Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/jptcp.v31i4.5580

DECIPHERING THE ROLE OF CDK1 GENE IN HEAD AND NECK SQUAMOUS CELL CARCINOMA (HNSC) VIA THE MULTIFACETED BIOINFORMATICS APPROACH

Hafeez Ullah[1], Zahid Rehman[2], Abid Hussain[3], Syeda Amber Hameed[4], Reema Bughio[5], Junaid Farooq[6], Zainab lanjar[7], Abdul Waheed khan[8], Ghulam Mustafa Solangi[9], Syed Meesam Raza[10*], Habibullah Janyaro[11*]

[1]Department of Microbiology, Abasyn University Peshawar, Pakistan, Hafeezullah@gmail.com
[2]Institute of Paramedical Science Khyber Medical University Peshawar, Pakistan, zahid.ipms@kmu.edu.pk
[3]Faculty of Veterinary and Animal Sciences, Azad Jammu and Kashmir University of Bhimber, Bhimber-AJK, Pakistan, abidhussain@must.edu.pk
[4]Department of Microbiology, Emerson University Multan, Pakistan, amber.hameed@eum.edu.pk
[5]Department of Animal Breeding and Genetics, Shaheed Benazir Bhutto University of Veterinary & Animal Science Sakrand, Pakistan, reema.bughio@hotmail.com
[6]Institute of Biotechnology and Microbiology, Bacha Khan University Charsadda, Pakistan, junaid.farooq2009@gmail.com
[7]Department of Veterinary Microbiology, Shaheed Benazir Bhutto University of Veterinary & Animal Science Sakrand, Pakistan, zainab.makhdoom@yahoo.com
[8]Institute of Biotechnology and Microbiology, Bacha Khan University Charsadda, Pakistan, awk7780@gmail.com
[9*]Department of Veterinary Pathology, Shaheed Benazir Bhutto University of Veterinary & Animal Science Sakrand, Pakistan, drsolangipathologist@gmail.com
[10]Department of Microbiology, Quaid I Azam University Islamabad, Pakistan, 2019-cu-micro-005@cuvas.edu.pk
[11*]Department of Veterinary Surgery SBBUVAS Sakrand, Shaheed Benazir Bhutto University of Veterinary and Animal Sciences Sakrand, Pakistan, Janyaroh@gmail.com

***Corresponding Author:** Syed Meesam Raza, Habibullah Janyaro
[*]Department of Microbiology, Quaid I Azam University Islamabad, Pakistan, 2019-cu-micro-005@cuvas.edu.pk
[*]Department of Veterinary Surgery SBBUVAS Sakrand, Shaheed Benazir Bhutto University of Veterinary and Animal Sciences Sakrand, Pakistan, Janyaroh@gmail.com

Abstract

This study comprehensively analyzes the expression, promoter methylation, mutational, and survival status of CDK1 in Head and Neck Squamous Cell Carcinoma (HNSC) using various bioinformatics tools. Utilizing the UALCAN database, significant up-regulation of CDK1 expression is observed in HNSC tissues compared to normal controls, suggesting a potential role of CDK1 in HNSC proliferation. Concurrently, promoter methylation analysis reveals hyper-methylation of CDK1 in HNSC samples, indicating possible epigenetic dysregulation contributing to oncogenesis. Further investigation stratified by clinical parameters, including cancer stages, patient demographics, and age, unveils diverse relationships between CDK1 expression and these

variables, underscoring its complex role in HNSC pathogenesis. Survival analysis utilizing the Km plotter tool demonstrates that higher CDK1 expression is associated with poorer overall survival rates among HNSC patients, indicating its potential as a prognostic biomarker. Additionally, mutational analysis using the cBioPortal platform reveals a low mutation rate in HNSC samples, with observed genetic alterations primarily consisting of amplifications and missense mutations. These findings collectively provide insights into the involvement of CDK1 in HNSC progression, highlighting its potential as a diagnostic and prognostic marker and emphasizing the need for further research to elucidate its exact mechanistic role in HNSC oncogenesis.

Keywords: CDK1, HNSC, Biomarker, prognosis

Introduction

Cancer is characterized by the uncontrolled growth and proliferation of cells, ranking among the leading causes of death worldwide, with approximately one in six deaths attributed to cancer (1-5). In 2021 alone, there were approximately 19.3 million new cases and 10 million deaths due to cancer (1-5). Cancers are classified based on their site of origin, encompassing roughly 100 different types (1-5). Notably, Head and Neck cancer (HNC) ranks as the sixth most common type of cancer, with approximately 440,000 deaths and 870,000 new cases recorded in 2021. Projections suggest a surge to about 1.8 million HNC cases by 2030 (6-8). Head and Neck Squamous Cell Carcinoma (HNSC) represents the most prominent subtype, comprising approximately 90% of cases. HNSC affects areas such as the oropharynx, hypopharynx, larynx, and oral cavity, and is associated with a high mortality rate due to complications such as distorted breathing, speaking, and swallowing. Several risk factors for HNSC have been identified, including Human papillomavirus (HPV) infections, obesity, smoking, and alcohol consumption (9-13).

So, to address this disease, there is a pressing need to develop new diagnostic and therapeutic techniques (14, 15). The cell cycle is tightly regulated by cyclin-dependent kinases (CDKs), with Cyclin-dependent kinase 1 (CDK1) playing a pivotal role in cell cycle regulation and governing processes such as mRNA transcription, DNA repair, replication and segregation, and cell morphogenesis (16-18). Deregulation and oncogenic alterations of CDK1 are intimately linked with cancer. Moreover, CDK1 is consistently upregulated and overexpressed in cancer cells compared to normal cells, correlating with a decreased survival rate (19-21). Dysregulation of CDK1 leads to abnormal cell division, ultimately resulting in cancer development (22, 23). Previous studies have indicated that an increase in mRNA levels of CDK1 is associated with poor overall survival in HNSC (24-26). CDK1 is indeed overexpressed in HNSC, and its overexpression is correlated with genes in G2M, mTORC1, MYC, and P53 pathways (27-31). Therefore, the collective evidence suggests that CDK1 plays a significant role in HNSC. However, further elucidation of this role is warranted through integrated bioinformatics methodology.

In this study, a variety of bioinformatics methods were employed to analyze the role of CDK1 in the progression of HNSC. The Cancer Genome Atlas (TCGA) database, Kaplan-Meier database, and UALCAN databases were utilized to conduct this research.

Materials and methods

Expression analysis of CDK1 in HNSC

The UALCAN database was utilized to analyze the expression levels between normal tissues and cancer tissues (32). Known for its user-friendly interface, UALCAN facilitated the expression analysis of CDK1 in HNSC. Additionally, UALCAN was employed to examine CDK1 expression across different parameters such as patient's age, gender, and race. P-value < 0.05.

Promoter methylation analysis of CDK1

We conducted an analysis of the promoter methylation level of CDK1 in HNSC using the UALCAN database. UALCAN is commonly used to assess data related to viral infection, DNA

methylation, RNA expression, and clinical features of cancer patients (33). Furthermore, we investigated the promoter methylation level of CDK1 across various clinical parameters such as patient's age, gender, and race. P-value < 0.05.

Survival analysis of CDK1

Kaplan-Meier (KM) analysis is an optimal tool for assessing patient survival rates and determining the role of specific genes in overall survival (OS) of cancer patients (34, 35). In our study, we utilized the Kaplan-Meier (KM) plotter to analyze the impact of CDK1 on OS in HNSC patients. Additionally, we conducted an analysis to assess the role of CDK1 in OS of HNSC patients stratified based on different parameters. P-value < 0.05.

Mutational analysis of CDK1

The cBioPortal is a user-friendly database that enables researchers to analyze clinical pathways and genetic alterations across various cancers, making it a vital resource in cancer genomic research (23, 36). In our current study, we utilized cBioPortal to conduct a mutational analysis of CDK1 in HNSC. P-value < 0.05.

Results

Expression analysis of CDK1 in HNSC and normal control samples

Initially, we assessed the expression of CDK1 in HNSC and normal control samples using the UALCAN database (Figure 1). Our analysis unveiled a significant up-regulation of CDK1 expression in HNSC tissues compared to the control normal samples. This notable up-regulation suggests a potential correlation between CDK1 expression and the proliferation of HNSC cells. Consequently, these findings strongly suggest that CDK1 may play a pivotal role in driving the proliferation of HNSC.

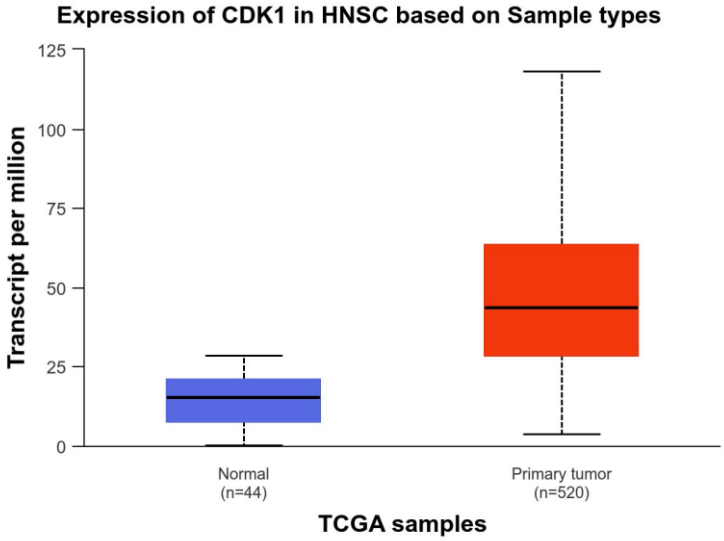


Figure 1: This graph depicts the expression of CDK1 in HNSC and normal samples via the UALCAN database. P-value < 0.05.

Expression analysis of CDK1 in HNSC samples divided based on different parameters

Simultaneously, we conducted an analysis of CDK1 expression in HNSC samples with various parameters, including individual cancer stages, patient's age, gender, and race (Figure 2). Initially, examining CDK1 expression at different cancer stages revealed a significant overexpression at various stages compared to normal tissues (Figure 2A). Subsequently, analyzing CDK1 expression in HNSC patients of multiple racial origins showed remarkable overexpression across samples of different races compared to normal samples (Figure 2B). Further, setting gender as a parameter to

explore CDK1 expression in HNSC patients revealed considerable up-regulation in both male and female HNSC samples (Figure 2C). Finally, analyzing CDK1 expression based on patient's age showed significant up-regulation across various age groups of HNSC patients (Figure 2D). Through a comprehensive analysis, we thoroughly investigated the up-regulation in CDK1 expression in HNSC samples across the observed parameters, revealing a considerable role of CDK1 in the proliferation of HNSC.

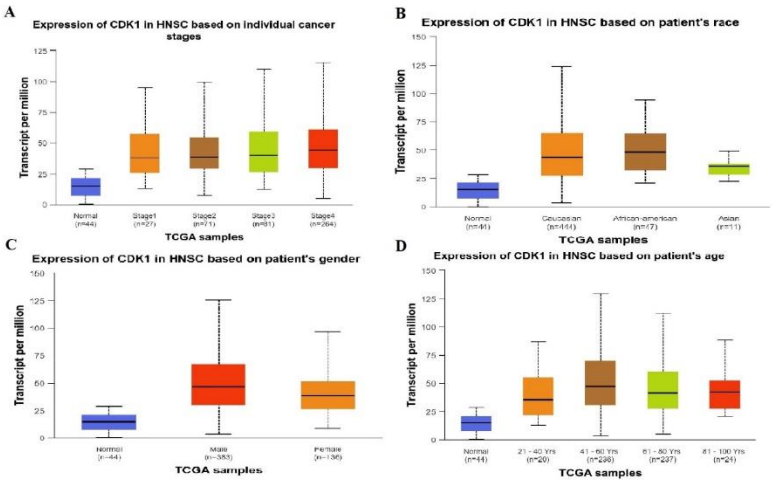
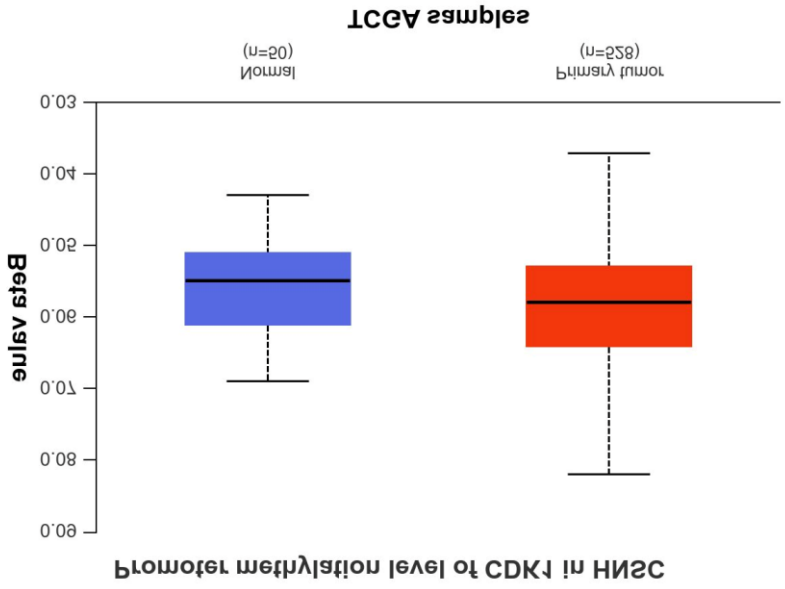


Figure 2: This graph depicts the expression of CDK1 in HNSC samples of different clinical variables and normal samples via the UALCAN database. P-value < 0.05.

Promoter methylation of CDK1 in HNSC and normal control samples

Prior investigations have elucidated the pivotal role of promoter methylation in regulating gene expression (37, 38). Consequently, we utilized the UALCAN database to examine the analysis of promoter methylation levels in HNSC and normal control samples. Our analysis revealed that CDK1 is hyper-methylated in HNSC samples compared to normal control samples (Figure 3). This analysis suggests potential epigenetic dysregulation of CDK1 and its association with HNSC development.



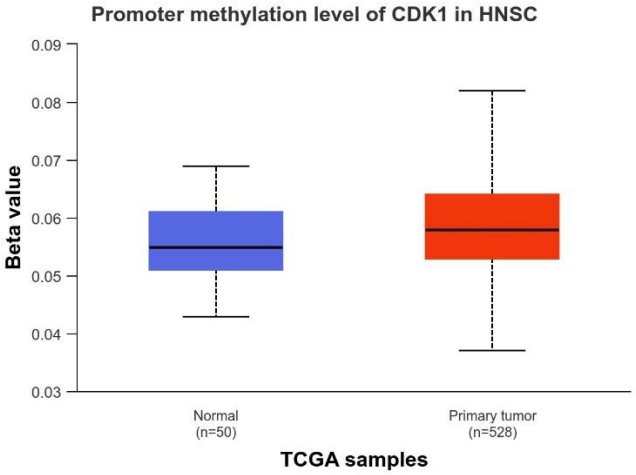


Figure 3: This graph depicts the promoter methylation level of CDK1 in HNSC and normal samples via the UALCAN database. P-value < 0.05.

Promoter methylation of CDK1 in HNSC samples divided based on different parameters

Concurrently, we investigated promotor methylation level of CDK1 in HNSC samples divided base on different parameters (Figure 4). Primarily, we examine promoter methylation level of CDK1 in HNSC patients across different stages. We found variation in Promotor methylation level but mostly hyper-methylation at various stages (Figure 4A). Subsequently, we set different races as our parameter to examine Promoter methylation of CDK1 in HNSC samples, observing hyper-methylation in CDK1 (Figure 4B). Furthermore, we investigated CDK1 promoter methylation in HNSC samples taking into account different genders. It revealed variation in promotor methylation in both male and female samples (Figure 4C). Moreover, we analyzed promotor methylation considering patient's age, revealing hyper-methylation in CDK1 at various age group in patients with HNSC (Figure 4D). These comprehensive analysis revealed diverse relationship in promotor methylation of CDK1 and various parameters that explains heterogeneous mechanism in CDK1 expression to regulate HNSC oncogenesis.

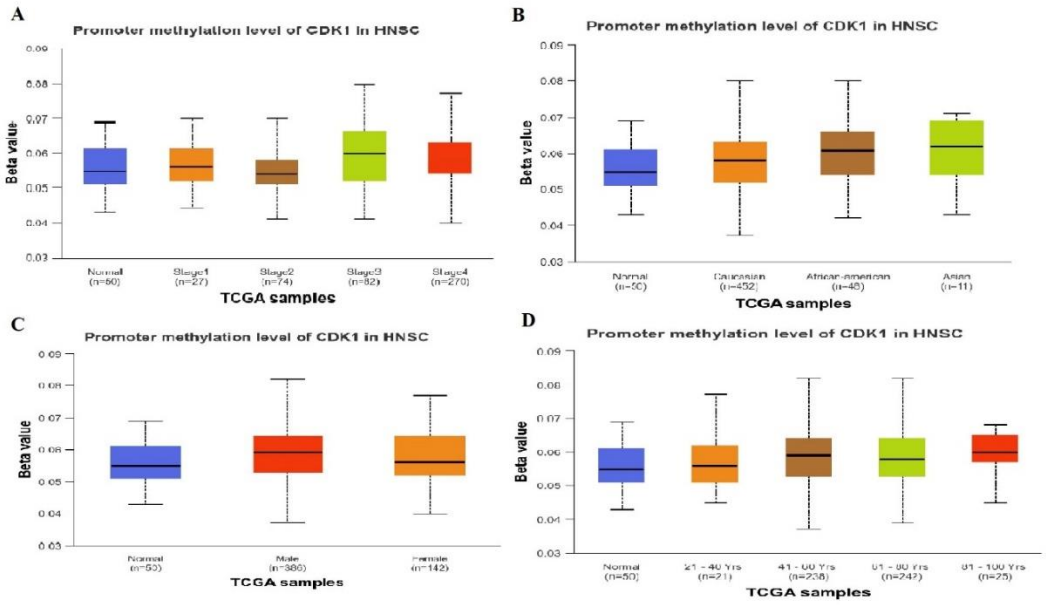


Figure 4: This graph depicts the promoter methylation level of CDK1 in HNSC samples of different clinical variables and normal samples via the UALCAN database. P-value < 0.05.

Survival analysis of CDK1

We utilized the Kaplan-Meier (KM) plotter to analyze overall survival (OS) in relation to CDK1 expression in patients with HNSC. The analysis revealed that higher expression of CDK1 was associated with a poor OS rate of HNSC patients, with a hazard ratio (HR) of 1.4 and p-value < 0.5 (Figure 5).

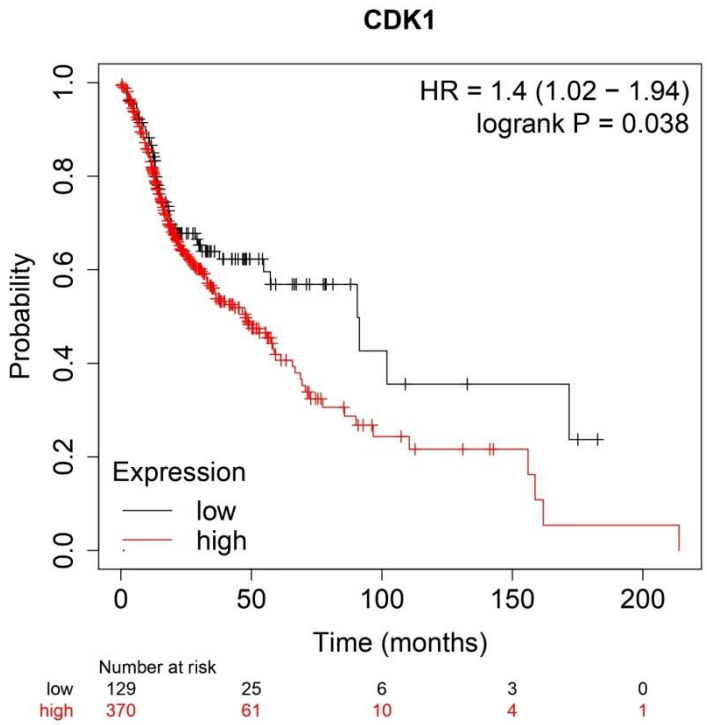


Figure 5: KM survival curve of the CDK1 in HNSC patients. P-value < 0.05.

Mutational analysis of CDK1 in HNSC

We utilized the cBioPortal platform to examine the mutational analysis of CDK1 in HNSC. Our analysis indicated a mutation rate of 1% in HNSC samples. The observed genetic alterations predominantly included amplifications and missense mutations (Figure 6). Therefore, our findings suggest that genetic variations have a nominal impact on the dysregulation of CDK1 in HNSC, but further exploration is required.

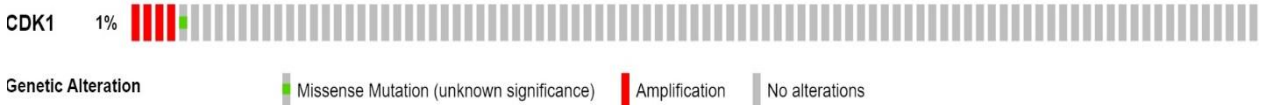


Figure 6: OncoPlot of CDK1 mutations across HNSC samples.

Discussion

The present analysis focused on elucidating the role of CDK1 in HNSC, encompassing its expression, promoter methylation, and prognostic implications. Through this comprehensive examination, we uncovered several constructive findings. To validate our results and enhance their robustness, we rigorously compared and computed our findings against existing data. This rigorous approach ensures the reliability and significance of our conclusions, contributing to the advancement of our understanding of the role of CDK1 in HNSC pathogenesis.

In our study, we initially investigated the expression profile of CDK1 in HNSC and normal control samples using the UALCAN database. Our analysis revealed a significant up-regulation of CDK1 expression in cancerous cells compared to normal cells, with a statistical significance of <1E-12.

These findings underscore the potential decisive role of CDK1 in HNSC progression. Interestingly, our results align with previous studies demonstrating that CDK1 expression is up-regulated in various cancers such as breast cancer, colon cancer, and lung cancer, and is associated with genes in the p53 pathway. Furthermore, we expanded our analysis by evaluating CDK1 expression in HNSC across different parameters including individual cancer stages, patient age, gender, and race. Our investigation revealed variations in expression across these parameters, but predominantly indicated up-regulation. These findings emphasize that CDK1 plays a vital role in the proliferation of HNSC and underscores its potential as a research subject.

Promoter methylation levels are recognized to play a pivotal role in cancer-related gene expression (42). Thus, we conducted an analysis of CDK1 promoter methylation in HNSC samples compared to controlled normal samples and found hyper-methylation in HNSC samples. Additionally, we investigated the promoter methylation level of CDK1 in HNSC based on different parameters and evaluated the extent of hyper-methylation. The observation of CDK1 exhibiting both hyper-methylation and up-regulation in expression suggests its abnormal behavior in HNSC, further emphasizing its potential role in the pathogenesis of the disease.

Furthermore, we investigated the significant correlation between the expression of CDK1 and prognosis in HNSC patients. Our analysis revealed that higher CDK1 expression was associated with lower overall survival (OS) rates. These findings underscore the potential of CDK1 as a prognostic indicator in cancer. Continuing our research, we utilized cBioPortal to perform mutational analysis. Our examination identified 1% genetic variation, primarily consisting of amplifications and missense mutations. While these mutations have a marginal effect on the dysregulation of CDK1 in HNSC, further analysis is essential for a more comprehensive understanding.

Furthermore, we investigated the significant correlation between the expression of CDK1 and prognosis in HNSC patients. Our analysis revealed that higher CDK1 expression was associated with lower overall survival (OS) rates. These findings underscore the potential of CDK1 as a prognostic indicator in cancer. Continuing our research, we utilized cBioPortal to perform mutational analysis. Our examination identified 1% genetic variation, primarily consisting of amplifications and missense mutations. While these mutations have a marginal effect on the dysregulation of CDK1 in HNSC, further analysis is essential for a more comprehensive understanding.

Conclusion

In conclusion, our study provides a comprehensive analysis of CDK1 in HNSC, shedding light on its expression patterns, promoter methylation status, and prognostic implications. These findings contribute valuable insights into the potential role of CDK1 as a biomarker and therapeutic target in HNSC. Further experimental validations are warranted to strengthen the robustness of these observations and pave the way for potential clinical applications.

Conflict of interest

None

Acknowledgement

None

References

1. Krieghoff-Henning E, Folkerts J, Penzkofer A, Weg-Remers S. Cancer – an overview. Med Monatsschr Pharm. 2017 Feb;40(2):48-54.
2. Chandraprasad MS, Dey A, Swamy MK. 1 - Introduction to cancer and treatment approaches. In: Swamy MK, Pullaiah T, Chen Z-S, editors. Paclitaxel: Academic Press; 2022. p. 1-27.

3. Upadhyay A. Cancer: An unknown territory; rethinking before going ahead. Genes Dis. 2021 Sep;8(5):655-61.
4. Ahmad M, Khan M, Asif R, Sial N, Abid U, Shamim T, et al. Expression characteristics and significant diagnostic and prognostic values of ANLN in human cancers. International Journal of General Medicine. 2022:1957-72.
5. Khan M, Hameed Y. Discovery of novel six genes-based cervical cancer-associated biomarkers that are capable to break the heterogeneity barrier and applicable at the global level. Journal of Cancer Research and Therapeutics. 2023.
6. Li Q, Tie Y, Alu A, Ma X, Shi H. Targeted therapy for head and neck cancer: signaling pathways and clinical studies. Signal Transduct Target Ther. 2023 Jan 16;8(1):31.
7. Xu W, Li H, Hameed Y, Abdel-Maksoud MA, Almutairi SM, Mubarak A, et al. Elucidating the clinical and immunological value of m6A regulator-mediated methylation modification patterns in adrenocortical carcinoma. Oncology Research. 2023;31(5):819.
8. Hameed A, Condò C, Tauseef I, Idrees M, Ghazanfar S, Farid A, et al. Isolation and characterization of a cholesterol-lowering bacteria from Bubalus bubalis raw milk. Fermentation. 2022;8(4):163.
9. Choi SY, Cheong HK, Lee MK, Kang JW, Lee YC, Oh IH, et al. Metabolic Diseases and Risk of Head and Neck Cancer: A Cohort Study Analyzing Nationwide Population-Based Data. Cancers (Basel). 2022 Jul 4;14(13).
10. Schicho A, Habicher W, Wendl C, Stroszczynski C, Strotzer Q, Dollinger M, et al. Clinical Value of Diffusion-Weighted Whole-Body Imaging with Background Body Signal Suppression (DWIBS) for Staging of Patients with Suspected Head and Neck Cancer. Tomography. 2022 Oct 9;8(5):2522-32.
11. Ribeiro IP, Esteves L, Caramelo F, Carreira IM, Melo JB. Integrated Multi-Omics Signature Predicts Survival in Head and Neck Cancer. Cells. 2022 Aug 16;11(16).
12. Usman M, Hameed Y. GNB1, a novel diagnostic and prognostic potential biomarker of head and neck and liver hepatocellular carcinoma. Journal of Cancer Research and Therapeutics. 2023.
13. Identification of Key Biomarkers for the Future Applications in Diagnostics and Targeted Therapy of Colorectal Cancer. Current Molecular Medicine. 2022.
14. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. Ca Cancer J Clin. 2021;71(1):7-33.
15. Mehraj U, Ganai RA, Macha MA, Hamid A, Zargar MA, Bhat AA, et al. The tumor microenvironment as driver of stemness and therapeutic resistance in breast cancer: New challenges and therapeutic opportunities. Cellular Oncology. 2021:1-21.
16. Enserink JM, Kolodner RD. An overview of Cdk1-controlled targets and processes. Cell division. 2010;5:1-41.
17. Morgan DO. The cell cycle: principles of control: New science press; 2007.
18. Panagopoulos A, Altmeyer M. The hammer and the dance of cell cycle control. Trends in biochemical sciences. 2021;46(4):301-14.
19. Bednarek K, Kiwerska K, Szaumkessel M, Bodnar M, Kostrzewska-Poczekaj M, Marszalek A, et al. Recurrent CDK1 overexpression in laryngeal squamous cell carcinoma. Tumor Biology. 2016;37:11115-26.
20. Sung W-W, Lin Y-M, Wu P-R, Yen H-H, Lai H-W, Su T-C, et al. High nuclear/cytoplasmic ratio of Cdk1 expression predicts poor prognosis in colorectal cancer patients. BMC cancer. 2014;14:1-7.
21. Li M, He F, Zhang Z, Xiang Z, Hu D. CDK1 serves as a potential prognostic biomarker and target for lung cancer. Journal of International Medical Research. 2020;48(2):0300060519897508.
22. Cicenas J, Valius M. The CDK inhibitors in cancer research and therapy. Journal of cancer research and clinical oncology. 2011;137:1409-18.

23. Usman M, Hameed Y, Ahmad M. Does epstein–barr virus participate in the development of breast cancer? A brief and critical review with molecular evidences. Biomedical and Biotechnology Research Journal (BBRJ). 2020;4(4):285-92.
24. Sofi S, Mehraj U, Qayoom H, Aisha S, Almilaibary A, Alkhanani M, et al. Targeting cyclin-dependent kinase 1 (CDK1) in cancer: molecular docking and dynamic simulations of potential CDK1 inhibitors. Med Oncol. 2022 Jun 20;39(9):133.
25. Hameed Y. Decoding the significant diagnostic and prognostic importance of maternal embryonic leucine zipper kinase in human cancers through deep integrative analyses. Journal of Cancer Research and Therapeutics. 2023;19(7):1852-64.
26. Karamat U, Ejaz S, Hameed Y. In silico-analysis of the multi-omics data identified the ataxia telangiectasia mutated gene as a potential biomarker of breast invasive carcinoma. Genetic Testing and Molecular Biomarkers. 2021;25(4):263-75.
27. Dong Y, Wu X, Xu C, Hameed Y, Abdel-Maksoud MA, Almanaa TN, et al. Prognostic model development and molecular subtypes identification in bladder urothelial cancer by oxidative stress signatures. Aging. 2024;16(3):2591-616.
28. Hu H, Umair M, Khan SA, Sani AI, Iqbal S, Khalid F, et al. CDCA8, a mitosis-related gene, as a prospective pan-cancer biomarker: implications for survival prognosis and oncogenic immunology. American Journal of Translational Research. 2024;16(2):432.
29. Abdel-Maksoud MA, Ullah S, Nadeem A, Shaikh A, Zia MK, Zakri AM, et al. Unlocking the diagnostic, prognostic roles, and immune implications of BAX gene expression in pan-cancer analysis. American Journal of Translational Research. 2024;16(1):63.
30. Chen P, Yawar W, Farooqui AR, Ali S, Lathiya N, Ghous Z, et al. Transcriptomics data integration and analysis to uncover hallmark genes in hypertrophic cardiomyopathy. American Journal of Translational Research. 2024;16(2):637.
31. Abdel-Maksoud MA, Ullah S, Nadeem A, Khan QUA, Zia MK, Ali S, et al. PTPN3 in cancer: unveiling its immune-mediated impact on prognosis and dysregulated signaling pathways. American Journal of Translational Research. 2023;15(11):6464.
32. Li T, Fu J, Zeng Z, Cohen D, Li J, Chen Q, et al. TIMER2.0 for analysis of tumor-infiltrating immune cells. Nucleic Acids Res. 2020 Jul 2;48(W1):W509-w14.
33. Yeung ML, Tam TS, Tsang AC, Yao KM. Proteolytic cleavage of PDZD2 generates a secreted peptide containing two PDZ domains. EMBO Rep. 2003 Apr;4(4):412-8.
34. Jia B, Zhao X, Wang Y, Wang J, Wang Y, Yang Y. Prognostic roles of MAGE family members in breast cancer based on KM-Plotter Data. Oncol Lett. 2019 Oct;18(4):3501-16.
35. Hameed Y, Ahmad M, Ejaz S, Liang S. Identification of Key Biomarkers for the Future Applications in Diagnostics and Targeted Therapy of Colorectal Cancer. Curr Mol Med. 2022 Aug 19.
36. Cerami E, Gao J, Dogrusoz U, Gross BE, Sumer SO, Aksoy BA, et al. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. Cancer Discov. 2012 May;2(5):401-4.
37. McCleary-Wheeler AL, Lomberk GA, Weiss FU, Schneider G, Fabbri M, Poshusta TL, et al. Insights into the epigenetic mechanisms controlling pancreatic carcinogenesis. Cancer Lett. 2013 Jan 28;328(2):212-21.
38. Yen CY, Huang HW, Shu CW, Hou MF, Yuan SS, Wang HR, et al. DNA methylation, histone acetylation and methylation of epigenetic modifications as a therapeutic approach for cancers. Cancer Lett. 2016 Apr 10;373(2):185-92.
39. Wijnen R, Pecoraro C, Carbone D, Fiuji H, Avan A, Peters GJ, et al. Cyclin dependent kinase-1 (CDK-1) inhibition as a novel therapeutic strategy against pancreatic ductal adenocarcinoma (PDAC). Cancers. 2021;13(17):4389.
40. Huang H-M, Huang X-Y, Wu S-P, Chen C-K, He X-H, Zhang Y-F. RETRACTED ARTICLE: Parecoxib inhibits esophageal squamous cell carcinoma progression via the PDK1–AKT pathway. Cellular & molecular biology letters. 2022;27(1):28.

41. Malumbres M, Barbacid M. Cell cycle, CDKs and cancer: a changing paradigm. Nature reviews cancer. 2009;9(3):153-66.
42. Akar RO, Selvi S, Ulukaya E, Aztopal N. Key actors in cancer therapy: epigenetic modifiers. Turkish Journal of Biology. 2019;43(3):155-70.