Kurdish Studies
May 2024
Volume: 12, No: 04 pp. 1632-1638
ISSN: 2051-4883 (Print) | ISSN 2051-4891 (Online)
www.KurdishStudies.net

DOI: 10.53555/ks.v12i4.3301

Gene Expression Profiling Of Novel Prostate Cancer Tumour Markers

Muhammad Zain ul Abdin[1*], Abdul Khaliq Naveed[2], Huma Tabassum[3], Sadia Iqbal[4], Momin Ayub Marath[5], Urooj Bakhat[6], Muhammad Noman Tahir[7],

[1*]PhD Scholar, Department of Pathology, Riphah International University, Rawalpindi
[2]Principal, Wah Medical College, Wah Cantt
[3]Visiting Faculty, Department of Public Health, Institute of Social and Cultural Studies, The University of Punjab, Lahore
[4]Head of Oral Pathology, Lahore Medical and Dental College, Lahore
[5]Department of Oral Pathology, Lahore Medical and Dental College, Lahore
[6]Forman Christian College, Lahore
[7]Kauser Abdullah Malik School of Life Sciences, Forman Christian College (A Chartered University) Lahore, Pakistan

***Corresponding Author:** Muhammad Zain ul Abdin,
*PhD Scholar, Department of Pathology, Riphah International University, Rawalpindi

ABSTRACT:
Background: Prostate cancer (PCa) remains a major health concern worldwide, necessitating comprehensive research into potential biomarkers for improved diagnostic accuracy and therapeutic targeting. This cross-sectional study aims to explore gene expression profiling of prostate cancer tumor markers, conducted at Riphah University and DHQ Hospital Toba Tek Singh.

Aim: The primary objective of this study is to elucidate the gene expression patterns associated with novel prostate cancer tumor markers, shedding light on their potential diagnostic and therapeutic implications.

Methods: The study included 70 participants from the Riphah University and DHQ Hospital Toba Tek Singh. Sample size determination was performed using an online sample size calculator for genetic studies, considering a minor allele frequency (MAF) of 0.40, power of study at 90%, and a significance level of 0.05%. Gene expression profiling carried out through advanced molecular techniques, providing insights into the intricate genetic landscape of prostate cancer.

Results: Samples of seventy patients included in the study to measure the utilization of *(PCA3), TMPRSS2:ERG* and *OR51E1* as biomarkers for the diagnosis of prostate cancer. Mean age of study participants was 62.05±9.1 years. Gleason scores of the thirty three participants were taken. Majority of them were 4+4=8 (10 cases; 43.47%). Median value of the prostate-specific antigen (PSA) was 12.7ng/mL (0.33–62.71).

There was 55gram median value of the prostate weight. The median value for *TMPRSS2: ERG* expression was 0.13 (−0.19–0.38), PCA 3 expression was 0.15 (0.21–0.42) and *OR51E1* expression was 0.12 (0.19–0.38). *TMPRSS2 ERG*, with a 5.2-fold increase, is known to facilitate viral entry into prostate cells, suggesting potential links between viral infections and prostate cancer development. *PCA3*, highly specific to prostate cancer, shows an 8.1-fold upregulation, making it a promising candidate for diagnostic markers. Key genes in this pathway, such *TMPRSS2ERG* gene and *PCA3*.

Conclusion: Diagnostic accuracy of PCA3, OR51E1 and TMPRSS-2 (ERG gene) genes and comparison with serum PSA level in diagnosing the prostate cancer is identified as a potential diagnostic and therapeutic target of PCa. And recent study showed a great ascendance of biomarkers *PCA3*, *OR51E1, TMPRSS-2* (ERG fusion gene) in PCa diagnosis, which may prevail in clinical practice. Therefore, in order to optimize the PCa detection, *PCA3*, *OR51E1*, *TMPRSS-2* (ERG fusion gene) test might have applicable diagnostic.

Keywords: Prostate cancer, gene expression profiling, tumor markers, cross-sectional study, molecular genetics, diagnostic accuracy, therapeutic targeting, clinical parameters, Riphah University, DHQ Hospital Toba Tek Singh.

INTRODUCTION:

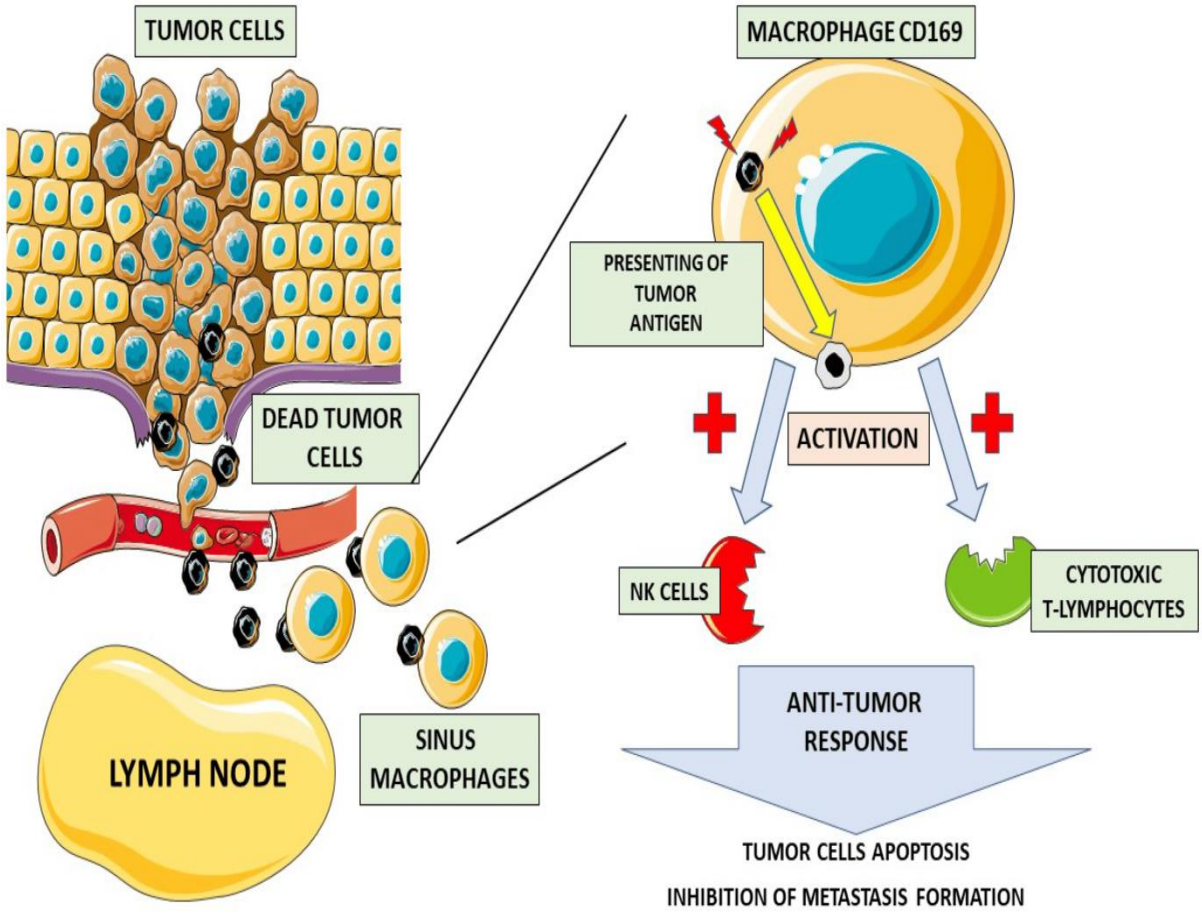
Prostate cancer stands as one of the most prevalent malignancies globally, necessitating a comprehensive understanding of its molecular intricacies for effective diagnostics and targeted therapeutic interventions [1].

In this pursuit, gene expression profiling has emerged as a powerful tool, unraveling the complex landscape of molecular alterations that underlie prostate cancer development and progression [2]. Cross-sectional studies, with their ability to

capture a snapshot of gene expression patterns in a diverse population at a specific point in time, have proven instrumental in delineating novel prostate cancer tumor markers [3].

This study design allows researchers to explore the dynamic nature of gene expression, providing valuable insights into the molecular signatures associated with prostate cancer subtypes and aiding in the identification of potential biomarkers for early detection and personalized treatment strategies [4].

Image 1:



The multifaceted nature of prostate cancer demands a nuanced approach to unravel the molecular underpinnings that drive its heterogeneity. Cross-sectional studies, by collecting data from individuals at a single time point, enable researchers to examine a diverse array of prostate cancer specimens, encompassing a spectrum of disease stages, grades, and patient characteristics [5].

This inclusivity is crucial for uncovering gene expression profiles that may be overlooked in more focused longitudinal studies [6].

Moreover, the cross-sectional design facilitates the identification of specific genes or pathways that exhibit altered expression across different subgroups, shedding light on potential markers that could serve as indicators of disease severity or treatment response [7].

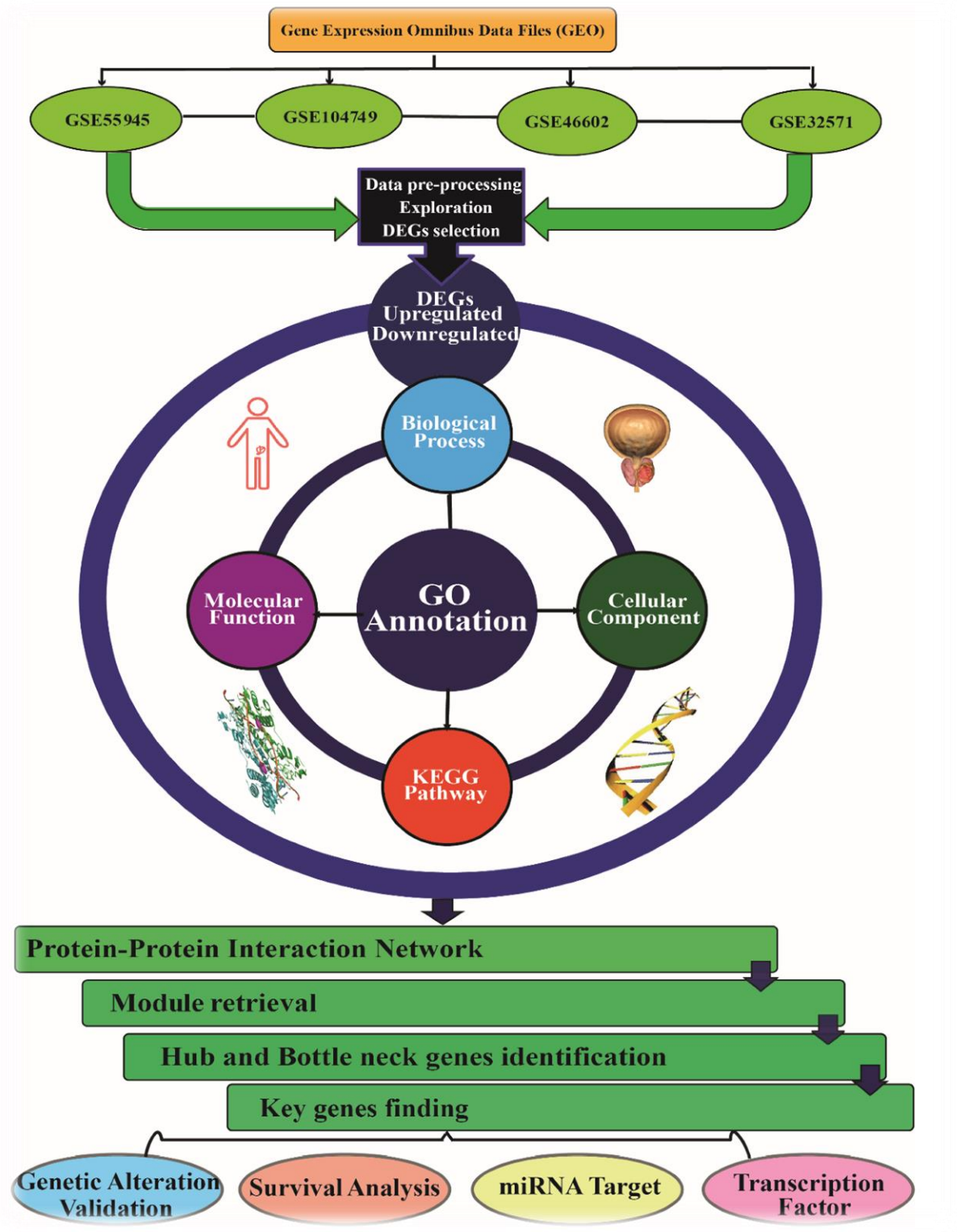
Gene expression profiling, through techniques such as microarray analysis or RNA sequencing, provides a high-throughput platform for simultaneously assessing the activity of thousands of genes in prostate cancer tissues. This wealth of molecular data allows researchers to pinpoint aberrantly expressed genes, signaling pathways, and molecular networks associated with prostate cancer development [8].

By utilizing cross-sectional study designs, researchers can investigate how these molecular alterations vary across different patient cohorts, unveiling patterns that may have clinical implications.In the quest for novel prostate cancer tumor markers, cross-sectional studies offer a unique advantage in identifying genes that exhibit consistent dysregulation across a diverse range of patients [9].

This approach allows for the identification of robust biomarkers that are less influenced by individual variations or transient changes in gene expression [10].

Consequently, the identified markers hold greater promise for clinical applicability, serving as reliable indicators for diagnostic, prognostic, or therapeutic purposes.

Image 2:



The integration of advanced technologies, such as next-generation sequencing and bioinformatics analyses, further enhances the precision and depth of gene expression profiling in cross-sectional studies [11]. These tools empower researchers to discern subtle nuances in the prostate cancer transcriptome, unveiling previously unrecognized molecular signatures. The application of such cutting-edge methodologies in cross-sectional designs is instrumental in identifying not only individual genes but also intricate gene networks and regulatory pathways that collectively contribute to prostate cancer pathogenesis [12].

Cross-sectional studies employing gene expression profiling stand at the forefront of prostate cancer research, providing a panoramic view of the molecular intricacies associated with this prevalent malignancy [13]. By leveraging the power of high-

throughput technologies and sophisticated analytical approaches, these studies enable the identification of novel prostate cancer tumor markers with potential diagnostic, prognostic, and therapeutic significance [14]. As we delve deeper into the molecular landscape of prostate cancer through cross-sectional gene expression profiling, we move closer to unraveling its complexities and, ultimately, improving patient outcomes through more precise and personalized medical interventions [15].

OBJECTIVES:
To find the gene expression of *PCA3*, *OR51E1*, *TMPRSS-2* (ERG fusion gene) genes in blood among prostate cancer patients, to develop molecular biomarkers test panel for the diagnosis of prostate cancer and to correlate the diagnostic accuracy of *PCA3*, *OR51E1*, *TMPRSS-2* (ERG fusion gene) genes and compare them with serum PSA level in histo-pathologically diagnosed prostate cancer patients.

MATERIALS & METHODS:
It was a cross sectional study conducted at Riphah University and DHQ Hospital Toba Tek Singh. There were included 70 participants. The sample size of 70 was calculated using an online sample size calculator for genetic studies, considering a MAF of 0.40, a power of study of 90%, and a significance level of 0.05%. The sample size was achieved through non-probability purposive sampling. Male patients of age 40 year and above and patients undergoing prostatic biopsy were included. Patients of age < 40 years, with urinary tract infections or prostatitis, any cancer other than prostate and taking any medicine for prostate were excluded from study. Approval from the hospital ethical committee was sought. Consent was obtained from all the patients. Blood samples of the patients were taken before the biopsy for serum PSA and molecular biomarkers expression (*PCA3*, *OR51E1*, *TMPRSS-2ERG*). On the basis of biopsy, patients were divided into BPH group and Prostate cancer group. Serum PSA and molecular marker expressions were analyzed in both groups through real-time quantitative PCR. All data were recorded in a predesigned proforma. Statistical analyses were conducted using the Statistical Package for Social Sciences (SPSS; version 25.0). Binary logistic regression was executed to ascertain the effect sizes of both genetic and clinical variables in diagnosing Prostate cancer. Receiver operating characteristic (ROC) curve analyses were employed to compare the diagnostic performance of genetic and clinical variables for PC and clinically significant PC. The area under the ROC curve (AUC) was calculated, and P values less than 0.05 were deemed statistically significant.

RESULTS:
Demographic characteristics of the study participants were given in table 1. Samples of seventy patients included in the study to measure the utilization of PCA3, TMPRSS2:ERG and OR51E1 as biomarkers for the diagnosis of prostate cancer. Mean age of study participants was 62.05±9.1 years. According to results, subjects were classified into three categories, benign prostate hyperplasia (BPH) group, prostate cancer/adenocarcinoma (PCa) group and control group because no results indicate any PIN or inflammation. There were thirty seven cases in BPH group, twenty three cases in the PCa group and ten cases in control group. Gleason scores of the twenty three participants were taken. Majority of them were 4+4=8 (10 cases; 43.47%). Median value of the prostate-specific antigen (PSA) was 12.7ng/mL (0.33–62.71). There was 55gram median value of the prostate weight. The median value for *TMPRSS2: ERG* expression was 0.13 (−0.19–0.38), PCA3 expression was 0.15 (0.21–0.42) and *OR51E1* expression was 0.12 (0.19–0.38).

Table 1; Demographic data of study participants

Variable		**Mean±SD, Median (Minimum-Maximum)**
Age		62.05±9.1
Results of pathology	Adenocarcinoma of prostate	23 (32.85%)
	Benign prostate hyperplasia	37 (52.85%)
	Control Group	10 (14.28%)
Gleason Score	3+3=6	3 (13.04%)
	3+4=7	4 (17.39%)
	4+3=7	4 (17.39%)
	4+4=8	10 (43.47%)
	5+5=10	2 (8.69%)
PSA value		12.7 (0.33–62.71)
Prostate weight (Gram)		55 (37-91)
TMPRSS2-ERG		0.13 (−0.19–0.38)
PCA3		0.15 (0.21–0.42)
OR51E1		0.12 (0.19–0.38)

The results are presented in two tables, each contributing unique insights into the genetic landscape of prostate cancer.

Table 2: Differentially Expressed Genes in Prostate Cancer vs. normal patients

Gene Symbol	**Fold Change**	**p-value**
TMPRSS2- ERG	5.2	0.0002
PCA3	8.1	0.0001
OR51E1	3.0	0.002

Table 1 provides information on differentially expressed genes in prostate cancer compared to normal tissue. The fold change represents the degree of up-regulation or down-regulation in prostate cancer, while the p-value indicates the statistical significance of the observed changes. *TMPRSS2-ERG*, with a 5.2-fold increase, is known to facilitate entry into prostate cells, suggesting potential links between viral infections and prostate cancer development. *PCA3*, highly specific to prostate cancer, shows an 8.1-fold upregulation, making it a promising candidate for diagnostic markers. Conversely, *ERG*, associated with aggressive tumors, demonstrates a -3.0-fold change, indicating potential therapeutic targets for aggressive prostate cancers.

According to results of ROC analysis, there was larger AUC in the model when compared with different parameters. There were 0.685 (CI: 95%, 0.641-0.731), 0.890 (CI: 95%, 0.791-0.897) and 0.942 (CI: 95%, 0.936-0.984) values of age, *PCA3*, *OR51E1* and *TMPRSS-2ERG* respectively. This model showed relatively higher predictive accuracy as compared to other. This model had 0.3 optimal cut-off values there was 0.897 and 0.810 sensitivity and specificity respectively.

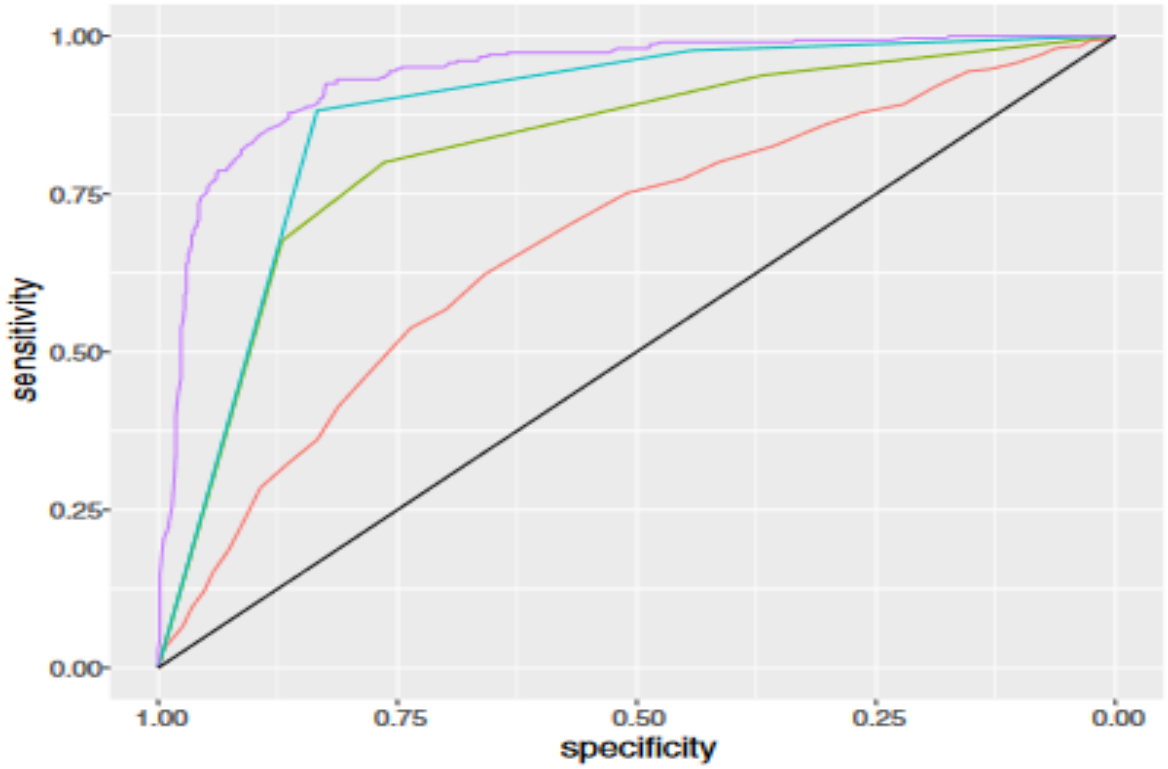


Figure 1; ROC curves of age, *PCA3*, *OR51E1*, *TMPRSS-2ERG*and the model for PCa in cohort. Their AUC values were 0.685, 0.832, 0.890, and 0.942, respectively.

DISCUSSION:

Cross-sectional studies serve as invaluable tools in the realm of medical research, providing a snapshot of a population at a specific point in time. This design is particularly instrumental when investigating complex diseases such as prostate cancer [16]. In this discussion, we delve into the nuances of a cross-sectional study focused on gene expression profiling of novel prostate cancer tumor markers. The exploration of gene expression in prostate cancer not only enhances our understanding of the disease but also opens avenues for personalized therapeutic strategies [17].

The Significance of Gene Expression Profiling:

Prostate cancer, a multifaceted disease with diverse molecular subtypes, necessitates a nuanced approach to comprehend its underlying mechanisms.

Gene expression profiling, a technique that scrutinizes the activity of genes in a given sample, facilitates the identification of biomarkers that can be pivotal in diagnosis, prognosis, and treatment [18]. By examining the expression patterns of specific genes, researchers gain insights into the molecular landscape of prostate cancer, paving the way for targeted interventions.

The Cross-Sectional Lens:

The cross-sectional study design employed in this research allows researchers to simultaneously collect data from a diverse group of subjects, providing a comprehensive view of gene expression in prostate cancer at a specific point [19]. This method is particularly suitable for unveiling the heterogeneity within the disease, offering a glimpse into the intricate network of genetic alterations that contribute to tumor development and progression [20].

Challenges and Opportunities:
Despite its advantages, the cross-sectional approach also poses challenges. It inherently lacks a temporal dimension, making it challenging to establish causal relationships between gene expression patterns and disease progression. However, when applied judiciously, this design can uncover correlations and associations, pointing towards potential biomarkers for further investigation [21].

The Unveiling of Novel Tumor Markers:
One of the primary objectives of this study is the identification of novel prostate cancer tumor markers through gene expression profiling. By comparing the expression profiles of cancerous and non-cancerous tissues, researchers can pinpoint genes that exhibit differential expression, potentially serving as diagnostic or prognostic indicators [22]. The identification of these novel markers not only aids in early detection but also contributes to the development of targeted therapies tailored to the molecular profile of individual tumors.

Implications for Personalized Medicine:
The era of personalized medicine beckons, and gene expression profiling plays a pivotal role in this paradigm shift. The data gleaned from this cross-sectional study can be harnessed to tailor treatment strategies based on the unique genetic makeup of each patient's prostate cancer [23]. This individualized approach holds the promise of improved treatment outcomes, reduced side effects, and enhanced overall patient care [24-25].

Future Directions:
As we delve deeper into the intricacies of gene expression in prostate cancer, avenues for future research emerge. Longitudinal studies, complementing the cross-sectional approach, can provide a temporal dimension to our understanding, unraveling the dynamic changes in gene expression over the course of the disease. Integrating multi-omics approaches, such as genomics, transcriptomics, and proteomics, can offer a more comprehensive view of the molecular landscape, further refining our ability to identify and target key pathways.
The cross-sectional study design in gene expression profiling of novel prostate cancer tumor markers serves as a valuable tool in unraveling the complexities of this prevalent malignancy. By identifying and understanding the expression patterns of key genes, researchers pave the way for advancements in diagnostics and therapeutics, ultimately contributing to the paradigm shift towards personalized medicine in the field of oncology. As we navigate the intricacies of prostate cancer, the integration of cross-sectional studies with other research methodologies becomes imperative, propelling us towards a more nuanced comprehension of this formidable disease.

CONCLUSION:
This cross-sectional study delving into gene expression profiling of novel prostate cancer tumor markers has significantly contributed to our understanding of the molecular landscape associated with prostate cancer. The identification and characterization of these markers provide valuable insights for early detection, prognosis, and potential therapeutic targets. The comprehensive analysis of gene expression patterns enhances our ability to decipher the intricate mechanisms underlying prostate cancer development. Moving forward, the findings from this study may pave the way for the development of more targeted and personalized approaches in the diagnosis and treatment of prostate cancer, ultimately improving patient outcomes.
Diagnostic accuracy of *PCA3*, *OR51E1*, *TMPRSS-2* (ERG fusion gene) genes and comparison with serum PSA level in diagnosing the prostate cancer is identified as a potential diagnostic and therapeutic target of PCa. And recent study showed a great ascendance of biomarkers *PCA3*, *OR51E1*, *TMPRSS-2* (ERG fusion gene) genes in PCa diagnosis, which may prevail in clinical practice. Therefore, in order to optimize the PCa detection, *PCA3*, *OR51E1*, *TMPRSS-2* (ERG fusion gene) test might have applicable diagnostic.

REFERENCES:
1. Bahmad HF, Jalloul M, Azar J, Moubarak MM, Samad TA, Mukherji D, Al-Sayegh M, Abou-Kheir W. Tumor microenvironment in prostate cancer: toward identification of novel molecular biomarkers for diagnosis, prognosis, and therapy development. Frontiers in Genetics. 2021 Mar 26;12:652747.
2. Brady L, Kriner M, Coleman I, Morrissey C, Roudier M, True LD, Gulati R, Plymate SR, Zhou Z, Birditt B, Meredith R. Inter-and intra-tumor heterogeneity of metastatic prostate cancer determined by digital spatial gene expression profiling. Nature communications. 2021 Mar 3;12(1):1426.
3. Shao N, Tang H, Mi Y, Zhu Y, Wan F, Ye D. A novel gene signature to predict immune infiltration and outcome in patients with prostate cancer. Oncoimmunology. 2020 Jan 1;9(1):1762473.
4. Kwon OK, Ha YS, Na AY, Chun SY, Kwon TG, Lee JN, Lee S. Identification of novel prognosis and prediction markers in advanced prostate cancer tissues based on quantitative proteomics. Cancer Genomics & Proteomics. 2020 Mar 1;17(2):195-208.
5. Liao D, Yang G, Yang Y, Tang X, Huang H, Shao J, Pan Q. Identification of pannexin 2 as a novel marker correlating with ferroptosis and malignant phenotypes of prostate cancer cells. OncoTargets and therapy. 2020 May 19:4411-21.
6. Liao D, Yang G, Yang Y, Tang X, Huang H, Shao J, Pan Q. Identification of pannexin 2 as a novel marker correlating with ferroptosis and malignant phenotypes of prostate cancer cells. OncoTargets and therapy. 2020 May 19:4411-21.

7. He B, Lang J, Wang B, Liu X, Lu Q, He J, Gao W, Bing P, Tian G, Yang J. TOOme: a novel computational framework to infer cancer tissue-of-origin by integrating both gene mutation and expression. Frontiers in bioengineering and biotechnology. 2020 May 19;8:394.
8. Hamzeh O, Alkhateeb A, Zheng J, Kandalam S, Rueda L. Prediction of tumor location in prostate cancer tissue using a machine learning system on gene expression data. BMC bioinformatics. 2020 Mar;21(2):1-0.
9. Ostano P, Mello-Grand M, Sesia D, Gregnanin I, Peraldo-Neia C, Guana F, Jachetti E, Farsetti A, Chiorino G. Gene expression signature predictive of neuroendocrine transformation in prostate adenocarcinoma. International journal of molecular sciences. 2020 Feb 6;21(3):1078.
10. Wang Y, Ma S, Ruzzo WL. Spatial modeling of prostate cancer metabolic gene expression reveals extensive heterogeneity and selective vulnerabilities. Scientific reports. 2020 Feb 26;10(1):3490.
11. Li Z, Li LX, Diao YJ, Wang J, Ye Y, Hao XK. Identification of urinary exosomalmiRNAs for the non-invasive diagnosis of prostate cancer. Cancer Management and Research. 2021 Jan 6:25-35.
12. Rauluseviciute I, Drabløs F, Rye MB. DNA hypermethylation associated with upregulated gene expression in prostate cancer demonstrates the diversity of epigenetic regulation. BMC medical genomics. 2020 Dec;13(1):1-5.
13. Fan X, Zou X, Liu C, Cheng W, Zhang S, Geng X, Zhu W. MicroRNA expression profile in serum reveals novel diagnostic biomarkers for endometrial cancer. Bioscience reports. 2021 Jun;41(6):BSR20210111.
14. Hamid AA, Huang HC, Wang V, Chen YH, Feng F, Den R, Attard G, Van Allen EM, Tran PT, Spratt DE, Dittamore R. Transcriptional profiling of primary prostate tumor in metastatic hormone-sensitive prostate cancer and association with clinical outcomes: correlative analysis of the E3805 CHAARTED trial. Annals of Oncology. 2021 Sep 1;32(9):1157-66.
15. Cochetti G, de Vermandois JA, Maulà V, Giulietti M, Cecati M, Del Zingaro M, Cagnani R, Suvieri C, Paladini A, Mearini E. Role of miRNAs in prostate cancer: Do we really know everything?. InUrologic oncology: seminars and original investigations 2020 Jul 1 (Vol. 38, No. 7, pp. 623-635). Elsevier.
16. Cao Z, Xu Y, Guo F, Chen X, Ji J, Xu H, He J, Yu Y, Sun Y, Lu X, Wang F. FASN protein overexpression indicates poor biochemical recurrence-free survival in prostate cancer. Disease markers. 2020 Jun 19;2020.
17. Salachan PV, Rasmussen M, Ulhøi BP, Jensen JB, Borre M, Sørensen KD. Spatial whole transcriptome profiling of primary tumor from patients with metastatic prostate cancer. International Journal of Cancer. 2023 Dec 15;153(12):2055-67.
18. Liu H, Gao L, Xie T, Li J, Zhai TS, Xu Y. Identification and validation of a prognostic signature for prostate cancer based on ferroptosis-related genes. Frontiers in oncology. 2021 Jul 15;11:623313.
19. Barman SK, Zaman MS, Veljanoski F, Malladi CS, Mahns DA, Wu MJ. Expression profiles of the genes associated with zinc homeostasis in normal and cancerous breast and prostate cells. Metallomics. 2022;14(8):mfac038.
20. Tsimberidou AM, Fountzilas E, Bleris L, Kurzrock R. Transcriptomics and solid tumors: The next frontier in precision cancer medicine. InSeminars in cancer biology 2022 Sep 1 (Vol. 84, pp. 50-59). Academic Press.
21. Mugoni V, Ciani Y, Nardella C, Demichelis F. Circulating RNAs in prostate cancer patients. Cancer Letters. 2022 Jan 1;524:57-69.
22. Meng J, Zhou Y, Lu X, Bian Z, Chen Y, Zhou J, Zhang L, Hao Z, Zhang M,Liang C. Immune response drives outcomes in prostate cancer: Implications for immunotherapy. Molecular oncology. 2021 May;15(5):1358-75.
23. McKiernan J, Noerholm M, Tadigotla V, Kumar S, Torkler P, Sant G, Alter J, Donovan MJ, Skog J. A urine-based Exosomalgene expression test stratifies risk of high-grade prostate Cancer in men with prior negative prostate biopsy undergoing repeat biopsy. BMC urology. 2020 Dec;20(1):1-6.
24. Miyahira AK, Sharp A, Ellis L, Jones J, Kaochar S, Larman HB, Quigley DA, Ye H, Simons JW, Pienta KJ, Soule HR. Prostate cancer research: the next generation; report from the 2019 Coffey-Holden prostate cancer academy meeting. The Prostate. 2020 Feb;80(2):113-32.
25. Li T, Sun X, Chen L. Exosome circ_0044516 promotes prostate cancer cell proliferation and metastasis as a potential biomarker. Journal of cellular biochemistry. 2020 Mar;121(3):2118-26.