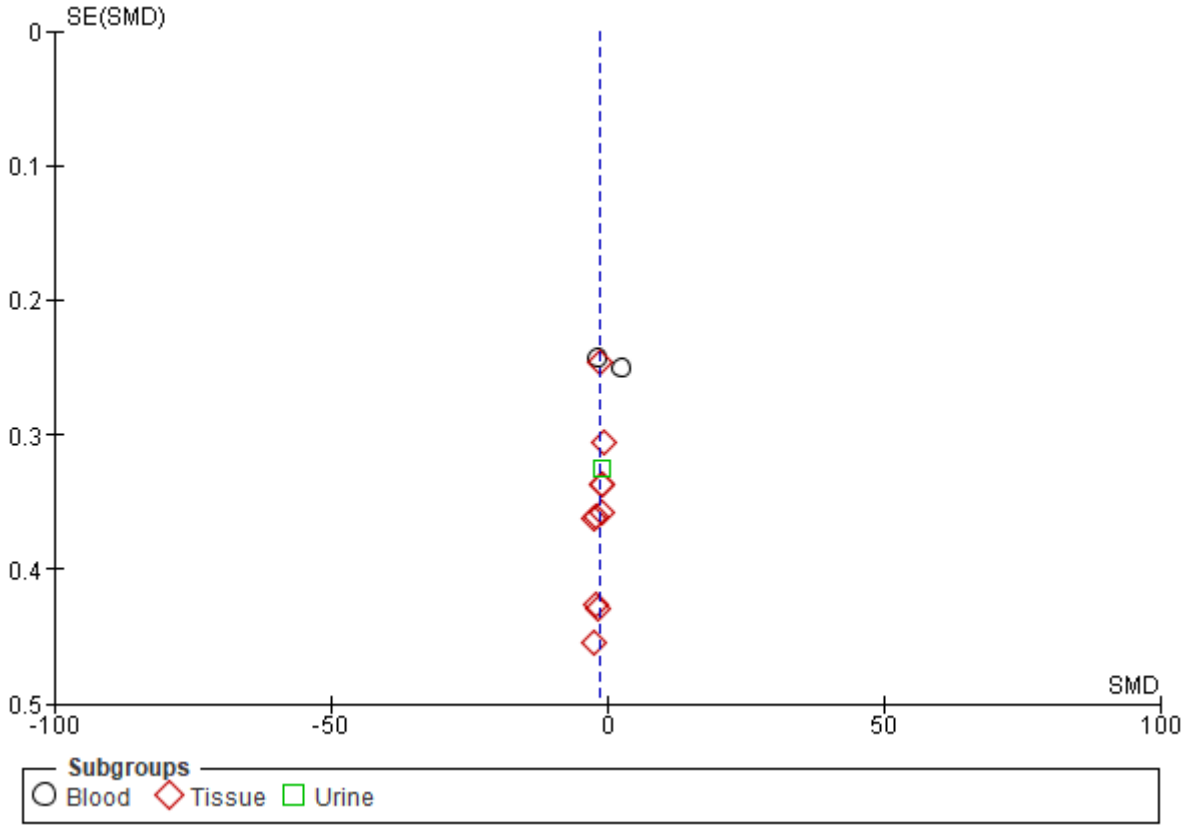

Figure 5. funnel plot of standardized mean difference in sample types subgroups in random effect.

3.5. Bioinformatics analysis

A total of 373 genes were predicted from miRDB, 6991 genes from miRPathDB, and 592 genes from Targetscan. Subsequently, 273 overlapping target genes were identified (Figure 6). Based on these overlapping target genes, the most significant and crucial enriched pathways from the Gene Ontology (GO) analysis were as follows: Tube morphogenesis (GO:0035239), Tube development (GO:0035295), and Neurogenesis (GO:0022008). These pathways ranked as the top three in the biological process category (Figure 7A). Moreover, the target genes demonstrated significant clustering in terms of molecular function, including DNA-binding transcription activator activity (GO:0001216), transcription factor binding (GO:0008134), and protein domain-specific binding (GO:0019904) (Figure 7B).

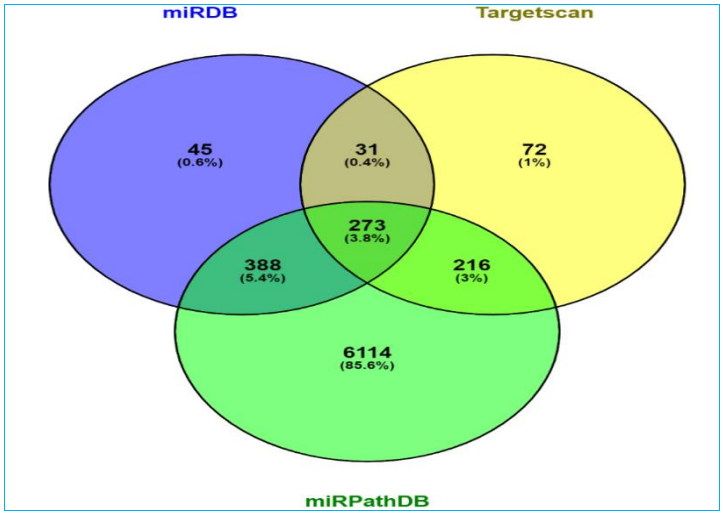

Figure 6. Venny diagram of overlapping miR-205-5p target genes.

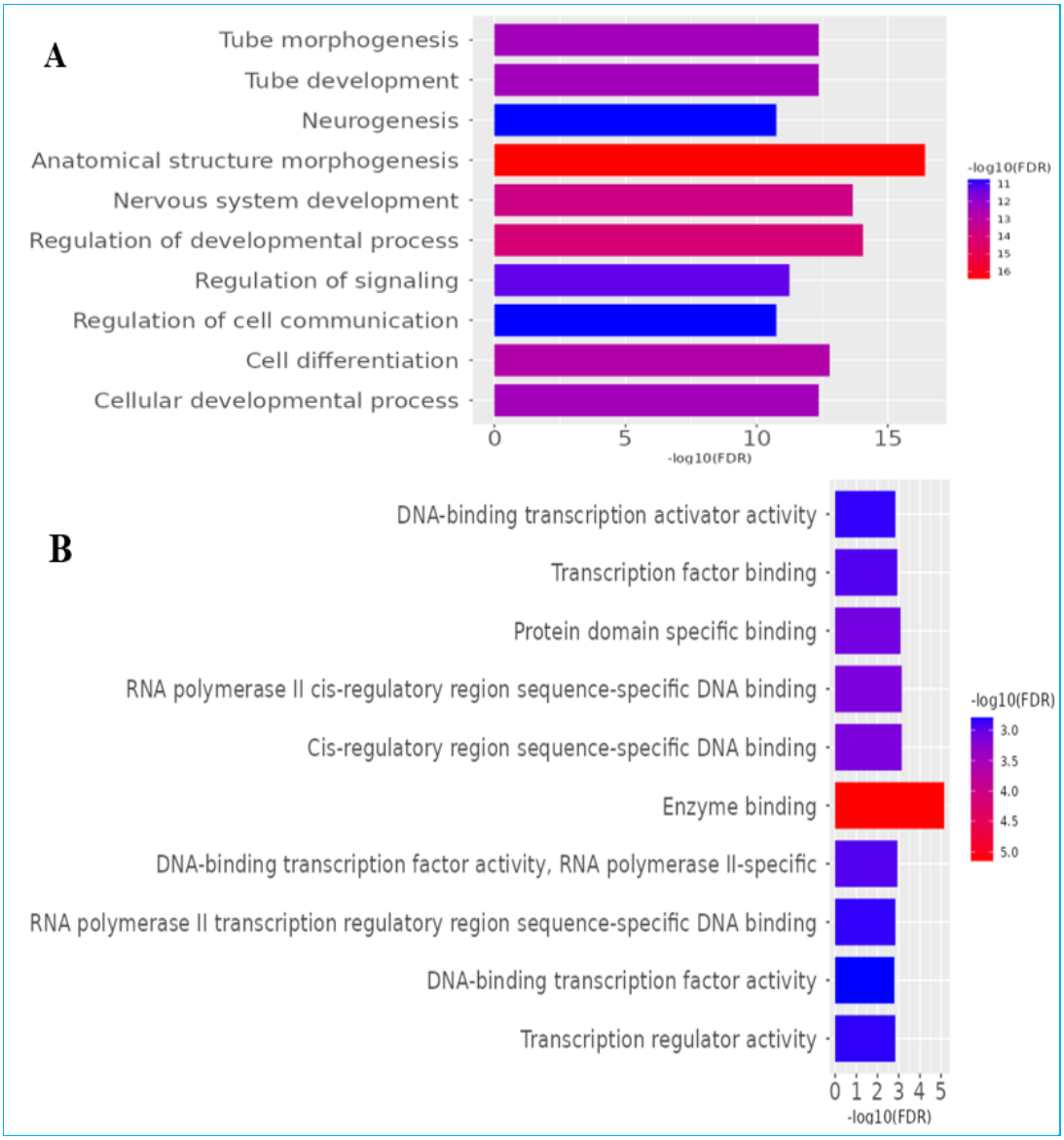

Figure 7. GO enrichment, A) Biological process; B) Molecular function.

With regard to cellular component, the top three terms proposed by these target genes were cell-cell junction (GO:0005911), anchoring junction (GO:0070161) and chromatin (GO:0000785) (Figure 8A). With respect to KEGG pathway analysis, the 10 significant signaling pathways for the target genes of miR-205-5p were Adherens junction, MicroRNAs in cancer, Hippo signaling pathway, Rap1 signaling pathway, Wnt signaling pathway, Axon guidance, Proteoglycans in cancer, MAPK signaling pathway, PI3K-Akt signaling pathway and Human papillomavirus infection (all P and Q values < 0.05) (Figure 8B). Additionally, molecular pathways and processes were computed to construct a Protein-Protein Interaction (PPI) network. The pertinent PPI network was visually represented, encompassing 273 nodes and 162 edges (Figure 9). Using cytoHUBBA, hub genes were extracted from the PPI network, with YAP1 and PTEN emerging as the most connected genes. These two genes are identified as potential target genes of miR-205-5p and may play crucial roles in the regulatory mechanisms within PCa.

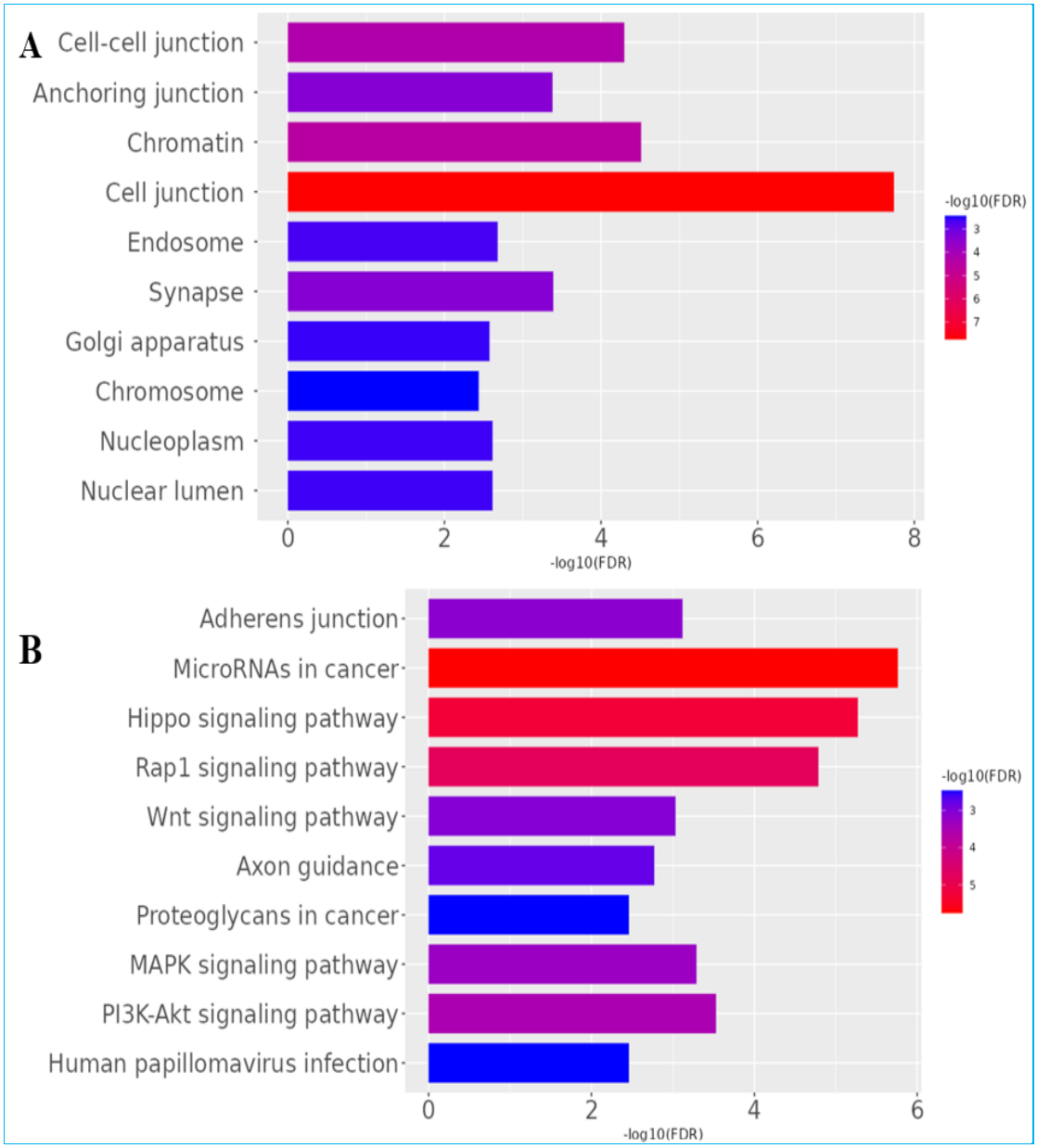

Figure 8. A) GO enrichment, Cellular component and B) KEGG.

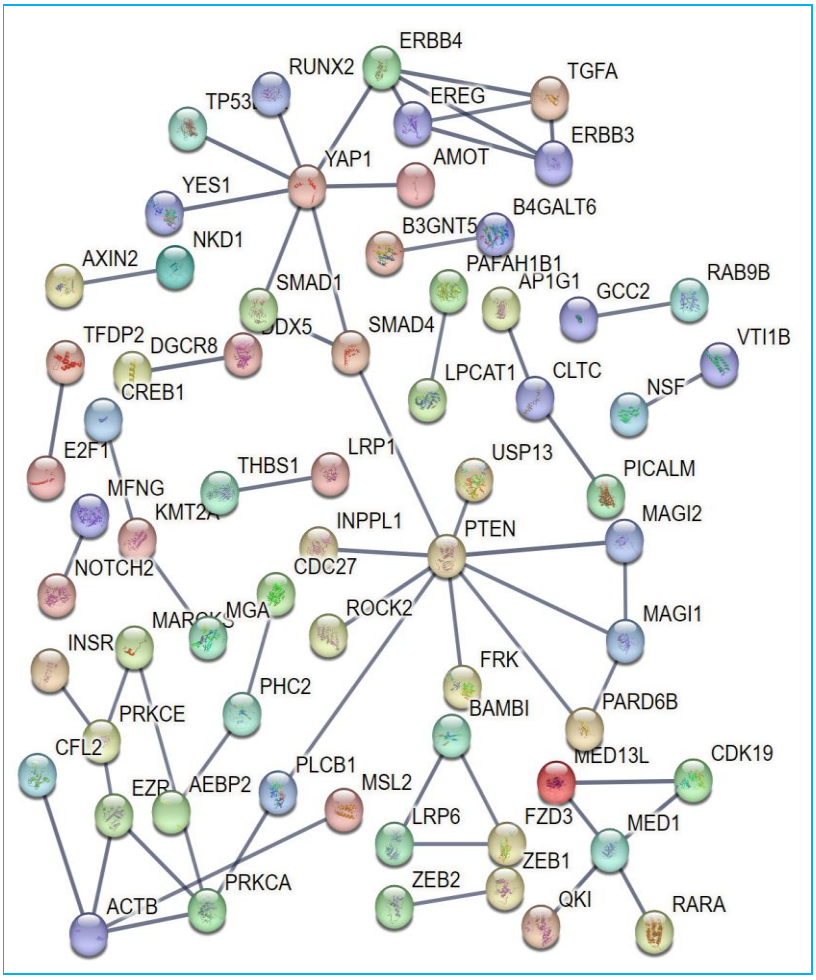

Figure 9. PPI network showing the highly connected genes.

3.6. The expression and prognostic validation of the miR-205-5p Target Genes

Two potential target genes of miR-205-5p associated with PCa (YAP1 and PTEN) were identified to be downregulated in PCa tissues when compared to controls additionally, miR-205-5p itself was found to be downregulated in PCa. This observation suggests that miR-205-5p may play a role in the regulation of these genes in PCa (Figure 10A, B). in the survival analysis, there was no significant association between the expression and overall survival ($p>0.05$) (Figure 11A, B).

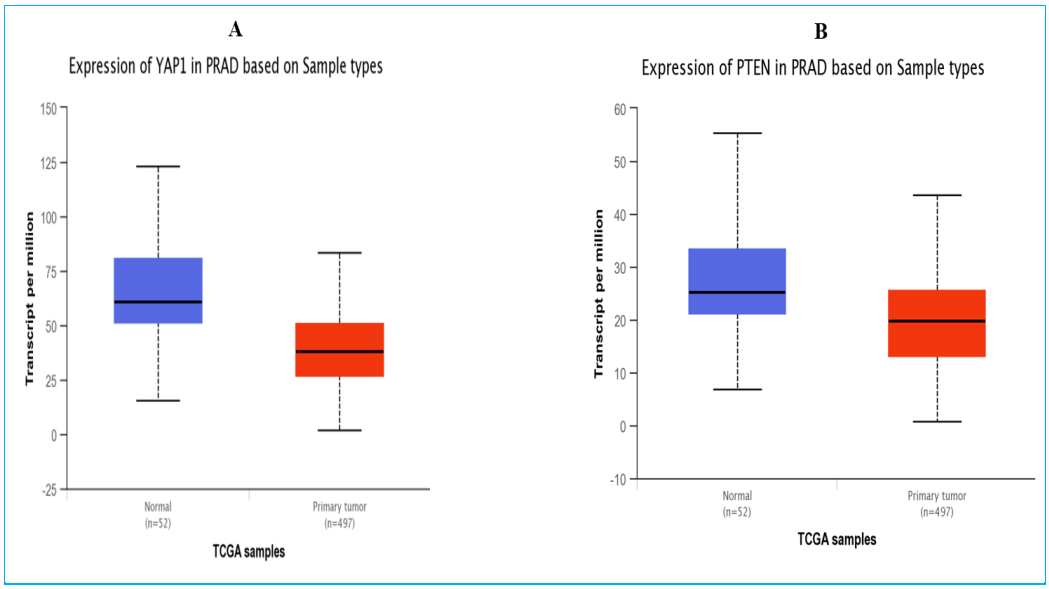

Figure 10. Validation of the miR-205-5p Target Genes, A) YAP1 expression, B) PTEN expression.

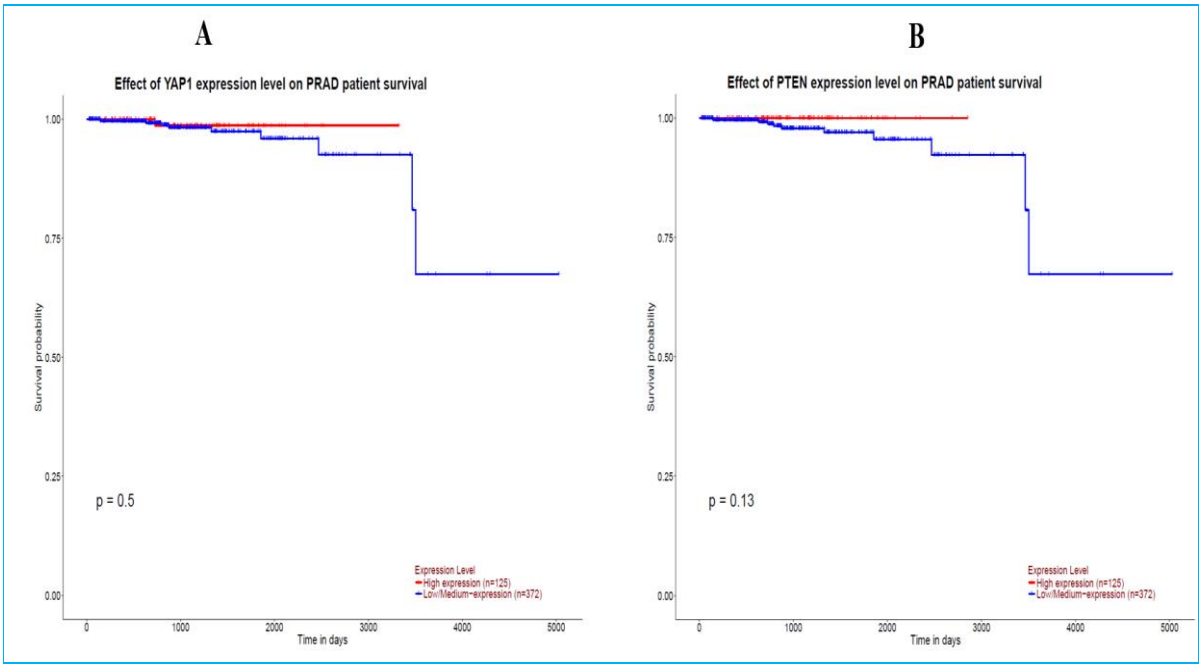

Figure 11. Validation of the miR-205-5p Target Genes, A) KM of YAP1, B) KM of PTEN, KM: Kaplan Meier.

Then Spearman's correlation analysis revealed that the of expression miR-205-5p have a positive significant correlation with YAP1(r=0.122, p<0.01) and no significant correlation with PTEN (r=-0.001, p>0.01) in PCa. (Figure 12A, B). These findings suggest that miR-205-5p may regulate the expression of YAP1 and potentially influencing the pathogenesis and progression of PCa.

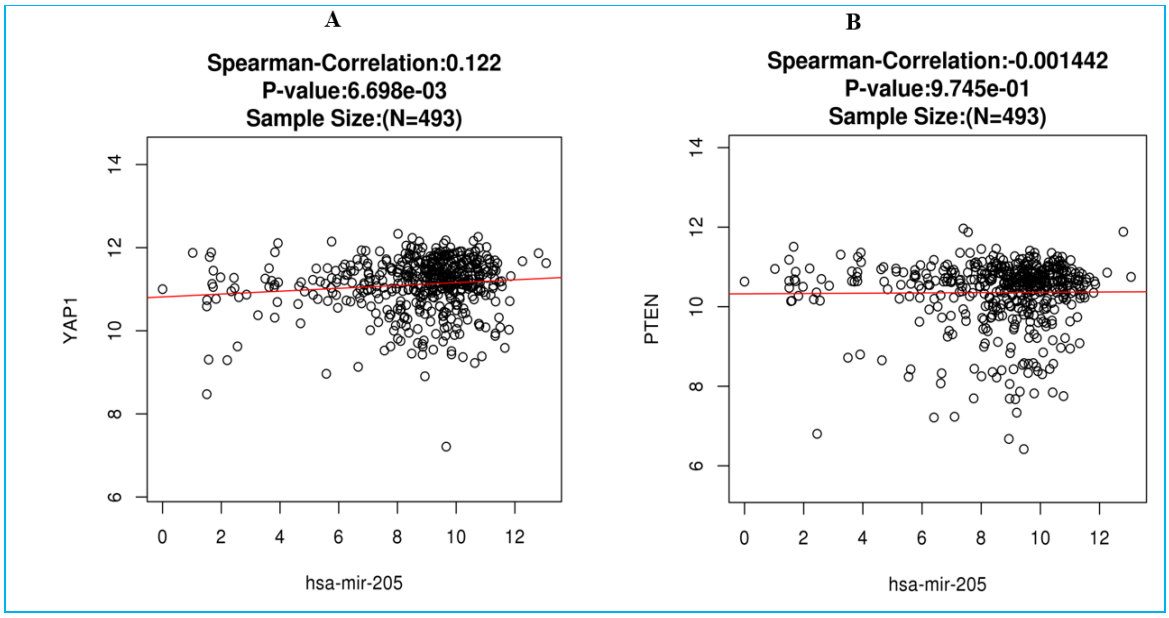

Figure 12. Validation of the miR-205-5p Target Genes, A) Spearman correlation between YAP1 and miR-205-5p, B) Spearman correlation between PTEN and miR-205-5p.

4. DISCUSSION

PCa is the most common type of cancer in males globally (1). The identification of molecular markers that can be used to diagnose and predict disease progression is critical for better understanding the disease behavior and designing successful therapeutic options. MicroRNAs have emerged as possible biomarkers in multiple tumors including PCa (5).

Although several studies have evaluated the expression of miR-205 in the PCa, to our knowledge only the meta-analysis of Sum et al. was conducted up to December 2019 on available published datasets with only one literature study included (39), but any was performed to draw evidence on the miR-205 expression in prognosis outcomes. Then, the current study aimed to comprehensively investigate the expression of miR-205 in PCa and its prognosis besides a bioinformatics analysis to validate findings.

The summary SMD of -1,58 p = 0,00001 in our meta-analysis demonstrated a significant downregulation of miR-205 expression in PCa. It was also significantly underexpressed in either all ethnicity subgroups and sample

type tissue subgroup ($p<0.05$). this was consistent with the results of others previous studies (40,41).

Additionally, differential expression in cancer progression of miR-205 between primary and advanced cases was not significant in crude analysis (SMD = -0.23; random effect, p = 0.06), however the decrease in its expression was associated with the grade subgroup (SMD = -0.47; p = 0.007), Same findings were reported by Wang et al and Kalogirou et al stating that the expression of miR-205 has been associated with the clinicopathological stage (35) and the cancer aggressiveness (33).

Nevertheless, the metastasis status has no significance in the current study which be linked to the limited number of included study, this was opposed by Sun and colleagues who demonstrated that miR-205 is downregulated in both PCa and more decreasing in bone metastatic PCa (39). The downregulation of miR-205 plays a crucial role in conferring resistance to apoptosis in advanced PCa (42).

Our meta-analysis found a statistically significant overall association between miR-205 expression and prognosis in PCa patients, HR = 2,61 p = 0,002. This finding shows that the underexpression of miR-205 could be used to predict the prognosis of CaP patients.

We used bioinformatics to identify the probable molecular pathways behind the association of miR-205 and PCa. Among the highly connected genes, YAP1 had a significant positive correlation with miR-205-5p expression (Spearman's correlation coefficient, r=0.122, p=0.01). KEGG pathway analysis suggested that miR-205 may exert its effects via multiple signaling pathways, mainly the Hippo signaling system. This pathway have previously been linked to PCa (43).

YAP1 is a recognized oncogene that is engaged in a variety of signaling pathways related to carcinogenesis and progression (44) and its activation has been linked to a variety of malignancies, including PCa, it is associated with a poor prognosis. The positive correlation between miR-205-5p and YAP1 expression reveals a potential regulatory relationship, which could implicate YAP1 in miR-205's downstream effects in PCa. YAP1 is an important transcriptional co-activator and downstream effector of the Hippo signaling system, which is involved in tumor growth, metastasis, and apoptosis (45,46).

Our bioinformatics findings shed light on the probable mechanisms behind the relation between miR-205 and PCa. The positive correlation with YAP1 expression, as well as the involvement of the Hippo signaling pathway suggest that miR-205 may be involved in contributing to PCa development and progression.

Overall, the miR-205 emerge as a promising candidate for early detection and prognostic evaluation of CaP. its potential as a non-invasive biomarker offers new perspectives for disease screening and management.

It is important to recognize some limitations in this study. First, the heterogeneity seen in the miR-205 expression analysis can be ascribed to a variety of factors, including differences in sample sources, and patient characteristics between the included studies, implying that these findings should be interpreted with caution. Second, the small number of progression and prognosis eligible studies included in this meta-analysis may restrict the generalizability of our findings. Third, while the majority of control subjects were appropriately chosen to meet criteria for case-control study design, particularly cancer-free status, some of them had benign hyperplasia prostate, which could be a selection bias because those participants are strongly suspected of developing PCa. Fourth, there were not enough studies on the American African ethnic group to consider a subgroup analysis. Fifth, because the databases were only asked to list publications authored in English and French, other high-quality research may be missing. Lastly, it should not overshadow the significance of risk factors and mistakenly provide patients with a sense of false reassurance, also, it is crucial to underscore that this miR holds no current clinical implications, and consequently, routine investigations into it are not advisable.

5. CONCLUSION

In summary, the current study demonstrated that miR-205 is downregulated in CaP and it has a potential prognostic relevance. Furthermore, miR-205 may be involved in the carcinogenesis and the evolution of CaP by regulating the YAP1 gene via the Hippo signaling system. More research is needed to validate these findings and determine the precise role of miR-205 in PCa.

Authors' Contributions

H.G. and A.D. conceived and designed this study. H.G. and M.E. were responsible for collection of data and performing the statistical analysis and article preparation. A.A and A.D. were responsible for checking the data. All authors were responsible for drafting the article, read and approved the final version.

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Availability of data:

The authors confirm that the data supporting the findings can be found within the article. The supplementary file is available upon request.

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