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Performance of Predictive Models in Cervical Cancer Recurrence: A Systematic Review and Meta-Analysis of Biomarkers and Prognosis

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***Abstract* - This study investigates the use of Predictive Analytics Frameworks (PAF) for identifying biomarkers of recurrent cervical cancer and predicting prognosis. It addresses the limited comprehensive evaluations of the effectiveness of predictive models in this area, despite the growing application of machine learning in healthcare. The purpose of this systematic review and meta-analysis is to assess the performance of predictive analytics models in terms of sensitivity, accuracy, specificity, and the area under the curve (AUC-ROC) for identifying cervical cancer biomarkers and predicting prognosis. To address this research problem, a systematic review and meta-analysis was conducted, covering studies published between 2014 and 2024. A total of 1,515 studies were initially identified from the PubMed and Scopus databases, with 50 research studies meeting the inclusion criteria. Repeated measures ANOVA and meta-analysis were applied using data collected over an 8-year period to evaluate recurrence trends and the predictive power of various models. The findings suggest that predictive analytics models show significant potential for improving diagnostic accuracy in identifying cervical cancer biomarkers. However, the review also highlights several limitations, including the small number of included studies, heterogeneity across studies, and potential bias in retrospective analyses. In conclusion, while predictive analytics frameworks demonstrate promise in improving cervical cancer prognosis and biomarker identification, further research is required to validate these findings and assess their broader clinical utility. The study underscores the importance of continued exploration of predictive models to enhance decision-making in oncology.**
Keywords: **Predictive Analytics Frameworks, Cervical Cancer, Biomarkers, Prognosis, Machine Learning**

I. INTRODUCTION

Cervical cancer is one of the most prevalent malignancies affecting women worldwide, with over 500,000 new cases and more than 300,000 deaths reported annually, predominantly in low- and middle-income countries where access to organized screening and HPV vaccination is limited [1]. High-risk human papillomavirus (HPV) is recognized as the primary etiological factor behind this cancer [2]. While advancements in screening programs have significantly reduced incidence in high-income countries, the prognosis remains poor for women with metastatic or recurrent cervical cancer [3]. Despite some progress made through treatments such as chemoradiation and the addition of bevacizumab, which has extended overall survival in advanced cases, recurrent cervical cancer remains a major challenge [4].

Although cervical cancer is preventable through vaccination and screening, recurrent cases present difficulties in early detection and effective treatment. This review addresses this gap by focusing on the application of predictive analytics in cervical cancer research. Predictive analytics, utilizing machine learning techniques, allows for the analysis of vast genomic and proteomic datasets to identify biomarkers critical for early detection and personalized treatment of recurrent cervical cancer [5]. The aim of this work is to evaluate the efficacy of predictive analytics frameworks in identifying recurrent cervical cancer biomarkers and predicting patient prognosis. By leveraging these models, healthcare professionals can improve diagnostic accuracy, enhance prognostic predictions, and develop personalized treatment plans, ultimately reducing the global burden of cervical cancer recurrence and improving patient outcomes [5-6].

II. METHODOLOGY

A. Search Strategy

The method used for this comprehensive investigation follows the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020). Any adjustments to the protocol and rationale throughout the systematic review will be clearly documented in the final report. The databases utilized for the planned approach include Google Scholar, PubMed, and Scopus. Searches were conducted in February 2024 using a combination of keywords and queries.

B. The Search was Conducted using the Following Search Query in Scopus (39): Articles Found

TITLE-ABS-KEY (“cervical cancer” OR “cervical carcinoma” OR “cervical neoplasms”) AND (“biomarkers” OR “biomarker discovery” OR “biomarker identification”) AND (“predictive analytics” OR “predictive modeling” OR “predictive algorithms” OR “machine learning” OR “data mining” OR “artificial intelligence”) AND (LIMIT-TO(DOCTYPE, “ar”)) AND (LIMIT-TO(PUBSTAGE, “Final”)) AND (LIMIT-TO(SRCTYPE, “j”)) AND (LIMIT-TO(LANGUAGE, “English”)) AND (LIMIT-TO(OA, “all”))

C. PubMed: (1476) Articles Ffound using this Advanced Search Index

("Cervical Cancer"[Mesh] OR "Cervical Neoplasms"[Mesh] OR "Uterine Cervical Neoplasms"[Mesh]) AND ("Biomarkers"[Mesh] OR "Biomarkers, Tumor"[Mesh]) AND ("Recurrence"[Mesh] OR "Recurrence, Local"[Mesh] OR "Recurrence, Tumor"[Mesh]) AND ("Predictive Analytics"[Mesh] OR "Machine Learning"[Mesh] OR "Artificial Intelligence"[Mesh])

This query combines Medical Subject Headings (MeSH) terms for cervical cancer, biomarkers, recurrence, and predictive analytics to narrow down the search to articles specifically related to identifying recurrent cervical cancer biomarkers using predictive analytics.

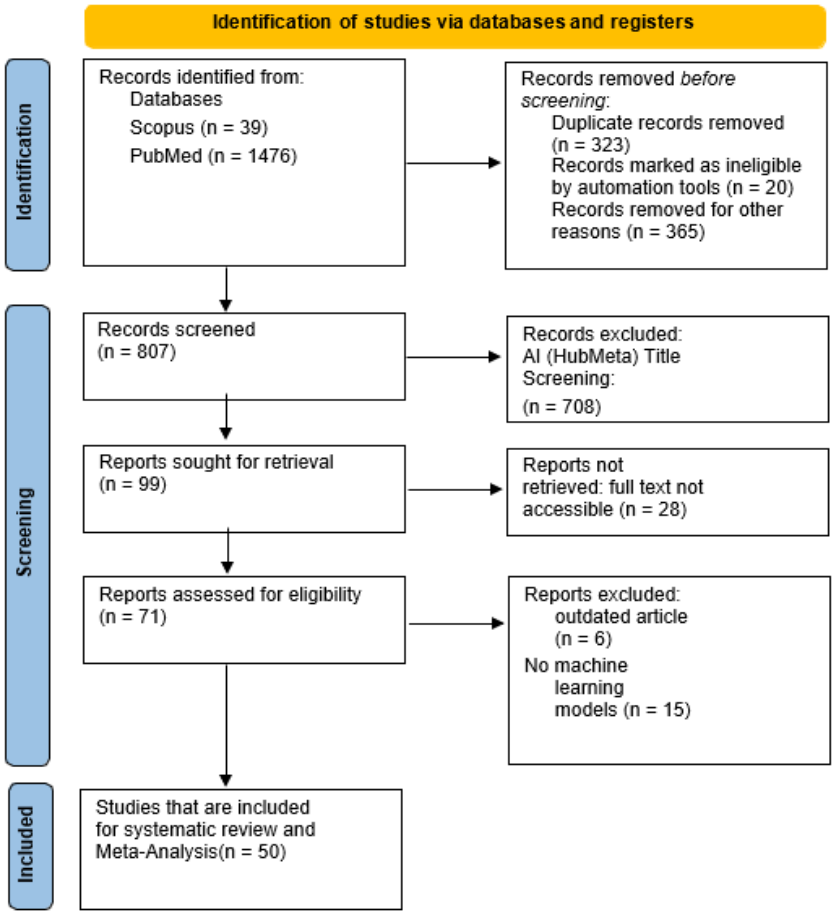

Fig. 1 The Flow diagram shows the study eventually screened

Subsequently, criteria for inclusion and exclusion were defined to assess the suitability of the articles for analysis.

D. Defining Exclusion Criteria

1. Research that does not utilize machine learning models with clinical data and gene expression profiles to predict survival in colorectal cancer patients.
2. Studies focusing on primary cohorts of patients with various types of cancer.
3. Research that does not provide accuracy metrics for predictive models.
4. Publications not published in English.
5. Full-text articles that are not accessible.
6. Conference abstracts, letters, editorials, case reports, reviews, and meta-analyses.

E. Defining Inclusion Criteria

In this study, the researchers employed the PICOS framework (Participants, Interventions, Comparator, Outcomes, and Study Design) to establish the inclusion criteria for selecting studies.

1. *Population:* Women diagnosed with cervical cancer, drawn from either the general population or treatment-seeking groups, including adolescents and adult females, were considered eligible for inclusion. The studies examined focused on the classification and prognosis of cervical cancer.
2. *Interventions:* The interventions involved predictive analytics frameworks that utilized deep learning and machine learning algorithms [56] to identify cervical cancer biomarkers and predict prognosis. Insights

derived from the meta-analysis were used to evaluate the effectiveness of various treatments or strategies.
3. *Comparisons:* Different predictive analytics frameworks from the 50 identified publications were compared.
4. *Outcomes:* The primary outcomes of interest were the sensitivity, accuracy, and area under the curve (AUC-ROC) of the predictive models in identifying cervical cancer biomarkers and predicting prognosis. Secondary outcomes included task performance in areas such as lesion segmentation, classification, survival prediction, and the overall impact of the frameworks on clinical decision-making.
5. *Study Design:* Studies selected for this review reported the development of predictive analytics frameworks for cervical cancer. The review adhered to PRISMA guidelines, focusing on studies published between 2014 and 2024 that implemented machine learning models to classify and predict the prognosis of cervical cancer subtypes. It addressed key questions regarding the performance and limitations of these models.

The researchers conducted the screening process by retrieving study titles and abstracts and evaluating them against the predefined inclusion and exclusion criteria. Full-text articles were obtained for studies that met these criteria.

F. Data Extraction, Sorting, and Selection

Information from the studies was gathered using a standardized data extraction form, and discrepancies were resolved through AI-assisted screening and judgment. Extracted data included study characteristics, participant details, interventions, outcomes, and results. The selection process involved three stages.

1. Search results were imported into Mendeley and HubMeta, with duplicate articles removed.
2. Titles and abstracts were screened by an AI assistant and a reviewer based on the PICOS criteria.
3. Full-text articles were reviewed to confirm eligibility.

G. Data Items

Study Details: Title, authorship, publication year, journal title, research methodology, sample size, inclusion and exclusion criteria, and data origins.

H. Predictive Analytics Framework Specifics

Model Details: Model category, algorithmic approach, feature subset selection, data preprocessing techniques, model validation methods, performance evaluation criteria, and constraints.

I. Cervical Cancer Biomarkers Identification

Performance Metrics: Sensitivity, accuracy, specificity, positive predictive value, and negative predictive value.

J. Prognostic Prediction

Survival Metrics: Overall survival rate, cancer survival duration, time to cancer progression, response rate, and progression-free survival period.

K. Research Findings

Performance Assessment: Evaluation of the Predictive Analytics framework for identifying cervical cancer biomarkers and prognostic prediction, along with identified limitations and future avenues for investigation.

L. Access to Data and Resources

All data and materials referenced in this study originate from articles retrieved from the PubMed and Scopus databases.

M. Strategy for Data Integration and Synthesis

The study followed PRISMA guidelines to guide the selection process. A flowchart was developed to illustrate the number of papers retained at each stage. A narrative synthesis was conducted to summarize the findings of the included studies, with results presented in a tabular format. When a sufficient number of studies were available, a meta-analysis was performed using a random-effects model, and heterogeneity was assessed using the I^2 statistic.

As the review aimed to explore learning methods for identifying cervical cancer biomarkers and predicting prognosis, the results were presented qualitatively. A table was also constructed to highlight study characteristics, features of the predictive analytics frameworks, identified biomarkers, prognosis predictions, and study outcomes.

N. Assessment of Quality

Each study underwent a quality assessment based on four key criteria:
1. Potential selection bias,
2. Instrumentation accuracy,
3. Management of missing data, and
4. Reporting of measurement results.

Various biases such as selection, performance, detection, attrition, and reporting bias-were assessed using predefined criteria. Any inconsistencies were reviewed and addressed. Studies with a high risk of bias were excluded from the final review to ensure that the synthesis was based on high-quality evidence.

O. Measures of Summary

The study summarized key measures, including odds ratios (OR), hazard ratios (HR), and 95% confidence intervals (CI), to evaluate the classification and prognostic accuracy of the predictive analytics frameworks.

P. Synthesis of Results

A narrative synthesis was conducted to present the findings of the included studies in tabular format. When sufficient studies were available, a meta-analysis was performed using a random-effects model, with heterogeneity assessed using the I^2 statistic.

Q. Results

The features of the 50 studies are summarized in Table I. These studies were published between 2014 and 2024. Sample sizes varied significantly, ranging from 50 to 500,000 patients. Various forms of cervical cancer imaging data were utilized across the studies, including CT scans, PET scans, and biomarkers. Additionally, diverse deep learning and machine learning algorithms were employed for predictive analytics related to the classification of cervical cancer biomarkers and the prediction of prognosis.

TABLE I RESULTS OF INDIVIDUAL STUDIES OF 50 PUBLICATIONS

Sl. No.	Title/Author/Year	Biomarkers	Result
1	Cervical Cancer. Cohen, Paul, *et al.,* (2019) [1]	High-risk indicators for HPV	Rates of cervical cancer occurrence and death
2	MicroRNA expression in cervical cancer: novel diagnostic and prognostic biomarkers," Gao *et al.,* (2018) [2].	MiRNA	Prognosis of cervical cancer
3	Identification of hub genes as potential prognostic biomarkers in cervical cancer using comprehensive bioinformatics analysis and validation studies. Xue, *et al.,* (2021) [3]	CDC45, GINS2, MCM2, PCNA	Predicting prognosis in cervical cancer patients
4	Integrative meta-analysis of gene expression profiles identifies FEN1 and ENDOU as potential diagnostic biomarkers for cervical squamous cell carcinoma. Zhang, *et al.,* (2021) [4]	FEN1, ENDOU	Discovering biomarkers linked to the development of cervical cancer
5	Integrative analysis of DNA methylation and gene expression identified cervical cancer-specific diagnostic biomarkers. Xu, *et al.,* (2019) [5]	cg07211381 (RAB3C), cg12205729 (GABRA2), cg20708961 (ZNF257), cg26490054 (SLC5A8)	Unveiling DNA methylation markers specific to cervical cancer
6	Identification of key pathways and genes in the progression of cervical cancer using bioinformatics analysis. Wu, *et al.,* (2018) [6]	PCNA, CDK2, VEGFA, PIK3CA	Investigation of key pathways and genes in cervical cancer progression
7	Squamous cell carcinoma antigen (SCC-Ag) during follow-up of cervical cancer patients: role in the early diagnosis of recurrence. Salvatici, *et al.,* (2016) [7]	Levels of SCC-Ag	Assessment of SCC-Ag for early diagnosis of cancer recurrence in cervical cancer patients
8	A prognostic nomogram integrating novel biomarkers identified by machine learning for cervical squamous cell carcinoma. Li, *et al.,* (2020) [8]	mRNA-based marker	Predicting prognosis for cervical squamous cell carcinoma (CSCC)
9	Identification of a novel six-gene signature with potential prognostic and therapeutic value in cervical cancer. Qu, *et al.,* 2021) [9]	APOC1	Identification of a six-gene prognostic signature for cervical cancer
10	Tumor DNA methylation profiles enable diagnosis, prognosis prediction, and screening for cervical cancer. Tu, *et al.,* (2022) [10]	CpG	Discovering DNA methylation diagnostic biomarkers and prognostic prediction models for cervical cancer
11	Identification of potential biomarkers in cervical cancer through combined analysis of public mRNA and miRNA expression microarray data. Wang, *et al.,* (2018) [11]	RhoB, STMN1, CCNB1, mRNA	Uncovering pivotal genes implicated in cervical cancer
12	Systematic identification of key genes and pathways in the development of invasive cervical cancer. Niu, *et al.,* (2017) [12]	CDKN2A, IL1R2, RFC4	Uncovering essential genes contributing to the development and advancement of cancerous cell
13	Potential new biomarkers for squamous carcinoma of the uterine cervix. Van Dam, *et al.,* (2018) [13]	DTL, HMGB3, KIF2C, NEK2, RFC4	Discovered novel biomarkers for cervical carcinoma

14	Screening and discovery of new potential biomarkers and small molecule drugs for cervical cancer: a bioinformatics analysis. Qiu, *et al.,* (2020) [14]	CDC45	Identification of potential genes and drugs for CC diagnosis and targeting therapies
15	Promoter methylation analysis of DKK2 may serve as a potential biomarker for the early detection of cervical cancer. Zhang, *et al.,* (2022) [15]	mRNA	Investigation of DKK2 mRNA expression and promoter methylation levels in cervical cancer and their clinicopathological associations
16	Systematic assessment of cervical cancer initiation and progression uncovers genetic panels for deep learning-based early diagnosis and proposes novel diagnostic and prognostic biomarkers. Nguyen Phuoc, *et al.,* (2017) [16]	FANCI	Identified upregulation of FANCI with amplification in cervical cancer tumor tissues
17	Identification of key genes and construction of a regulatory network for the progression of cervical cancer. Rajput, *et al.,* (2020) [17]	N/A	Identification of differentially expressed genes (DEGs) and enriched pathways in cervical cancer. 36 common DEGs were screened. GO analysis and PPI network used to find relationships among DEGs. Gene-miRNA interaction networks constructed.
18	Expression signatures of HOX cluster genes in cervical cancer pathogenesis: impact of human papillomavirus type 16 oncoprotein E7. Saha, *et al.,* (2017) [18]	HPV	prognostic prediction for cervical cancer
19	Prediction of lymphovascular space invasion using a combination of tenascin-C, COX-2, and PET/CT radiomics in patients with early-stage cervical squamous cell carcinoma. Li, *et al.,* (2021) [19]	N/A	Identification of higher Rad-score in LVSI patients compared to non-LVSI patients. Significant correlation between LVSI and Rad-score ($r = 0.631$, $p < 0.001$). Correlation of TNC with Rad-score ($r = 0.244$, $p = 0.024$) and COX-2 ($r = 0.227$, $p = 0.036$). Establishment of machine learning models including radiomics model, protein model, and combined model using logistic regression algorithm. Evaluation of models by ROC curve analysis.
20	Strategies for screening and early detection of anal cancers: a narrative and systematic review and meta-analysis of cytology, HPV testing, and other biomarkers. Garbett, *et al.,* (2014) [20]	Explored unique HPV biomarker signatures for cervical cancer using a combined approach	Significant discrimination observed relative to the extent of disease, with strong differentiation of CIN from healthy controls and IC, and amongst patients with IC between FIGO Stage I and advanced cancer. No clear effect of demographic factors such as age, ethnicity, smoking status, and parity.
21	The promise of combining cancer vaccines and checkpoint blockade for treating HPV-related cancers. Shibata, *et al.,* (2019) [21]	HPV	Evaluation of combination therapy using immune checkpoint inhibitor and HPV therapeutic vaccine for treating HPV-associated cancers
22	A new biomarker for cervical squamous cell carcinoma and endocervical adenocarcinoma (CESC) based on public database mining. Ding, *et al.,* (2020) [22]	miRNA	Conducted differential expression analysis, revealing 773 long non-coding RNAs (lncRNAs), 94 microRNAs (miRNAs), and 2466 messenger RNAs (mRNAs)
23	Potential biomarkers and therapeutic targets in cervical cancer: insights from the meta-analysis of transcriptomic data within a network biomedicine perspective. Kori, M;One, K Yalcin Arga - PLoS; 2018, undefined. (2018) [23]	miRNA	Identified various receptors (e.g. ephrin receptors EPHA4, EPHA5, and EPHB2; endothelin receptors EDNRA and EDNRB; nuclear receptors NCOA3, NR2C1, and NR2C2), miRNAs (e.g., miR-192-5p, miR-193b-3p, and miR-215-5p), transcription factors (particularly E2F4, ETS1, and CUTL1), other proteins (e.g., KAT2B, PARP1, CDK1, GSK3B, WNK1, and CRYAB), and metabolites (particularly, arachidonic acids) as novel biomarker candidates and potential therapeutic targets. Cross-validated differential expression profiles of all reporter biomolecules in independent RNA-Seq and miRNA-Seq datasets. Demonstrated prognostic power of several reporter biomolecules, including KAT2B, PCNA, CD86, miR-192-5p, and miR-215-5p.
24	Candidate genes and pathways in cervical cancer: a systematic review and integrated bioinformatic analysis. Elias, *et al.,* (2023) [24]	Identified candidate genes implicated in relevant Gene Ontology (GO) terms and interactions with other genes in a	Identified 6 studies and extracted 1128 DEGs. Selected 62 differentially expressed genes from at least two studies for further analysis using DAVID, STRING, and Cytoscape software. Revealed three significant clusters with high intermolecular interactions from the Protein-Protein Interaction (PPI) network complex

		Protein-Protein Interaction (PPI) network by examining undirected first neighbor nodes.	indicating three major molecular mechanisms: cell signaling, cell cycle, and cell differentiation. Chose eight candidate genes based on their involvement in relevant gene ontology (GO) and their interaction with other genes in the PPI network through undirected first neighbor nodes.
25	Identification of hub genes and the role of CDKN2A as a biomarker in cervical cancer: an in-silico approach. Sudha, *et al.,* (2022) [25]	CDKN2A	Identified 18 differentially expressed genes highly associated with DNA replication and cell proliferation pathways in cervical cancer. Network analysis revealed CDKN2A as a biomarker for cervical cancer prognosis. Analysis of CDKN2A expression and interactions with bioinformatic tools showed significant interactions with transcription factors, signaling molecules, and miRNAs. In-silico analysis of microarray data suggests CDKN2A as a gene target for cervical cancer diagnosis.
26	LC/MS-based polar metabolite profiling identified unique biomarker signatures for cervical cancer and cervical intraepithelial neoplasia using global and targeted approaches. Khan, *et al.,* (2019) [26]	HPV	Identified 28 metabolites exhibiting discriminating levels among normal, CIN, and cervical cancer patients (Kruskal-Wallis test $p < 0.05$). Pathway analysis showed significantly altered alanine, aspartate, and glutamate metabolic pathways (FDR p-value < 0.05) in both discovery and validation phases. Seven metabolites (AMP, aspartate, glutamate, hypoxanthine, lactate, proline, and pyroglutamate) were discriminated between CINs and cervical cancer versus normal (area under the curve (AUC) value > 0.8). Elevated levels of these metabolites combined with positive HPV status were correlated with substantial risk of cancer progression.
27	Characterization of long non-coding RNA expression profiles in lymph node metastasis of early-stage cervical cancer. Shang, *et al.,* (2016) [27]	N/A	Identified 234 differentially expressed lncRNAs significantly associated with pelvic lymph node metastasis in early-stage cervical cancer. qRT-PCR results were consistent with the mining analysis ($P<0.05$). Functional enrichment analysis suggested involvement of these lncRNAs in the biological process of lymph node metastasis. ROC curves demonstrated satisfactory discrimination power of MIR100HG and AC024560.2 with areas under the curve of 0.801 and 0.837, respectively. Survival curve also indicated that patients with high MIR100HG expression had a tendency of poor prognosis.
28	Increased expression of SRPK1 (serine/arginine-rich protein-specific kinase 1) is associated with progression and unfavorable prognosis in cervical squamous cell carcinoma. Dong, *et al.,* (2022) [28]	SRPK1, mRNA	SRPK1 mRNA significantly upregulated in CESC samples. Higher SRPK1 protein abundance in CESC specimens associated with worse survival. SRPK1 identified as an independent prognostic factor of CESC. SRPK1 function validated in cellular experiments showing enhanced CESC proliferation, migration, and invasion.
29	Gene expression analysis in cervical cancer progression: toward unveiling alterations from normal to tumoral tissue. Abreu, Fernanda Pessi de; Casa, Pedro Lenz; Rossetto, Marcos Vinicius;de Oliveira, Nikael Souza; Benvenuti, Jean Lucas; Cassol, Matheus Pedron; Brollo, Janaina; Sartor, Ivaine Tais Sauthier; de Avila e Silva, Scheila. (2022) [29]	CDKN2A, CRCT1, CRISP3, CRNN, SG1, ESR1, FCGBP, HOPX, IVL, KRT1, KRT4, KRT13, MAL, PPP1R3C, SPINK5, SPRR1A, SPRR3, TCN1, UPK1A	19 DEGs involved in cervical cancer progression identified. CDKN2A upregulated, while 18 genes (CRCT1, CRISP3, CRNN, SG1, ESR1, FCGBP, HOPX, IVL, KRT1, KRT4, KRT13, MAL, PPP1R3C, SPINK5, SPRR1A, SPRR3, TCN1, and UPK1A) downregulated. Closer histological stages showed more similar expression profiles
30	Genetic polymorphisms in DNA repair genes and their association with cervical cancer. Abbas, M.; Srivastava, K.; Imran, M.; Banerjee, M. (2019) [30]	XRCC1+399A/G, XRCC2+31479G/A, XRCC3+18067C/T	XRCC1+399A/G genotype associated with 2.4-3.8 fold higher risk of cervical cancer ($P = 0.001$). The +399A* allele significantly linked with cervical cancer ($P = 0.002$). XRCC2+31479G/A and XRCC3+18067C/T polymorphisms showed no statistically significant associations.

31	Cervical cancer subtypes harboring integrated and/or episomal HPV16 portray distinct molecular phenotypes based on transcriptome profiling of mRNAs and miRNAs. Mandal, *et al.,* (2019) [31]	HPV16, mRNA	Investigation of mRNA and miRNA signatures among different categories of cervical cancer (CaCx) samples based on HPV16 physical status
32	Inhibition of inducible nitric oxide synthase (iNOS) by andrographolide and in vitro evaluation of its antiproliferative and pro-apoptotic effects on cervical cancer. Pasha, *et al.,* (2021) [32]	N/A	Examination of inducible nitric oxide synthase (iNOS) expression levels in cervical cancer, along with assessment of the potential inhibitory effects of andrographolide on iNOS.
33	Exploration of the molecular mechanisms of cervical cancer based on mRNA expression profiles and predicted microRNA interactions. Zhao, *et al.,* (2018) [33]	CHEK1, Mrna, CDKN2A, SOX17	Contribution to the characterization of underlying regulatory mechanisms of cervical cancer
34	Development and validation of blood-based predictive biomarkers for response to PD-1/PD-L1 checkpoint inhibitors: evidence of a universal systemic core of 3D immunogenetic profiling across multiple oncological indications. Hunter, *et al.,* (2023) [34]	PD-1/PD-L1	Development and validation of a predictive clinical blood test for response to PD-1/PD-L1 immune checkpoint inhibitors (ICIs)
35	Dynamics of fecal microbiota with and without invasive cervical cancer and its application in early diagnosis. Kang, *et al.,* (2020) [35]	Fecal microbiota-derived biomarkers	Creation of a diagnostic model aimed at early prediction of ICC, along with the discovery of potential biomarkers derived from fecal microbiota through the analysis of amplicon sequencing data
36	Application of deep learning in the automated analysis of molecular images in cancer: A survey. Xue, Yong; Chen, Shihui; Qin, Jing; Liu, Yong; Huang, Bingsheng; Chen, Hanwei. (2017) [36]	N/A	An overview of the utilization of deep learning techniques in molecular imaging for various cancer-related tasks, including tumor lesion segmentation, tumor classification, and survival prediction, was conducted.
37	Mathematical modeling of cervical precancerous lesion grade risk scores: linear regression analysis of cellular protein biomarkers and human papillomavirus E6/E7 RNA staining patterns. Bumrungthai, *et al.,* [37]	Cortactin, p16INK4A, Ki-67, HPV E6/E7	Patient age range and biomarker levels (cortactin, p16INK4A, Ki-67 by immunohistochemistry [IHC], and HPV E6/E7 ribonucleic acid [RNA] by in situ hybridization [ISH])
38	Predicting tumor budding status in cervical cancer using MRI radiomics: linking imaging biomarkers to histologic characteristics. Chong, *et al.,* (2021) [38]	LR, RF	AUC values and accuracy for LR: 0.742 and 0.769, RF: 0.782 and 0.731, SVM: 0.849 and 0.885, NN: 0.891 and 0.731, respectively, in the test dataset
39	A study on survival analysis methods using neural networks to prevent cancers. Bae, *et al.,* (2023) [39]	N/A	Introduction of a novel cancer prediction model based on recurrent survival deep learning algorithms
40	Senescence-associated secretory phenotype determines survival and therapeutic response in cervical cancer. Purohit, *et al.,* (2020) [40]	Senescence-associated secreted phenotype (SASP) proteins	Disease Specific Survival (DSS)
41	Spinal epidural metastasis from cervical cancer: report of two cases and literature review. Sun, *et al.,* (2022) [41]	N/A	Spinal epidural metastasis (SEM) from cervical cancer is extremely rare, mostly occurring in poorly differentiated carcinoma. Hematogenous spread is primary mechanism. Patients present with clinical manifestations of nervous system due to spinal cord compression. SEM from cervical cancer indicates late event with poor prognosis. Local treatments include surgery decompression and radiotherapy. Combining local and systemic therapy may prolong survival.
42	Effect of concurrent radiochemotherapy and chemotherapy on serum proteins as prospective predictors in patients with HPV-induced cervical cancer. Dasari, *et al.,* (2014) [42]	HPV 16/18 viral DNA, squamous cell carcinoma antigen, soluble CD44, and cancer antigen-125	Effectiveness of radiochemotherapy and chemotherapy on HPV-induced cervical cancer patients
43	Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. Bray, *et al.,* (2018) [43]	N/A	An update on the worldwide impact of cancer utilizing the GLOBOCAN 2018 projections

44	Prognostic factors associated with 5-year overall survival in cervical cancer patients treated with radical hysterectomy followed by adjuvant concurrent chemoradiation therapy at a tertiary care center in Eastern Europe. Stancac (2021) [44]	N/A	157 patients alive (70.07%): Out of the participants, 157 were still alive, accounting for 70.07%.
45	Prediction of postoperative pathologic risk factors in cervical cancer patients treated with radical hysterectomy using machine learning. Ou, Zhengjie, *et al.,* (2022) [45]	Blood markers associated with PRF: D-dimer and uric acid	Diagnostic prediction on pathologic risk factors (PRF) in cervical cancer before surgical intervention
46	CDKN2A inhibits cell proliferation and invasion in cervical cancer through the LDHA-mediated AKT/mTOR pathway. Luan, *et al.,* (2021) [46]	CDKN2A	Effect of CDKN2A on cell proliferation, invasion, and cell cycle in cervical cancer
47	Combination of radiomics and machine learning with diffusion-weighted MR imaging for clinical outcome prognostication in cervical cancer. Jajodia, *et al.,* (2021) [47]	GLSZM	Recurrence in 12 patients (23%), Metastasis in 15 patients (28%)
48	Meta-signature of human endometrial receptivity: a meta-analysis and validation study of transcriptomic biomarkers. Alitame, *et al.,* (2017) [48]	microRNA	Identification of meta-signature of endometrial receptivity involving 57 mRNA genes as putative receptivity markers
49	UHRF1 epigenetically downregulates UbcH8 to inhibit apoptosis in cervical cancer cells. Zhang, *et al.,* (2018) [49]	UHRF1, UbcH8, ISG15, HPV	Investigation of UHRF1 regulation in HPV oncogene E7 expressing cells and HPV-positive cervical cancer cells
50	Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. Sung, *et al.,* (2021) [50]	Female breast, lung, colorectal, prostate, stomach cancers	Update on global cancer burden using GLOBOCAN 2020 estimates

R. Summary of Evidence

This systematic review examined the development and application of predictive analytics frameworks for identifying biomarkers and predicting prognosis in cervical cancer [55]. Through a comprehensive analysis of 50 studies, the findings revealed the significant potential of predictive models to enhance accuracy in biomarker identification and prognosis prediction. Several key studies demonstrated how predictive analytics models could effectively segment cervical cancer lesions, diagnose the disease, and integrate novel biomarkers into machine learning frameworks to improve prognostic tools. For instance, the integration of specific biomarkers into prognostic nomograms was shown to significantly enhance accuracy, particularly in cases of cervical squamous cell carcinoma. Additionally, machine learning algorithms were employed to predict cervical cancer by identifying DNA methylation diagnostic biomarkers, achieving high sensitivity and specificity. These models not only distinguished cancerous tissue from normal tissue but also categorized patients into high-risk and low-risk groups for prognosis and survival predictions using imaging techniques such as computed tomography. Further research highlighted the potential of machine learning in analyzing bioinformatics data, advancing treatment strategies, and improving prognostic outcomes. Mathematical models were also developed to predict cervical cancer progression based on complex clinical imaging data, underscoring the growing role of predictive analytics in cervical cancer research. Overall, the review underscored the transformative potential of predictive analytics frameworks in enhancing diagnostic precision and personalizing treatment for cervical cancer while acknowledging the need for further research to refine these models and ensure their broad clinical applicability.

III. META-ANALYSIS

The study conducted a meta-analysis to evaluate the recurrence of biomarkers over time and predict prognosis using the predictive analytics tool GraphPad Prism, employing repeated measures ANOVA. This method was appropriate due to the presence of multiple measurements taken from the same subjects over an eight-year period.

A. Data Entry

The researchers entered the data into GraphPad Prism, organizing it with columns representing different biomarkers and rows corresponding to subjects or time points. Each cell contained the measurement of the respective biomarker for a subject at a specific time point.

B. Selection of Analysis

They accessed the “Analyze” menu in GraphPad Prism and selected “Repeated Measures ANOVA” from the list of available analyses.

C. Input Data

The team selected the appropriate data table and designated the columns containing biomarker measurements as dependent variables. They specified the independent variable as time (e.g., years) and defined the repeated measures

structure, indicating the occurrences and corresponding time points.

D. Adjustment of Settings

The researchers adjusted the analysis settings in GraphPad Prism by choosing the appropriate ANOVA model type (such as within-subjects factors or mixed models with between-subjects factors), managing any missing data, and adjusting for sphericity as necessary.

E. Interpretation of Results

After running the repeated measures ANOVA, they interpreted the results by examining the main effects of time and biomarkers, as well as any interactions between them. They considered significance levels and effect sizes to determine the clinical relevance of the findings.

F. Post-Hoc Tests

When significant effects were identified by the repeated measures ANOVA, the researchers conducted post-hoc tests to explore specific pairwise comparisons between time points or biomarkers. GraphPad Prism offered various post-hoc options, such as Tukey's multiple comparisons test and Bonferroni correction, which were utilized as appropriate.

G. Visualization of Data

To illustrate trends in biomarker recurrence over time, the team created visualizations, including line graphs and bar charts, using GraphPad Prism. These visual representations aided in the interpretation and presentation of the study's findings. This comprehensive approach enabled the researchers to effectively analyze longitudinal biomarker data, enhancing their understanding of biomarker recurrence and its prognostic implications in cervical cancer.

TABLE II DATA EXTRACTED FROM SYSTEMATIC REVIEWED PUBLICATIONS

Year	Biomarkers	MrNA	CDKN2A	HPV	UHRFI	SCC-AG
Year 1	2014			2		
Year 2	2016					1
Year 3	2017	1	1	1		1
Year 4	2018	2	1	1	1	
Year 5	2019	1	1	4	1	
Year 6	2020	1				
Year 7	2022	2	2			
Year 8	2023			1		

TABLE III DESCRIPTIVE STATISTICS

Particulars	MrNA	CDKN2A	HPV	UHRFI	SCC-AG
Number of Cases	5	4	5	2	2
Minimum	1.000	1.000	1.000	1.000	1.000
Maximum	2.000	2.000	4.000	1.000	1.000
Range	1.000	1.000	3.000	0.000	0.000
Mean	1.400	1.250	1.800	1.000	1.000
Std. Deviation	0.5477	0.5000	1.304	0.000	0.000
Std. Error of Mean	0.2449	0.2500	0.5831	0.000	0.000
Lower 95% CI of mean	0.7199	0.4544	0.1811	1.000	1.000
Upper 95% CI of mean	2.080	2.046	3.419	1.000	1.000
Coefficient of variation	39.12%	40.00%	72.44%	0.000%	0.000%
Lower 95% CI of geo. mean	0.8235	0.6851	0.7019	1.000	1.000
Upper 95% CI of geo. mean	2.114	2.064	3.273	1.000	1.000
Skewness	0.6086	2.000	1.714		
Kurtosis	-3.333	4.000	2.664		
Sum	7.000	5.000	9.000	2.000	2.000

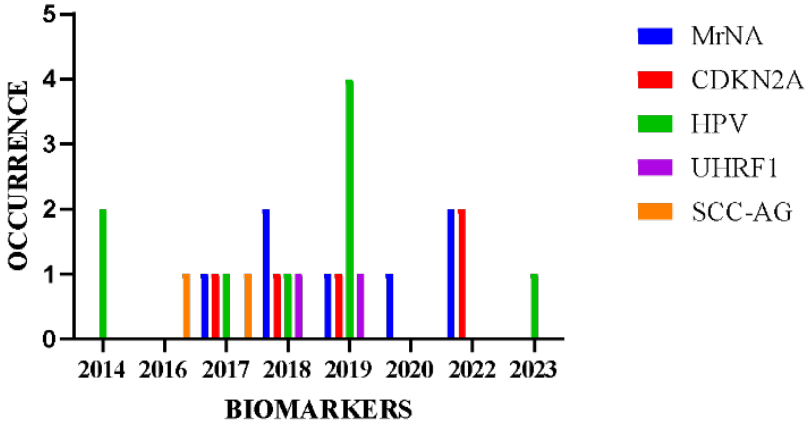

Fig. 2 Visualized Data of 5 Biomarkers Recurrence Over Time

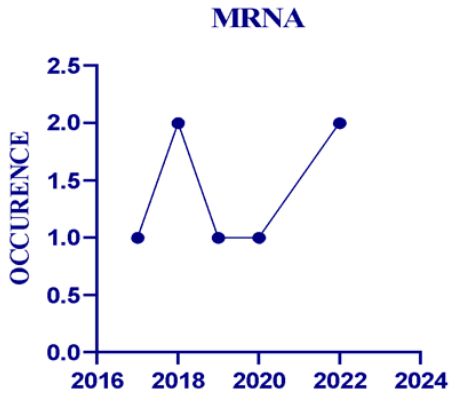

Fig. 2 (a) mRNA Biomarker

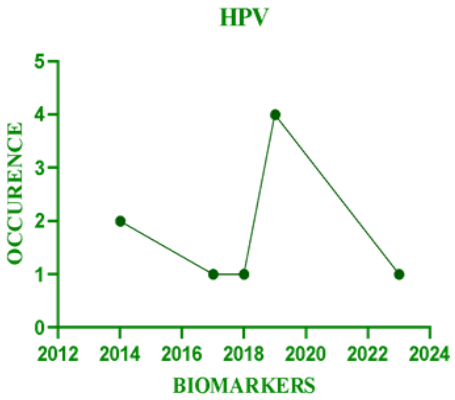

Fig. 2 (c) HPV Biomarker

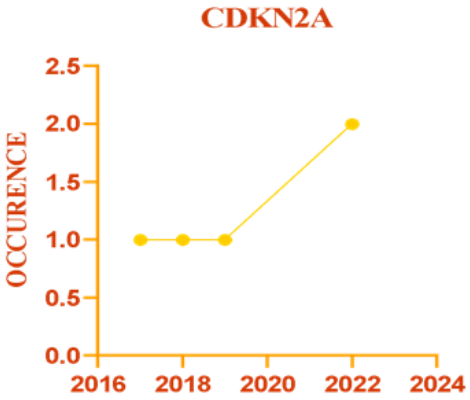

Fig. 2 (b) CDKN2A Biomarker

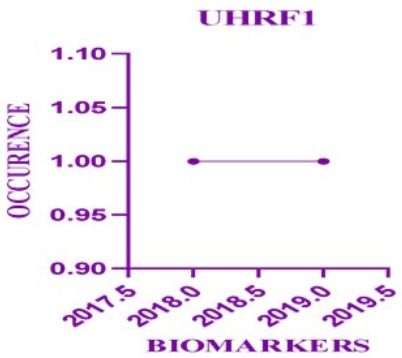

Fig. 2 (d) UHRF1 Biomarker

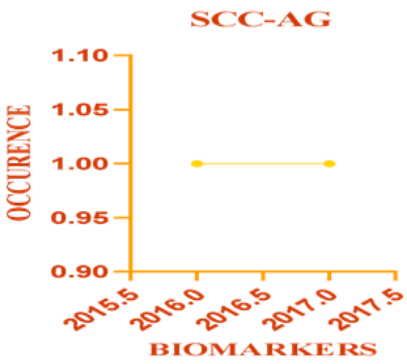

Fig. 2 (e) SCC-AG Biomarker

TABLE IV DESCRIPTIVE STATISTICS

Table Analyzed	Biomarkers Recurrence
Data sets analyzed	A-E
ANOVA Summary	
F	0.5675
P value	0.6908
P value summary	ns
Significant diff. among means (P < 0.05)?	No
R squared	0.1486
Brown-Forsythe test	
F (DFn, DFd)	0.5675 (4, 13)
P value	0.6908
P value summary	ns
Are SDs significantly different (P < 0.05)?	No
Data Summary	
Number of treatments (columns)	5
Number of values (total)	18

By performing repeated measures one-way ANOVA in GraphPad Prism, as shown in Table IV, and interpreting the results, the researchers were able to assess biomarker recurrence over time and facilitate informed prognostic evaluations based on the data.

H. Synthesis of Meta-Analysis Findings

The meta-analysis in this study utilized repeated measures ANOVA to analyze cervical cancer biomarker recurrence over an 8-year span, revealing critical insights into biomarker behavior, as shown in Table II, and their implications for cancer progression and prognosis.

The findings, which highlighted the dynamic nature of biomarker expression on table III, are discussed in detail below:

1. mRNA Levels

a. *Initial Absence and Gradual Increase:* mRNA levels were initially absent in 2014 but began to appear in subsequent years, as shown in Figure 2 (a). The gradual increase suggests that mRNA expression may correlate with specific cancer stages or treatment responses over time. The rising trend, peaking in 2022 and 2023, indicates a significant role in the recurrence of cervical cancer. This trend could be linked to changes in gene expression as the disease progresses or responds to therapeutic interventions.

b. *Implications for Cancer Progression:* The fluctuation in mRNA levels highlights its potential as a marker for both diagnosis and monitoring recurrence. Variations in mRNA may reflect the reactivation of certain genes tied to oncogenesis or tumor suppression, underscoring its importance in the tumor microenvironment.

2. CDKN2A

a. *Consistent Presence from 2017:* CDKN2A, as shown in Figure 2 (b), is a well-known tumor suppressor gene involved in cell cycle regulation. It exhibited a consistent presence from 2017 onward, with steady but irregular fluctuations. This consistent activity implies that CDKN2A could be a stable and reliable biomarker for predicting cervical cancer recurrence.

b. *Role in Recurrence and Prognosis:* As a key regulator of cell division, CDKN2A's persistent presence may indicate its role in controlling cellular mechanisms during recurrence. The observed irregularities might reflect the body's attempts to counteract the proliferation of malignant cells. Monitoring CDKN2A could provide valuable information for prognosis, particularly in assessing the risk of tumor progression.

3. HPV

a. *Sharp Increase in 2019 and Subsequent Disappearance:* The sharp rise in HPV activity, as shown in Figure 2 (c), in 2019, followed by its sudden absence in subsequent years, suggests episodic viral reactivation or a transient role in later stages of cervical cancer. HPV is the primary cause of cervical cancer, and its fluctuating presence may be related to viral latency and reactivation during cancer progression.

b. *Reactivation and Therapeutic Targeting:* The transient nature of HPV activity may have implications for treatment, particularly in considering whether therapeutic strategies should focus on early interventions targeting HPV. Its temporary spike in 2019 could also be linked to changes in immune system responses, potentially due to treatments such as radiation or chemotherapy.

4. UHRF1 and SCC-AG

a. *Sporadic but Consistent Activity:* UHRF1 and SCC-AG exhibited sporadic but consistent activity, as shown in Figure 2 (d), across the 8-year span. UHRF1, which is involved in epigenetic regulation, and SCC-AG, a well-established tumor marker, both demonstrated irregular peaks. Their sporadic activity may be tied to specific phases of cancer recurrence or shifts in tumor biology.
b. *Predictive Potential for Treatment Responses:* The behavior of UHRF1, in particular, suggests its role in DNA methylation processes, which are crucial for regulating gene expression. These sporadic patterns might indicate epigenetic modifications during tumor recurrence. Similarly, SCC-AG's consistent presence supports its continued use as a prognostic marker, particularly in detecting tumor burden or response to treatment.

I. Prognosis

The observed trends in biomarkers, particularly the consistency of CDKN2A and SCC-AG, suggest prolonged disruption in pathways related to cell cycle regulation and cancer progression. The fluctuating presence of mRNA and UHRF1 may reflect shifts in gene expression and epigenetic modifications. Additionally, the transient behavior of HPV, especially the spike in 2019, implies periods of heightened viral activity or reactivation. These findings underscore the complexity of cervical cancer recurrence, where multiple factors, including viral presence, epigenetic changes, and cell cycle disruptions, contribute to the overall prognosis. Continuous monitoring of these biomarkers is recommended to develop more precise prognostic models for cervical cancer patients.

IV. DISCUSSION

The findings from both the systematic review presented in Table I and the meta-analysis shown in Figure 2 clearly underscore the transformative potential of predictive analytics frameworks in the early diagnosis and prognosis of cervical cancer. The systematic review revealed how machine learning models, particularly deep learning frameworks, have been instrumental in identifying key biomarkers, segmenting cervical lesions, and predicting patient outcomes. These models, as evidenced by various studies, demonstrated high sensitivity and specificity, providing clinicians with enhanced diagnostic tools that surpass traditional methods reliant on subjective evaluations. This advancement offers substantial promise in reducing observer variability, a common challenge in cervical cancer diagnosis.

The meta-analysis further reinforced the value of predictive analytics by highlighting the recurrence patterns of biomarkers such as mRNA, CDKN2A, HPV, UHRF1, and SCC-AG. By analyzing individual biomarker levels, as shown in Figure 2, over an extended period, the study provided valuable insights into the temporal dynamics of cervical cancer progression and recurrence. Specifically, the fluctuations in mRNA and UHRF1 indicate that these biomarkers may be subject to changes in tumor biology or treatment response over time. This observation highlights the need for continuous monitoring of biomarker levels in patients, as these variations could have critical implications for treatment decisions and the timing of interventions.

Despite these promising findings, several challenges remain. One key challenge lies in the variability of biomarker expression, as depicted in Figure 2, which was evident in the inconsistent presence of mRNA, HPV, and UHRF1 over the 8-year span. This variability suggests that while these biomarkers have potential, their expression is influenced by a range of factors, including treatment modalities, tumor heterogeneity, and genetic variability among patients. This underscores the need for further research to refine predictive models, ensuring they can account for such fluctuations and provide more consistent results across diverse patient populations. Additionally, future studies should explore the biological mechanisms driving these fluctuations, which could reveal new therapeutic targets or strategies for preventing recurrence.

Another challenge is the need for further validation of biomarkers such as CDKN2A and SCC-AG. Although these markers showed consistent presence and promise as reliable indicators of prognosis, as illustrated in Figure 2 (e), it is crucial to validate their effectiveness across larger and more diverse patient cohorts. This validation is especially important in low- and middle-income countries, where cervical cancer prevalence is higher but access to advanced diagnostic tools remains limited. Validating these markers in such settings could have a profound impact on global cervical cancer management, enabling early detection and improving outcomes for patients in resource-limited regions.

The integration of machine learning models with clinical data represents a significant advancement in personalized medicine, particularly for cervical cancer. These models have the potential to improve diagnostic accuracy and inform personalized treatment plans that consider the unique biological profile of each patient's cancer. This shift toward personalized care is critical, as it enables clinicians to tailor interventions based on individual risk factors and biomarker profiles, ultimately leading to better patient outcomes.

However, the success of predictive analytics frameworks depends on several factors. First, expanding datasets is crucial to improve the robustness and generalizability of these models. Large, diverse datasets that include patients from various geographic regions, ethnic backgrounds, and clinical settings will help ensure that predictive models are applicable across different populations. Second, addressing the limitations of current models, such as their reliance on retrospective data and potential biases in training datasets, will be key to enhancing their clinical utility. This includes ensuring that models are validated using prospective studies

and that biases related to age, ethnicity, and socioeconomic status are accounted for in model development.

Lastly, collaboration between clinicians, data scientists, and researchers is essential to fully realize the potential of predictive analytics in cervical cancer care. Interdisciplinary efforts can help bridge the gap between data-driven insights and practical clinical applications, ensuring that predictive models are not only accurate but also feasible to implement in real-world healthcare settings. As the field of predictive analytics continues to evolve, it holds the promise of revolutionizing cervical cancer diagnosis, treatment, and prognosis, ultimately reducing the global burden of this disease.

In conclusion, while predictive analytics frameworks have demonstrated significant potential in improving cervical cancer diagnosis and prognosis, ongoing research and development are essential to overcome the current challenges. By expanding datasets, refining models, and validating key biomarkers, these frameworks can become indispensable tools in personalized cervical cancer care.

IV. CONCLUSION

This study highlights the transformative role that predictive analytics frameworks can play in improving the diagnosis and prognosis of cervical cancer. By leveraging the power of machine learning, these frameworks offer enhanced precision in identifying key biomarkers and predicting disease progression, thus providing clinicians with valuable tools for early detection and personalized treatment planning. The integration of clinical data with predictive analytics not only addresses the challenges of subjectivity in traditional diagnostic methods but also opens new avenues for improving patient outcomes, especially for recurrent cervical cancer cases. However, while the results are promising, they also underscore the complexity of cervical cancer and the variability in biomarker expression over time. These findings remind us that cancer is not static, and neither should our approaches to fighting it. Continuous monitoring and a deeper understanding of the biological mechanisms driving recurrence are essential for refining these models. This will ensure that predictive frameworks remain accurate and applicable across diverse patient populations. Moving forward, collaboration between data scientists, clinicians, and researchers will be critical in bridging the gap between innovative analytics and practical clinical applications. As the field evolves, the hope is that these frameworks will empower healthcare professionals to offer more individualized and effective care, ultimately leading to better survival rates and quality of life for women diagnosed with cervical cancer. In essence, predictive analytics is not just a tool for understanding disease; it represents a shift toward more proactive, data-driven, and patient-centered healthcare. The journey ahead involves refining and validating these frameworks, but the path promises a brighter, more personalized future for cervical cancer care.

ABBREVIATIONS

CHEERS: Consolidated Health Economic Evaluation Reporting Standards
PICOS: Participants, Interventions, Comparators, Outcomes, Study Designs
PAF: Predictive Analytics Framework
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols
HPV: Human Papillomavirus
mRNA Messenger Ribonucleic Acid
CDKN2A: Cyclin Dependent Kinase Inhibitor 2A
UHRF1: Ubiquitin-like with PHD and Ring Finger Domains1
SCC-AG: Squamous Cell Carcinoma Antigen

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REFERENCES

[1] P. A. Cohen, A. Jhingran, A. Oaknin, and L. Denny, "Cervical cancer," *The Lancet*, vol. 393, no. 10167, pp. 169-182, Jan. 2019, doi: 10.1016/S0140-6736(18)32470-X.

[2] C. Gao, C. Zhou, J. Zhuang, L. Liu, and C. L., "MicroRNA expression in cervical cancer: novel diagnostic and prognostic biomarkers," *Wiley Online Library*, 2018. [Online]. Available: https://onlinelibrary.wiley.com/doi/abs/10.1002/jcb.27029. Accessed: Feb. 22, 2024.

[3] H. Xue, Z. Sun, W. Wu, D. Du, and S. Liao, "Identification of hub genes as potential prognostic biomarkers in cervical cancer using comprehensive bioinformatics analysis and validation studies," *Cancer Manag. Res.*, vol. 13, pp. 117-131, 2021, doi: 10.2147/CMAR.S282989.

[4] V. Basic, B. Zhang, J. Domert, U. Pellas, and T. Tot, "Integrative meta-analysis of gene expression profiles identifies FEN1 and ENDOU as potential diagnostic biomarkers for cervical squamous cell carcinoma," *Oncol. Lett.*, vol. 22, no. 6, pp. 1-9, Dec. 2021, doi: 10.3892/OL.2021.13101.

[5] W. Xu et al., "Integrative analysis of DNA methylation and gene expression identified cervical cancer-specific diagnostic biomarkers," *Signal Transduct. Target Ther.*, vol. 4, no. 1, 2019, doi: 10.1038/s41392-019-0081-6.

[6] K. Wu, Y. Yi, F. Liu, W. Wu, Y. Chen, and W. Zhang, "Identification of key pathways and genes in the progression of cervical cancer using bioinformatics analysis," *Oncol. Lett.*, vol. 16, no. 1, pp. 1003-1009, Jul. 2018, doi: 10.3892/OL.2018.8768.

[7] M. Salvatici et al., "Squamous cell carcinoma antigen (SCC-Ag) during follow-up of cervical cancer patients: Role in the early diagnosis of recurrence," *Gynecol. Oncol.*, vol. 142, no. 1, pp. 115-119, Jul. 2016, doi: 10.1016/j.ygyno.2016.04.029.

[8] Y. Li *et al.,* "A prognostic nomogram integrating novel biomarkers identified by machine learning for cervical squamous cell carcinoma," *J. Transl. Med.*, vol. 18, no. 1, pp. 1-12, 2020, doi: 10.1186/s12967-020-02387-9.

[9] X. Qu *et al.,* "Identification of a novel six-gene signature with potential prognostic and therapeutic value in cervical cancer," *Cancer Med.*, vol. 10, no. 19, pp. 6881-6896, Oct. 2021, doi: 10.1002/CAM4.4054.

[10] J. Tu *et al.,* "Tumor DNA methylation profiles enable diagnosis, prognosis prediction, and screening for cervical cancer," *Int. J. Gen. Med.*, vol. 15, pp. 5809-5821, 2022, doi: 10.2147/IJGM.S352373.

[11] S. Wang and X. Chen, "Identification of potential biomarkers in cervical cancer with combined public mRNA and miRNA expression

microarray data analysis," *Oncol. Lett.*, vol. 16, no. 4, pp. 5200-5208, Oct. 2018, doi: 10.3892/OL.2018.9323.

[12] G. Niu, D. Wang, Y. Pei, and L. Sun, "Systematic identification of key genes and pathways in the development of invasive cervical cancer," *Gene*, vol. 618, pp. 28-41, Jun. 2017, doi: 10.1016/j.gene.2017.03.018.

[13] P. A. Van Dam *et al.,* "Potential new biomarkers for squamous carcinoma of the uterine cervix," *ESMO Open*, vol. 3, no. 4, Jun. 2018, doi: 10.1136/esmoopen-2018-000352.

[14] H. Z. Qiu *et al.,* "Screening and discovery of new potential biomarkers and small molecule drugs for cervical cancer: A bioinformatics analysis," *Technol. Cancer Res. Treat.*, vol. 19, 2020, doi: 10.1177/1533033820980112.

[15] X. Zhang et al., "Promoter methylation analysis of DKK2 may be a potential biomarker for early detection of cervical cancer," *Asian Biomed.*, vol. 16, no. 4, pp. 181-189, 2022, doi: 10.2478/abm-2022-0022.

[16] N. P. Long *et al.,* "Systematic assessment of cervical cancer initiation and progression uncovers genetic panels for deep learning-based early diagnosis and proposes novel diagnostic and prognostic biomarkers," *Oncotarget*, vol. 8, no. 65, pp. 109436-109456, 2017, doi: 10.18632/oncotarget.22689.

[17] M. Rajput *et al.,* "Identification of key genes and construction of regulatory network for the progression of cervical cancer," *Gene Rep.*, vol. 21, 2020, doi: 10.1016/j.genrep.2020.100965.

[18] S. S. Saha *et al.,* "Expression signatures of HOX cluster genes in cervical cancer pathogenesis: Impact of human papillomavirus type 16 oncoprotein E7," *Oncotarget*, vol. 8, no. 22, pp. 36591-36602, May 2017, doi: 10.18632/ONCOTARGET.16619.

[19] X. Li *et al.,* "Prediction of lymphovascular space invasion using a combination of tenascin-C, cox-2, and PET/CT radiomics in patients with early-stage cervical squamous cell carcinoma," *BMC Cancer*, vol. 21, no. 1, pp. 1-13, 2021, doi: 10.1186/s12885-021-08596-9.

[20] N. C. Garbett *et al.,* "Strategies for screening and early detection of anal cancers: a narrative and systematic review and meta-analysis of cytology, HPV testing, and other biomarkers," *Wiley Online Library*, vol. 9, no. 1, p. 84710, Jan. 2014, doi: 10.1371/journal.pone.0084710.

[21] T. Shibata, B. J. Lieblong, T. Sasagawa, and M. Nakagawa, "The promise of combining cancer vaccine and checkpoint blockade for treating HPV-related cancer," *Cancer Treat. Rev.*, vol. 78, pp. 8-16, Aug. 2019, doi: 10.1016/j.ctrv.2019.07.001.

[22] H. Ding *et al.,* "The new biomarker for cervical squamous cell carcinoma and endocervical adenocarcinoma (CESC) based on public database mining," *Biomed. Res. Int.*, vol. 2020, 2020, doi: 10.1155/2020/5478574.

[23] M. Kori, K. Y. A.-Pl, "Potential biomarkers and therapeutic targets in cervical cancer: Insights from the meta-analysis of transcriptomics data within network biomedicine perspective," *PLOS ONE*, vol. 13, no. 7, Jul. 2018, doi: 10.1371/journal.pone.0200717.

[24] M. H. Elias, S. Das, and N. Abdul Hamid, "Candidate genes and pathways in cervical cancer: A systematic review and integrated bioinformatic analysis," *Cancers (Basel)*, vol. 15, no. 3, Feb. 2023, doi: 10.3390/cancers15030853.

[25] B. Sudha et al., "Identification of hub genes and role of CDKN2A as a biomarker in cervical cancer: An in-silico approach," *Human Gene*, vol. 33, p. 201048, Sep. 2022, doi: 10.1016/j.humgen.2022.201048.

[26] I. Khan *et al.,* "LC/MS-based polar metabolite profiling identified unique biomarker signatures for cervical cancer and cervical intraepithelial neoplasia using global and targeted," *Cancers (Basel)*, vol. 11, p. 511, 2019, doi: 10.3390/cancers11040511.

[27] C. Shang *et al.,* "Characterization of long non-coding RNA expression profiles in lymph node metastasis of early-stage cervical cancer," *Oncol. Rep.*, vol. 35, no. 6, pp. 3185-3197, 2016, doi: 10.3892/or.2016.4715.

[28] Z. Dong, X. Chang, L. Xie, Y. Wang, and Y. Hou, "Increased expression of SRPK1 (serine/arginine-rich protein-specific kinase 1) is associated with progression and unfavorable prognosis in cervical squamous cell carcinoma," *Bioengineered*, vol. 13, no. 3, pp. 6100-6112, 2022, doi: 10.1080/21655979.2022.2034705.

[29] F. P. de Abreu et al., "Gene expression analysis in cervical cancer progression: Towards unveiling alterations from normal to tumoral tissue," *Human Gene*, vol. 34, Dec. 2022, doi: 10.1016/j.humgen.2022.201131.

[30] M. Abbas, K. Srivastava, M. Imran, and M. Banerjee, "Genetic polymorphisms in DNA repair genes and their association with cervical cancer," *Br. J. Biomed. Sci.*, vol. 76, no. 3, pp. 117-121, Jul. 2019, doi: 10.1080/09674845.2019.1592884.

[31] P. Mandal *et al.,* "Cervical cancer subtypes harbouring integrated and/or episomal HPV16 portray distinct molecular phenotypes based on transcriptome profiling of mRNAs and miRNAs," *Cell Death Discov.*, vol. 5, no. 1, Dec. 2019, doi: 10.1038/s41420-019-0154-x.

[32] A. Pasha *et al.,* "Inhibition of inducible nitric oxide synthase (iNOS) by andrographolide and in vitro evaluation of its antiproliferative and proapoptotic effects on cervical cancer," *Oxid. Med. Cell. Longev.*, vol. 2021, 2021, doi: 10.1155/2021/6692628.

[33] L. Zhao *et al.,* "Exploration of the molecular mechanisms of cervical cancer based on mRNA expression profiles and predicted microRNA interactions," *Oncol. Lett.*, vol. 15, no. 6, pp. 8965-8972, Jun. 2018, doi: 10.3892/ol.2018.8494.

[34] E. Hunter *et al.,* "Development and validation of blood-based predictive biomarkers for response to PD-1/PD-L1 checkpoint inhibitors: Evidence of a universal systemic core of 3D immunogenetic profiling across multiple oncological indications," *Cancers (Basel)*, vol. 15, no. 10, 2023, doi: 10.3390/cancers15102696.

[35] G. U. Kang *et al.,* "Dynamics of fecal microbiota with and without invasive cervical cancer and its application in early diagnosis," *Cancers (Basel)*, vol. 12, no. 12, pp. 1-13, 2020, doi: 10.3390/cancers12123800.

[36] [36] Y. Xue, S. Chen, J. Qin, Y. Liu, B. Huang, and H. Chen, "Application of deep learning in automated analysis of molecular images in cancer: A survey," *Contrast Media Mol. Imaging*, vol. 2017, 2017, doi: 10.1155/2017/9512370.

[37] S. Bumrungthai *et al.,* "Mathematical modelling of cervical precancerous lesion grade risk scores: Linear regression analysis of cellular protein biomarkers and human papillomavirus E6/E7 RNA staining patterns," *Diagnostics*, vol. 13, no. 6, 2023, doi: 10.3390/diagnostics13061084.

[38] G. O. Chong *et al.,* "Predicting tumor budding status in cervical cancer using MRI radiomics: Linking imaging biomarkers to histologic characteristics," *Cancers (Basel)*, vol. 13, no. 20, 2021, doi: 10.3390/cancers13205140.

[39] C. Y. Bae, B. S. Kim, S. H. Jee, J. H. Lee, and N. D. Nguyen, "A study on survival analysis methods using neural network to prevent cancers," *Cancers (Basel)*, vol. 15, no. 19, 2023, doi: 10.3390/cancers15194757.

[40] S. Purohit *et al.,* "Senescence-associated secretory phenotype determines survival and therapeutic response in cervical cancer," *Cancers (Basel)*, vol. 12, no. 10, pp. 1-19, 2020, doi: 10.3390/cancers12102899.

[41] S. Sun, X. Gong, and F. Zhang, "Spinal epidural metastasis from cervical cancer: Report of two cases and literature review," *Gynecol. Oncol. Rep.*, vol. 44, Dec. 2022, doi: 10.1016/j.gore.2022.101096.

[42] S. Dasari, R. N. D. Shouri, W. Rajendra, and L. Valluru, "Effect of concurrent radiochemotherapy and chemotherapy on serum proteins for prospective predictors of patients with HPV induced cervical cancer," *Biomed. Pharmacother.*, vol. 68, no. 3, pp. 315-320, 2014, doi: 10.1016/j.biopha.2013.12.008.

[43] F. Bray, J. Ferlay, I. Soerjomataram, R. L. Siegel, L. A. Torre, and A. Jemal, "Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries," *CA Cancer J. Clin.*, vol. 68, no. 6, pp. 394-424, Nov. 2018, doi: 10.3322/caac.21492.

[44] M. Stanca and M. E. Căpîlna, "Prognostic factors associated with 5-year overall survival in cervical cancer patients treated with radical hysterectomy followed by adjuvant concurrent chemoradiation therapy at a tertiary care center in eastern Europe," *Diagnostics*, vol. 11, no. 3, Mar. 2021, doi: 10.3390/diagnostics11030570.

[45] Z. Ou *et al.,* "Prediction of postoperative pathologic risk factors in cervical cancer patients treated with radical hysterectomy by machine learning," *Curr. Oncol.*, vol. 29, no. 12, pp. 9613-9629, 2022, doi: 10.3390/curroncol29120755.

[46] Y. Luan, W. Zhang, J. Xie, and J. Mao, "CDKN2A inhibits cell proliferation and invasion in cervical cancer through LDHA-mediated AKT/mTOR pathway," *Clin. Transl. Oncol.*, vol. 23, no. 2, pp. 222-228, Feb. 2021, doi: 10.1007/s12094-020-02409-4.

[47] A. Jajodia *et al.,* "Combination of radiomics and machine learning with diffusion-weighted MR imaging for clinical outcome prognostication in cervical cancer," *Tomography*, vol. 7, no. 3, pp. 344-357, 2021, doi: 10.3390/tomography7030031.

[48] S. Altmäe *et al.,* "Meta-signature of human endometrial receptivity: A meta-analysis and validation study of transcriptomic biomarkers," *Sci. Rep.*, vol. 7, no. 1, Dec. 2017, doi: 10.1038/s41598-017-10098-3.

[49] Q. Zhang, L. Qiao, X. Wang, C. Ding, and J. J. Chen, "UHRF1 epigenetically down-regulates UbcH8 to inhibit apoptosis in cervical cancer cells," *Cell Cycle*, vol. 17, no. 3, pp. 300-308, Feb. 2018, doi: 10.1080/15384101.2017.1403686.

[50] H. Sung *et al.,* "Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries," *CA Cancer J. Clin.*, vol. 71, no. 3, pp. 209-249, May 2021, doi: 10.3322/caac.21660.

[51] B. Gousbi and A. R. Mohamed Shanavas, "A study: Breast cancer prediction using data mining techniques," *Asian Journal of Computer Science and Technology*, vol. 8, no. S2, pp. 52-56, Mar. 2019, doi: 10.51983/ajcst-2019.8.s2.2025.

[52] E. Onuiri, B. G. Akwaronwu, and K. C. Umeaka, "Environmental and genetic interaction models for predicting lung cancer risk using machine learning: A systematic review and meta-analysis," *Asian Journal of Computer Science and Technology*, vol. 13, no. 1, pp. 45-58, Apr. 2024.

[53] S. Shargunam and G. Rajakumar, "Predictive analysis on sensor data using distributed machine learning," *Asian Journal of Computer Science and Technology*, vol. 11, no. 1, pp. 1-4, Apr. 2022, doi: 10.51983/ajcst-2022.11.1.3071.

[54] B. Gousbi and A. R. Mohamed Shanavas, "A study: Breast cancer prediction using data mining techniques," *Asian Journal of Computer Science and Technology*, vol. 8, no. S2, pp. 52-56, Mar. 2019, doi: 10.51983/ajcst-2019.8.s2.2025.

[55] A. Journal, C. Science, and T. Issn, "Environmental and genetic interaction models for predicting lung cancer risk using machine learning: A systematic review and meta-analysis," *Asian Journal of Computer Science and Technology*, vol. 13, no. 1, 2024.

[56] S. Shargunam and G. Rajakumar, "Predictive analysis on sensor data using distributed machine learning," *Asian Journal of Computer Science and Technology*, vol. 11, no. 1, pp. 1-4, Apr. 2022, doi: 10.51983/ajcst-2022.11.1.3071.