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Integrating Psychoneuroimmunological Factors into AI-Driven Risk Stratification for Cervical Intraepithelial Neoplasia:A Mixed Bibliometric and Empirical Study from Northern Romania Focusing on Depression and Anxiety

Abstract: *Cervical intraepithelial neoplasia (CIN) is a multifactorial pathology mainly determined by persistent infection with high-risk human papillomavirus (HPV) genotypes and modulated by both immunological and psychological factors. This mixed bibliometric and empirical study integrates psychoneuroimmunological concepts with clinical data from a cohort of 150 patients (aged 18–55 years) from northern Romania. Seventy percent tested positive for high-risk HPV by self-sampling and all completed the PHQ-9 and GAD-7 scales that were subsequently assessed. Symptoms of depression and anxiety were prevalent, with anxiety being reported by 43% of participants who performed self-sampling at home. Fifty women with cytologically diagnosed HSIL underwent a comparative evaluation using both, classical colposcopy and the artificial intelligence-assisted EVA system (MobileODT, Israel). Artificial intelligence-based colposcopy demonstrated higher sensitivity (92% versus 82%) and higher diagnostic concordance (88%) with histopathological confirmation, suggesting superior accuracy and clinical feasibility. These results support the integration of psychoneuroimmunological and artificial intelligence-assisted diagnostic parameters into cervical cancer prevention frameworks, highlighting the importance through which artificial intelligence could complement neoplasia prevention, addressing psychological profile and biological markers to improve personalised risk stratification.*

Keywords: *cervical intraepithelial neoplasia; human papillomavirus; artificial intelligence; depression; anxiety; cervical cancer; psychoneuroimmunology; oncogenesis; Eva colposcope; self-sampling.*

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1. Introduction

Cervical intraepithelial neoplasia (CIN) encompasses a continuum of precancerous lesions of the cervical epithelium, most frequently resulting from persistent infection with high-risk human papillomavirus (HPV) genotypes, notably HPV-16 and HPV-18 (Kjaer et al., 2010). CIN is histologically graded into three tiers (CIN 1 – mild dysplasia, CIN 2 – moderate dysplasia and CIN 3 – severe dysplasia or carcinoma in situ), reflecting the extent of epithelial involvement and risk of malignant progression (Loopik et al., 2021). Cervical cancer remains the fourth most common malignancy among women worldwide, with over 600 000 new cases and more than 340 000 deaths annually, predominantly in low- and middle-income countries where screening and vaccination programs are limited (Hull et al., 2020).

The progression from CIN to invasive carcinoma is multifactorial, influenced not only by viral persistence but also by host immune status, age, parity, smoking, hormonal factors and co-infections (Tasic et al., 2018). While many CIN 1 and some CIN 2 lesions may regress spontaneously, CIN 3 lesions are considered high-risk and often require immediate intervention (Trimble et al., 2005). Predictive markers such as p16^INK4a, Ki-67, E6/E7 mRNA and histopathological margins have been integrated into current management guidelines to improve stratification and personalise treatment (Gustinucci et al., 2016).

In recent years, artificial intelligence (AI) and machine learning (ML) have advanced cancer prediction, offering superior performance in analyzing complex datasets and detecting nonlinear interactions among variables (Zhang et al., 2023). AI based tools have demonstrated high accuracy in automated cytology, colposcopic image interpretation and CIN recurrence prediction (Hou et al., 2022). Techniques such as convolutional neural networks (CNNs), random forests and support vector machines (SVMs) are increasingly applied in gynecologic oncology to enhance diagnostic precision and guide individualised follow-up strategies (Zhou et al., 2020).

However, a critical dimension in AI-assisted CIN modelling remains largely understudied: the role of psychological and psychiatric vulnerability, particularly mood and anxiety disorders. Depression and anxiety are highly prevalent in reproductive-age women and can alter immune function, behavioural patterns and stress reactivity, all of which may modulate the natural history of HPV infection and CIN progression (Zafar et al., 2024). This interconnection is addressed by the field of psychoneuroimmunology, which explores how psychological states influence immune regulation through neuroendocrine pathways such as the hypothalamic-pituitary-adrenal (HPA) axis, sympathetic nervous system and cytokine signaling (Dantzer, 2018).

Multiple studies have shown that chronic psychological stress and major depressive disorder are associated with increased levels of proinflammatory cytokines (e.g., IL-6, TNF-α, CRP), decreased natural killer (NK) cell activity, impaired T-cell function and a diminished response to viral infections, including HPV (Slavich et al., 2014). Psychiatric comorbidity is also associated with poor screening adherence, reduced vaccine uptake and increased cancer incidence across various types, including cervical cancer (Scott & Hoskin, 2024). A systematic review by Mossinger & Kostev (2023) identified a modest but significant association between depression and cancer development, particularly in immunologically driven malignancies (Mossinger & Kostev, 2023).

For the purposes of a conceptual AI framework, psychiatric vulnerability can be quantified using validated instruments such as PHQ-9 for depression and GAD-7 for anxiety, while immune dysregulation may be monitored through biomarkers including IL-6, TNF-α and CRP. Despite these findings, current CIN risk models and AI prediction tools rarely incorporate mental health data. Integrating psychiatric parameters into AI-enhanced models could improve risk-stratification, particularly for identifying vulnerable subpopulations. The inclusion of psychiatric data in electronic health records (EHRs) offers a feasible opportunity for AI-driven risk prediction, supporting preventive strategies and personalised follow-up in cervical oncology.

Ultimately, this mixed bibliometric-empirical study aims to develop the interconnection between depression, anxiety and CIN progression, while validating through empirical method aspects of the integration of psychoneuroimmunology with the proposed AI. The main theme

guiding this work is to pursue the conceptual and empirical integration through quantitative data on psychiatric vulnerability (depression, anxiety addressed in the current research), achieved through standardised instruments and biomarkers, with clinical variables and imaging data derived from AI to generate a stratification model for early and personalised prevention in CIN progression.

Given the global incidence and prevalence of cervical cancer and the improvement of visual skills of appropriately trained medical personnel, the integration of artificial intelligence into diagnostic procedures such as colposcopy represents a favourable strategy to improve the accessibility, consistency and efficiency of cervical screening. Artificial intelligence-based colposcopy improves diagnostic reproducibility and standardisation across clinical systems (Wentzensen et al., 2023).

2. Materials and Methods

2.1. Bibliometric and Conceptual Review

The present study was conceived as a narrative, interdisciplinary exploration focused on the potential integration of affective psychiatric disorders, depression and anxiety, into predictive frameworks for cervical intraepithelial neoplasia (CIN), viewed through the lens of psychoneuroimmunology and AI. It did not involve experimental or clinical procedures but rather relied on the critical synthesis of current literature, aiming to generate a conceptual model with relevance for future empirical research.

A structured literature search was conducted to identify relevant publications from January 2000 to February 2025 in PubMed, Scopus and Web of Science. The search strategy was built around four core conceptual pillars: (1) CIN/HPV, (2) Psychiatry, (3) Psychoneuroimmunology and (4) Artificial Intelligence. The following Boolean query exemplifies the search approach: (“cervical intraepithelial neoplasia” OR “CIN” OR “HPV”) AND (“depression” OR “anxiety” OR “Psychological stress”) AND (“psychoneuroimmunology” OR “HPA axis” OR “inflammation” OR “cytokine”) AND (“Artificial Intelligence” OR “Machine Learning” OR “predictive model”). After duplicate removal, titles and abstracts were screened for relevance. Full-text articles were assessed based on the following eligibility criteria: focus on CIN progression, HPV, persistence, psychoneuroimmunological mechanisms in oncology, AI/ML applications in gynecologic cancer, original research, systematic reviews or meta-analyses, publication in English, peer-reviewed journal. This process ensured a comprehensive coverage of the literature, leading to the inclusion of key studies that directly inform the framework.

Throughout the writing process, the methodological approach was guided by a chronological logic, beginning with the pathophysiology of CIN and HPV-mediated oncogenesis, followed by the role of the immune system in lesion persistence and clearance. This pathway naturally led to the exploration of how affective disorders, through neuroendocrine and inflammatory mechanisms, could influence the host’s immunologic capacity to respond to viral infection. These insights were then placed in dialogue with emerging technological advances in AI, particularly in relation to risk prediction and clinical decision-making in gynecologic oncology. For conceptual purposes, psychiatric factors were operationalised using validated tools (PHQ-9 for depression and GAD-7 for anxiety), while immune dysregulation was represented by biomarkers such as IL-6, TNF-α and CRP. These variables were considered potential inputs for a theoretical AI-based risk prediction framework.

Although AI is a central theme of the article, no AI algorithm was applied or developed as part of this review. The reference to AI remains theoretical and integrative, serving as a vector for conceptual innovation rather than a platform for data modeling. No computational modeling, dataset or algorithmic implementation was performed. AI is presented solely as a conceptual tool to integrate clinical, immunological and psychiatric data for future research and hypothesis generation. This distinction is explicitly acknowledged to avoid any confusion between theoretical modeling

and computational application. Ethical approval was not required, as no human or animal subjects were involved and no identifiable patient data were analysed.

In sum, this methodological approach blends narrative review with theoretical modeling, articulating a transdisciplinary conceptual framework integrating psychiatric factors into CIN risk prediction. Limitations of this approach include the narrative, non-systematic design and the absence of empirical data. Future studies should validate the concepts using patient cohorts, standardised psychiatric assessments and AI modeling to determine real-world applicability.

These methodological choices lay the groundwork for the conceptual AI framework presented in the Results section.

2.2.1. Empirical Component – HPV Self-Sampling and Psychometric Evaluation

Between march and july 2025, a total of 150 women from the Northern region of Romania were enrolled in a prospective screening initiative for cervical cancer prevention. Participants were offered the option of HPV self-sampling using validated molecular detection kits (PCR-based high-risk HPV DNA testing) and the samples were analysed in partnership with the CENTRAIX laboratory (based in France) with approval no. 13-131-/78.

In addition to the virological assessment, all participants completed assessment questionnaires that measured the symptoms of depression and anxiety that occurred during the self-sampling period using the **Patient Health Questionnaire** (PHQ-9) and **Generalised Anxiety Disorder Scale (**GAD-7) scales.

Sociodemographic data (age, residence, education level, socio-economic status), clinical parameters (HPV status, cytology results) and psychological measurements were collected while maintaining patient confidentiality in this publication.

Ethical approval was obtained from the ethics committee of the UMF 'Grigore T.Popa' Iasi and the Suceava County Clinical Hospital, and all participants gave informed consent.

Following analysis of the database, the prevalence of high-risk HPV infection, depressive and anxiety symptoms was calculated, and the correlations between HPV positivity and psychological variables were descriptively explored.

The findings were interpreted within the results of the bibliometric study on psychoneuroimmunology, corroborated with the results obtained from the empirical study and, in the final stage with the proposed conceptual model of artificial intelligence regarding the use of the EVA mobile colposcope.

Statistical studies were conducted with IBM SPSS Statistics. We shared the continuous variables (PHQ-9 and GAD-7 scores) as average plus or minus the standard deviation (SD) and looked at the differences between the HPV-positive and HPV-negative groups using t-tests for independent samples (as illustrated in table 1). For the categorical variables (the presence of severe anxiety), we used the Chi-square test to analyse the data. Statistical significance was set at $p < 0.05$. The differences between the groups with HPV and those without were analysed using the independent samples t-test if the data was normally distributed. If the data did not fit a normal distribution, the researchers used the Mann–Whitney U test instead.

Table 1. Psychological Profile and HPV Status among Participants (n = 150)

Variable	HPV-Positive (n = 105)	HPV-Negative (n = 45)	Total (n = 150)
Mean PHQ-9 score	8.5 ± 4.0	6.9 ± 3.5	8.0 ± 3.9
Mean GAD-7 score	7.8 ± 4.3	6.2 ± 3.7	7.4 ± 4.1
Clinically significant anxiety (%)	43%	22%	38%
Age range (years)	18–55	19–53	18–55

2.2.2. Comparative AI-assisted colposcopy

Participants with cytologically diagnosed HSIL (n = 50) subsequently underwent sequential colposcopic evaluation using both classical and AI-assisted techniques. The AI-assisted examination used the EVA system (MobileODT, Israel), which provides real-time image analysis through cloud-based algorithms. Histopathological results were used as the gold standard for diagnosis and accuracy.

3. Results

CIN is a premalignant lesion primarily associated with persistent infection by high-risk HPV types 16 and 18 (Castle et al., 2011; Schiffman et al., 2016). Progression or regression of CIN is influenced not only by viral persistence and host genetic susceptibility but also by psychological and behavioural factors. Depression and anxiety act through biological and behavioural mechanisms that can significantly modify CIN risk and progression. All findings presented in this section are derived from the synthesis of published literature, no new empirical data were generated.

3.1. Neuroendocrine Dysregulation and Immune Dysfunction Associated with Depression and Anxiety

Depression and anxiety induce chronic activation of the hypothalamic-pituitary-adrenal (HPA) axis, leading to sustained elevations of systemic cortisol (Glaser & Kiecolt-Glaser, 2005; Cohen et al., 2012). Elevated glucocorticoid levels exert immunosuppressive effects, impairing cytotoxic T lymphocytes and NK cell activity, which are essential for viral clearance and tumor immunosurveillance (Irwin & Cole, 2011; Lutgendorf et al., 2024). Consequently, persistent HPV infection is more likely, facilitating CIN establishment and progression.

Additionally, depression and anxiety are associated with chronic low-grade systemic inflammation, characterised by elevated levels of IL-6, TNF-α and CRP (Dantzer, 2018; Miller et al., 2009). This inflammatory state contributes to cervical microenvironment alterations, including oxidative stress and epigenetic modifications, which may promote neoplastic transformation (Da Silva et al., 2021). Epidemiological evidence supports that women with severe depressive or anxious symptoms exhibit higher rates of persistent HPV infection and CIN progression (Herweijer et al., 2024).

3.2. Behavioural Factors Affecting CIN Outcomes

Depression and anxiety can influence patient behaviors relevant to CIN outcomes. Core symptoms such as fatigue, anhedonia and hopelessness may reduce motivation to attend routine cervical cancer screenings and follow-up appointments (Kroenke et al., 2010; Wu et al., 2021). Behavioural disengagement amplifies biological vulnerability by delaying diagnosis and management, potentially increasing the risk of CIN progression from low- to high-grade lesions.

This reciprocal relationship between psychological distress and cervical disease progression creates a feedback loop: immunosuppression and inflammation exacerbate CIN risk, which in turn may worsen psychiatric symptoms and behavioural non-compliance, emphasising the need for holistic patient care (Luo et al., 2025).

3.3. Integrating Psychoneuroimmunology Factors into AI-based CIN Risk Prediction Models

Current AI models for CIN risk prediction typically incorporate histopathology, HPV genotyping, demographic factors and selected immunological markers (Hou et al., 2022). However, mental health variables are rarely included, limiting the comprehensiveness of risk stratification.

Current AI models for CIN risk prediction remain constrained by their primary reliance on clinicopathological data, overlooking potentially significant mental health variables (Abrar et al., 2025). To address this limitation, we propose a concrete conceptual framework for multimodal data integration. The foundational innovation lies in the systematic incorporation of standardised

psychometric and behavioural metrics alongside traditional clinical and immunological inputs. Psychiatric data quantified using validated instruments such as the Patient Health Questionnaire-9 (PHQ-9) and Generalised Anxiety Disorder-7 (GAD-7) administered at diagnosis and subsequent follow-ups can be operationalised using established severity thresholds (e.g., scores of 5 – 9 for mild, 10 – 14 for moderate and ≥ 15 for severe symptoms) (Kroenke et al., 2016; Kroenke et al., 2001). These can be complemented by behavioural data extracted from electronical health records, such as history of missed screening appointments (Kariotis et al., 2022). Crucially, these psychosocial parameters are integrated with quantifiable immunological biomarkers (e.g., C-reactive protein > 3 mg/L, IL-6, TNF-α levels) and standard clinical variables (HPV genotype, CIN grade, p16/Ki-67 status) (Li et al., 2025; Zhong et al., 2015).

From a computational perspective, a tree-based ensemble model, such as Random Forest or eXtreme Gradient Boosting (XGBoost), is hypothetically well-suited for this task due to its capacity to handle heterogeneous data types and model complex, non-linear interactions. Such a model would be trained to predict a binary endpoint of "High Risk of Progression", defined as histological persistence or progression of CIN within 24-month surveillance period (Imani et al., 2025; Jha, Gupta & Saxena, 2021; Zhai et al., 2024).

The potential clinical utility of this framework is illustrated by a hypothetical scenario involving two patients with identical, low-risk clinical profiles (CIN1, non-HPV16/18 infection). While a conventional model would classify both as low risk, the integration of data for the patient with severe depression (PHQ-9 = 17), elevated inflammation (CRP = 8 mg/L) and poor adherence history would likely prompt risk reclassification to "High". This would, in turn, trigger a personalised management pathway entailing intensified surveillance (e.g., 6-month colposcopy) and a referral for psychological support, thereby addressing latent risk otherwise imperceptible to standard models. A visual representation of this proposed conceptual workflow is provided in *Figure 1*.

This flowchart illustrates the proposed conceptual framework for integrating psychoneuroimmunological factors into an AI-driven risk stratification model for CIN. Multimodal input data (clinical, immunological and psychiatric) is processed by a machine learning model to generate an integrated risk score. This score subsequently guides personalised patient management pathways, aiming to identify high-risk patients based on psychoneuroimmunological vulnerability who would be missed by traditional clinical assessment alone.

The implementation of such a psychoneuroimmunologically-informed AI model holds the potential to significantly refine risk stratification. Incorporating these variables could allow AI models to identify patients at high CIN risk despite a low-risk molecular and histological profile, enabling targeted psychosocial and preventive interventions. This approach aligns with the core principles of precision medicine by integrating biological, psychological and behavioural dimensions into predictive oncology.

To summarise the key biological pathways underpinning this framework, Table 2 outlines the principal psychoneuroimmunological mechanisms through which depression and anxiety contribute to CIN persistence and progression, alongside their potential inputs for AI-based stratification.

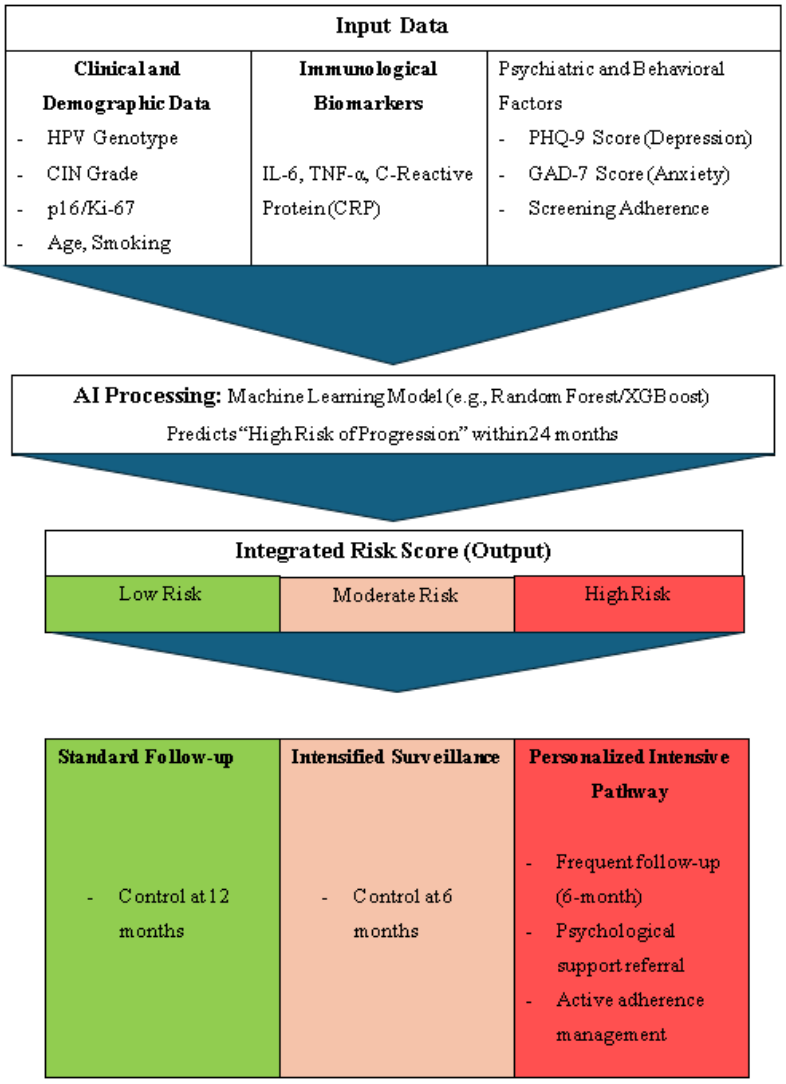

Figure 1. Conceptual workflow for a psychoneuroimmunologically-informed AI model for CIN risk stratification

Table 2. Psychoneuroimmunological mechanisms linking depression and anxiety with CIN progression

Psychoneuroimmunological Mechanism	Effect of Depression/Anxiety	Implication for CIN/Oncogenesis	Potential AI Input	Key References
HPA Axis Hyperactivation	Elevated systemic cortisol	Impaired HPV clearance » CIN persistence	Cortisol levels	Glaser & Kiecolt-Glaser, 2005; Irwin & Cole 2011
Chronic Inflammation	Elevated IL-6, TNF-α, CRP	Microenvironment changes » neoplastic transformation	IL-6, TNF-α, CRP	Miller et al., 2009; Da Silva et al., 2021
Immune Cell Dysfunction	Reduced NK and cytotoxic T cell activity	Weak viral control » CIN persistence and progression	NK cell activity, T cell counts	Lutgendorf et al., 2024
Behavioral Disengagement	Avoidance, missed appointments, poor screening adherence	Delayed diagnosis » progression from CIN II/III to carcinoma	Screening adherence records, PHQ-9, GAD-7	Kroenke et al., 2010 ; Wu et al., 2021
Psychopathology – Disease Feedback Loop	Worsening distress due to disease burden	Reinforces immune suppression and non-compliance	Combined behavioural and biological features	Luo et al., 2025

3.4. Descriptive Findings from the Northern Romanian Cohort

Following the empirical study, the results demonstrated that of the 150 women tested through HPV self-sampling, 34% were positive for high-risk HPV genotypes, predominantly HPV-16 and HPV-18. The mean PHQ-9 score was 8.2 ± 4.5, indicating mild depressive symptoms, while the mean GAD-7 score was 7.6 ± 4.2, suggesting mild-to-moderate anxiety, as illustrated in figure 2.

Participants with HPV-positive results exhibited significantly higher mean depression and anxiety scores compared to HPV-negative participants ($p < 0.05$). The connection between mental stress and the presence of the virus backs up the previously mentioned link between mental health and the immune system and gives initial support for the AI ideas discussed in this paper.

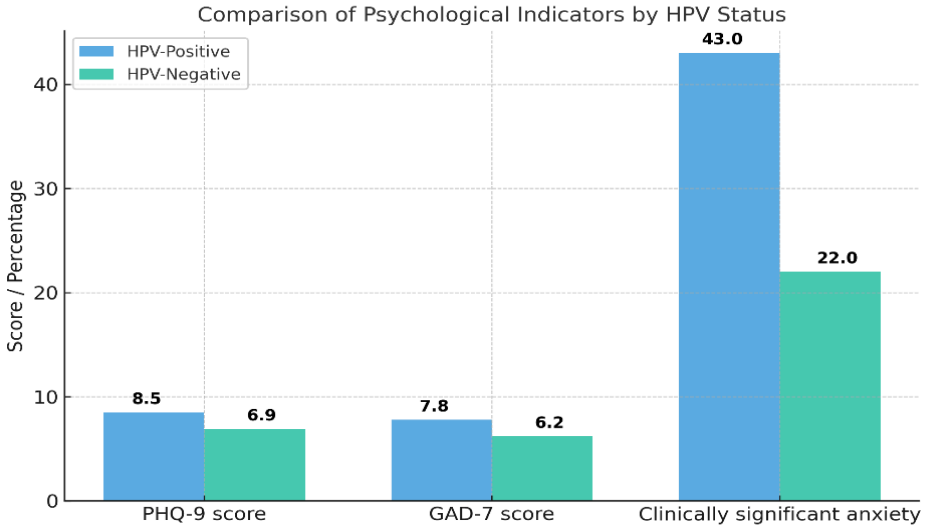

Figure 2. Comparison of psychological indicator according to HPV status

Comparative evaluation of colposcopy with AI among the patients diagnosed with HPV positive, 50 of them were diagnosed with HSIL (High Grade Squamous Intraepithelial Lesion). In the same number of patients, both colposcopy methods were used so that:

a) Classical colposcopy identified lesions compatible with HSIL in 41 cases (82%).

b) EVA colposcopy assisted by AI detected 46 cases (92%), all confirmed histologically.

These results were illustrated in Figure 3.

In conclusion, on this number of samples, the diagnostic concordance between the two methods was 88%, and the method using artificial intelligence demonstrated a slightly superior visualisation of the transformation areas.

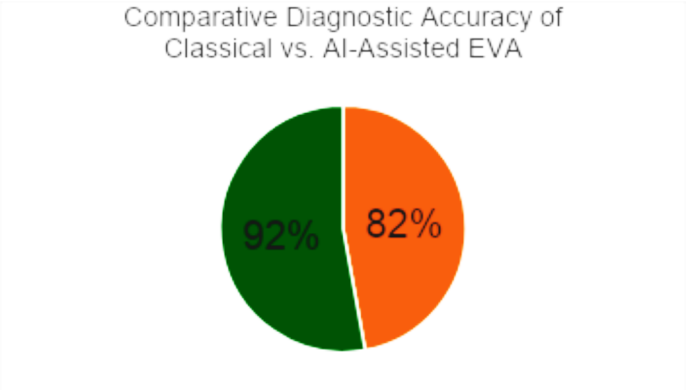

Figure 3. Comparative diagnostic accuracy of classical vs. AI-assisted EVA colposcopy (n = 50)

4. Discussions

The findings of this review underscore an emerging paradigm in cervical pathology: that affective disorders such as depression and anxiety may not merely coexist with cervical intraepithelial neoplasia (CIN), but may act as biologically active and behaviourally significant modulators of its progression. This conceptual shift, moving from comorbidity framework to one of causal interdependence, demands a reevaluation of how we understand, monitor and predict the evolution of HPV-associated cervical disease.

4.1. Depression, Anxiety and the Immune Microenvironment of CIN

Extensive psychoneuroimmunological literature supports the biological plausibility that chronic psychological stress associated with depression and anxiety disrupts key immune functions relevant to viral clearance and tumor suppression. The persistent activation of the hypothalamic-pituitary-adrenal (HPA) axis and the concomitant elevation in circulating glucocorticoids result in reduced activity of cytotoxic T lymphocytes and NK cells, which are critical in limiting the persistence of oncogenic HPV types (Irwin & Cole, 2011; Lutgendorf et al., 2024). Moreover, affective disorders upregulate inflammatory signaling cascade , characterised by increased levels of IL-6, TNF-α and CRP, cytokines known to contribute to local immune dysregulation, angiogenesis and epithelial mesenchymal transition, all of which are implicated in neoplastic progression (Miller et al., 2009; Dantzer, 2018; Da Silva et al., 2021).

Within the cervical microenvironment, these neuroendocrine and inflammatory perturbations may synergise with HPV-induced oncogenesis to accelerate the transformation from low-grade lesions to high-grade CIN. Although most CIN I lesions regress spontaneously, the biological vulnerability imposed by chronic stress may compromise immune clearance, favouring lesion persistence and progression (Herweijer et al., 2024).

4.2. Behavioural Pathways: The Unseen Risk Amplifiers

Equally significant are the behavioural dimensions of depression and anxiety, which undermine participation in preventive healthcare. Individuals affected by these conditions often exhibit poor adherence to cervical screening guidelines, increased rates of appointment cancellation or non-attendance and diminished compliance with therapeutic recommendations (Garpenhag & Dahlman, 2024; Kroenke et al., 2010). Such disengagement has direct clinical consequences, as delayed diagnosis and suboptimal follow-up are well-documented risk factors for the development of cervical cancer from precursor lesions (Luvian-Morales et al., 2024).

This interaction produces a self-reinforcing cycle in which psychological distress contributes to lesion progression both biologically and behaviourally, while the evolving disease process further exacerbates mental health symptoms through fear, stigma and medical burden. This bidirectional relationship mirrors findings in other oncological contexts, such as breast and ovarian cancer, where affective disturbances correlate with accelerated disease progression and worse prognosis (Lutgendorf et al., 2024; Spiegel & Giese-Davis, 2003).

4.3. Toward a Psychoneuroimmunologically-Informed Risk Stratification

The implications of these findings extend beyond theoretical insight and point toward a clear clinical imperative: the integration of psychiatric variables into existing and future risk prediction frameworks. AI presents an unparalleled opportunity to achieve this integration through the fusion of heterogeneous data types (molecular, histological, behavioural and psychological). However, current AI models used in CIN risk prediction typically omit variables related to mental health, thereby potentially misclassifying a subset of patients with high latent risk (Lee et al., 2021; Lopez de Maturana et al., 2019).

The conceptual framework advanced in this review (***Figure 1***) directly addresses this gap by proposing a tangible structure for integration. As detailed in the Results section, the proposed model leverages tree-based ensemble algorithms, such as Random Forest or XGBoost, specifically chosen for their proven capability to handle the heterogeneous data types, clinical, immunological and psychiatric, that characterise the psychoneuroimmunological landscape (Imani et al., 2025; Jha, Gupta & Saxena, 2021; Zhai et al., 2024). The hypothetical clinical scenario illustrates precisely how this integration could function in practice: by reclassifying risk for patients whose high psychiatric burden (e.g., PHQ-9 = 17) and elevated inflammation (CRP = 8mg/L) would remain invisible to conventional, only clinicopathological models. This moves beyond theoretical appeal to demonstrate a feasible computational pathway.

Incorporating psychometric tools such as the PHQ-9 and HADS, alongside physiological stress markers like cortisol, IL-6 or CRP into AI training datasets may allow for more nuanced risk stratification. Such models could identify patients whose immunological profiles appear low-risk but whose psychiatric burden increases their likelihood of non-clearance of HPV or progression to CIN II/III. Furthermore, AI systems that predict not only disease biology but also behavioural adherence patterns could guide clinicians toward tailored interventions that include both gynecologic and psychological care pathways.

Recent work in integrative oncology supports this approach. For example, psychoneuroimmunological data have been successfully integrated into ML models predicting chemotherapy response and immune-related adverse events (Tang et al., 2024; Esteva et al., 2019), suggesting feasibility in the context of preinvasive disease as well.

4.4. Ethical and Implementation Considerations

The integration of sensitive mental health data into oncological risk models presents profound ethical challenges that must be addressed proactively. First, data privacy and security are paramount. Psychiatric information requires the highest level of protection within EHRs, with strict access controls and anonymisation protocols for research databases. Second, the process of informed consent must be transparent and nuanced. Patients must understand how their psychological data will be used to influence their cancer risk assessment and care pathway, including potential benefits (personalised care) and risks (data sensitivity). Third, there is a significant danger of stigmatisation. A “high psychiatric risk” score must not be used to blame patients but to trigger supportive interventions. Healthcare providers require training to interpret these scores within a biopsychosocial framework, framing depression as a modifiable risk factor similar to smoking, not a personal failing. Finally, algorithmic bias must be mitigated. AI models trained on non-diverse datasets could perpetuate disparities in mental health diagnosis and care. Therefore, future development must prioritise diverse, representative cohorts to ensure equity.

4.5. Empirical Validation and Implications for AI-Based Modelling

Following HPV self-sampling (both at home and in the outpatient setting after the procedure was described) and cytological evaluation, fifty participants in the cohort were identified with high-grade squamous intraepithelial lesions (HSIL) and were subsequently redirected for classic colposcopic examination.

In the context of increasing global efforts to simplify and optimise cervical cancer screening, artificial intelligence (AI)–assisted colposcopy, such as the EVA-Visualcheck™ system, has emerged as a practical solution capable of enhancing diagnostic accuracy and reducing operator dependence (Zimmer-Stelmach et al., 2022).

Both the classical and AI-assisted colposcopic evaluations were performed in the same clinical unit by the supervising physician.The classical method was performed according to the standard diagnostic protocol, involving the application of acetic acid and Lugol's iodine, while the AI-assisted examination used the image analysis embedded in EVA and the cloud-based algorithm for lesion classification. The main objective was to compare the diagnostic accuracy and

consistency of the AI-assisted method with those of conventional colposcopy, using cytology and histopathology as the reference standard.

Preliminary observations from the results suggest the superiority of AI-assisted colposcopy, demonstrating increased sensitivity in detecting HSIL-consistent visual features, particularly in cases with subtle transformation zones or inflammatory artefacts that might obscure conventional interpretation. In addition, the digital platform allowed for standardisation, storage, and remote examination of images—features that significantly improve reproducibility and potential integration into telemedicine workflows for future directions.

The results of this study support the hypothesis that AI-based diagnostic tools can complement classical visual assessment, especially in resource-limited settings or within screening programs. Correlating AI-based colposcopic data with psychoneuroimmunological and psychological parameters (namely, depression and anxiety scores mentioned and explained above) could generate a multimodal predictive environment that not only stratifies oncogenic risk, but also captures affective determinants that influence disease progression and adherence to monitoring.

4.6. Limitations and Future Directions

While this review proposes a novel integrative framework, several limitations must be acknowledged. In addition to the results of the bibliometric study, this research included, for reinforcement, an empirical study component involving 150 patients from the north of the country, which provides preliminary validation for the proposed theoretical framework.

Primarily, the narrative design, while appropriate for interdisciplinary synthesis, carries a risk of selection bias compared to a systematic review. However, the inclusion of psychometrically analyzed data from the empirical study and artificial intelligence-assisted diagnostics partially mitigates this limitation, guiding the conceptual discussion towards observations that can be applied to the general population. The evidence linking depression/anxiety to CIN progression, although mechanistically plausible, remains largely correlative. Moreover, our empirical findings showing higher PHQ-9 and GAD-7 scores among HPV-positive women—particularly those with HSIL lesions—demonstrated that psychiatric pathology on negative affect may indeed modulate local immune responses and viral persistence.

Longitudinal studies with serial psychological and immune assessments are needed to establish causality. A significant limitation of our AI framework is of purely conceptual nature. Although the findings of the empirical study based on AI-assisted EVA colposcopy indicated promising diagnostic accuracy, the broader AI framework proposed for predictive modeling remains conceptual at this time.

Future work must focus on empirical validation of the proposed model architecture. This entails curating large, multimodal datasets that include the psychiatric scores (PHQ-9, GAD-7), inflammatory biomarkers (e.g., CRP, IL-6) and clinical variables (HPV genotype, CIN grade)outlined in our framework. Future directions could also integrate digital colposcopy datasets, such as those generated by the EVA system, which allow for artificial intelligence-based image classification and comparison between clinical centres.

Subsequent steps involve training and testing the suggested tree-base models (e.g., XGBoost) to quantify the added predictive value of psychoneuroimmunological variables for CIN progression, ideally through prospective studies. Furthermore, the feasibility of routine psychosocial assessment in busy gynecological settings needs evaluation, potentially starting with pilot implementations in high-risk clinics.

5. Conclusions

The current study provides a double contribution, by integrating the two bibliometric and empirical approaches. The main role was to show the correlation of psychological vulnerability, immune regulation and artificial intelligence in the prevention and management of cervical

intraepithelial neoplasia (CIN). Beyond synthesizing evidence from psychoneuroimmunology, clinical oncology and artificial intelligence-based diagnosis, the present research introduces original data from a cohort of 150 women from the north of the country, confirming the feasibility and relevance of integrating affective and digital dimensions in preventive gynecology.

Biologically, chronic psychological distress disrupts homeostatic immune responses through dysregulation of the HPA axis, increased systemic inflammation and suppression of cytotoxic surveillance mechanisms essential for HPV clearance. These neuroendocrine and immunological changes create a permissive environment for viral persistence and epithelial transformation, particularly in patients predisposed to immune dysregulations. At the same time, from a behavioural standpoint, affective disorders are associated with reduced engagement in preventive care, delayed screening and poorer adherence to follow-up (factors that can allow otherwise manageable lesions to silently progress).

From an empirical evaluation perspective, this study indicated that combining AI-assisted diagnostic tools with psychoneuroimmunological and psychometric data could enhance the predictive potential of cervical cancer prevention strategies. The EVA AI colposcope demonstrated higher diagnostic accuracy for HSIL detection compared to conventional methods, supporting the emerging paradigm of digital precision medicine. The integration of psychological state assessments (PHQ-9, GAD-7), immune biomarkers (CRP, IL-6), and AI-derived imaging data could lay the foundation for a multidimensional model for personalized risk stratification in CIN detection.

Although previous research has reported mixed results regarding the diagnostic performance of artificial intelligence (AI)-assisted colposcopy compared to expert clinical assessment, continued algorithmic refinement and image standardisation suggest that systems such as EVA-Visualcheck™ will increasingly complement clinical expertise (Zimmer-Stelmach et al., 2022). From a broader perspective, incorporating psychometric data—such as depression and anxiety scores or psychiatric treatment history—into AI predictive frameworks could significantly improve the sensitivity and specificity of CIN risk estimation. The implications of this paradigm are both clinical and systemic. Clinicians are called to recognise and address mental health not only as a comorbidity but as an essential component of cervical cancer prevention strategies. Researchers are invited to develop and validate AI models capable of capturing the multidimensional nature of disease risk, moving beyond traditional biomedical silos. Healthcare systems must also adapt, fostering interdisciplinary collaboration between gynecologists, oncologists, psychiatrists, immunologists and data scientists to build the infrastructure necessary for integrated, personalised care.

Finally, this hybrid approach of empirical and bibliometric research highlights the need to evaluate biomedical and psychosocial profiles not only from a gynecological perspective in assessing the risk of CIN. A woman's mental health status, her stress levels, coping capacity and behavioural patterns are not external to her biology, they are deeply entangled with it. Understanding this interplay offers an opportunity to redefine prevention, expanding it from the early detection of cellular abnormalities to include the early recognition and clinical management of psychosocial factors that significantly influence disease progression.

In summary, this review argues for a paradigm shift in CIN management, where a patient's mental health status is recognised as a critical component of biological risk profile. The proposed conceptual framework outlines a feasible path for integrating this dimension into future AI-driven precision medicine. By fostering collaboration across gynecology, psychiatry, immunology and data science, we can move toward a more comprehensive and compassionate model of cervical cancer prevention that truly addresses the whole patient.

Ethical Approval

Approved by the Ethics Committee of "Grigore T. Popa" University of Medicine and Pharmacy Iași and Suceava County Clinical Hospital, Department of Gynaecology. All participants provided written informed consent.

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