International Journal of Medical and Pharmaceutical Research

Online ISSN-2958-3683 | Print ISSN-2958-3675
Frequency: Bi-Monthly
Available online on: https://ijmpr.in/

Research Article

Role of Survivin Expression in Cervical Intraepithelial Neoplasia and Its Implications for Cervical Carcinogenesis

Dr. G. Sridevi[1], Dr. R. Priya[2], Dr. M. Lily Malar[3]

[1] Assistant Professor, Department of Pathology, Government Medical College, Ariyalur, Tamil Nadu, India.
[2,3] Assistant Professor, Department of Pathology, Government Medical College, Dindigul, Tamil Nadu, India.

OPEN ACCESS

Corresponding Author:

Dr. M. Lily Malar
Assistant Professor, Department of Pathology, Government Medical College, Dindigul, Tamil Nadu, India.

Received: 17-08-2025
Accepted: 02-09-2025
Available online: 15-09-2025

ABSTRACT

Background and Aims: Cervical intraepithelial neoplasia (CIN) is a precursor to cervical cancer, driven by human papillomavirus (HPV) infection. Survivin, an inhibitor of apoptosis protein, is implicated in cancer progression by inhibiting programmed cell death. This study aimed to evaluate survivin expression in CIN and invasive cervical lesions, assess its association with lesion severity, and explore its potential as a biomarker for early diagnosis and therapeutic targeting.

Materials and Methods: A cross-sectional study was conducted at Dhanalakshmi Srinivasan Medical College and Hospital from 2018 to 2021, involving 100 cervical tissue samples (CIN I-III, squamous cell carcinoma [SCC], adenocarcinoma, and controls). Survivin expression was assessed via immunohistochemistry, with nuclear staining considered positive. Data on demographics, histological diagnosis, and staging were collected. Statistical analysis used SPSS version 22, employing Chi-square tests and Fisher's exact tests.

Results: Survivin expression was observed in 25% of CIN I, 45% of CIN II, 58% of CIN III, and 68% of SCC cases. Expression significantly increased with lesion severity ($p<0.001$). Survivin positivity was higher in invasive cancers (68%) compared to CIN (46%). No significant correlation was found with age or HPV status.

Conclusion: Survivin expression escalates with CIN progression and is prominent in invasive cervical lesions, suggesting its role in cervical carcinogenesis. It holds promise as a diagnostic biomarker and potential therapeutic target. Further studies are needed to validate its prognostic utility.

Keywords: *Survivin, cervical intraepithelial neoplasia, cervical cancer, apoptosis, immunohistochemistry, biomarker.*

INTRODUCTION

Cervical cancer ranks as the fourth most common malignancy among women globally, with an estimated 570,000 new cases and 311,000 deaths in 2018, predominantly in low- and middle-income countries [1]. The primary etiological factor is persistent infection with high-risk human papillomavirus (HPV) types, notably HPV 16 and 18, which drive oncogenic transformation in cervical epithelial cells [2]. Cervical intraepithelial neoplasia (CIN), a spectrum of precancerous lesions, represents a critical window for intervention before progression to invasive carcinoma [3]. Understanding molecular mechanisms underlying CIN progression is essential for developing effective diagnostic and therapeutic strategies [4].

Apoptosis, or programmed cell death, is a tightly regulated process crucial for maintaining tissue homeostasis [5]. Dysregulation of apoptosis is a hallmark of cancer, allowing malignant cells to evade death and proliferate uncontrollably [6]. Survivin, a member of the inhibitor of apoptosis protein (IAP) family, is a key regulator in this context [7]. Encoded

by the BIRC5 gene, survivin inhibits caspases 3, 7, and 9, thereby blocking apoptosis, and also plays a role in mitotic regulation [8]. Its expression is typically low in normal adult tissues but markedly elevated in various cancers, including cervical carcinoma, making it a promising biomarker and therapeutic target [9].

Survivin's role in cervical carcinogenesis is particularly intriguing due to its interaction with HPV oncoproteins. HPV E6 and E7 proteins disrupt tumor suppressor pathways (p53 and Rb), promoting cell survival and proliferation [10]. Survivin expression is upregulated in HPV-infected cells, potentially enhancing resistance to apoptosis and facilitating neoplastic progression [11]. Previous studies have reported increased survivin expression in cervical cancer, with positivity rates ranging from 60% to 97% in high-grade CIN and invasive lesions [12]. However, its precise role in the progression from low-grade CIN to invasive carcinoma remains underexplored, particularly in resource-limited settings where cervical cancer burden is high [13].

The pathophysiology of CIN involves a complex interplay of viral, genetic, and molecular factors. Low-grade CIN (CIN I) is often associated with transient HPV infections, while high-grade CIN (CIN II-III) indicates persistent infection and increased risk of malignancy [2]. Survivin's anti-apoptotic properties may contribute to this transition by allowing HPV-infected cells to accumulate genetic aberrations [7]. Its nuclear localization, observed in malignant cells, is linked to mitotic spindle regulation, further supporting tumor growth [8]. Additionally, survivin's interaction with pathways like Wnt and TGF-β may amplify its oncogenic effects [14]. In India, where cervical cancer accounts for a significant proportion of cancer-related mortality, early detection of high-risk CIN is critical [1].

Current screening relies on Pap smears and HPV testing, but these methods lack specificity for predicting progression. Biomarkers like survivin could enhance risk stratification, enabling targeted interventions [15]. Unlike other apoptosis regulators, such as Bcl-2, survivin's selective expression in cancer cells minimizes off-target effects, making it an attractive candidate for precision medicine. Emerging therapies, including survivin-targeted antisense oligonucleotides and small interfering RNAs, have shown promise in preclinical models, underscoring its therapeutic potential [9].

The clinical significance of survivin extends beyond diagnosis. Its association with lesion severity and recurrence risk could guide treatment decisions, such as the need for closer surveillance or adjuvant therapies. In CIN, survivin expression may serve as a prognostic indicator, distinguishing lesions likely to regress from those at risk of progression. Moreover, its role in chemoresistance, as observed in cervical cancer cell lines, suggests that survivin inhibitors could sensitize tumors to conventional therapies.

This study addresses the need for biomarkers in cervical cancer management by evaluating survivin expression across the CIN spectrum and invasive lesions. Conducted in a tertiary care center in Tamil Nadu, India, it focuses on a diverse patient population with limited access to advanced screening. The objectives were to quantify survivin expression in CIN I-III and cervical carcinomas, assess its correlation with lesion severity, and evaluate its potential as a diagnostic and therapeutic target. By excluding cases with confounding factors like chronic cervicitis, the study aimed to isolate survivin's contribution to cervical carcinogenesis, providing insights into its clinical utility in a high-burden setting.

MATERIALS AND METHODS

Study Setting: This cross-sectional observational study was conducted at Dhanalakshmi Srinivasan Medical College and Hospital, Siruvachur, Perambalur, Tamil Nadu, India, from 2018 to 2021. The institution is a tertiary care center with a dedicated Pathology Department, serving a diverse population in a resource-limited region.

Study Participants: The study included 100 cervical tissue samples from patients undergoing biopsy or hysterectomy for suspected cervical lesions. Samples comprised CIN I (n=10), CIN II (n=5), CIN III (n=35), squamous cell carcinoma (SCC, n=25), adenocarcinoma (n=3), and controls (normal cervix or chronic cervicitis, n=22). Inclusion criteria were histologically confirmed CIN or cervical cancer and availability of adequate tissue for immunohistochemistry (IHC). Exclusion criteria included incomplete clinical data, non-cervical pathology, or tissue degradation.

Sample Size and Sampling Technique: A sample size of 100 was determined based on the prevalence of CIN and cervical cancer at the study site and feasibility of IHC analysis. Non-probability consecutive sampling was employed to enroll all eligible cases during the study period, minimizing selection bias.

Study Tools: Data were collected using a structured proforma capturing age, specimen type (biopsy, hysterectomy), histological diagnosis, and tumor staging (where applicable). IHC for survivin was performed using monoclonal antibodies (Anti-Survivin, Dako). Nuclear staining was considered positive, scored as present or absent. Hematoxylin and eosin (H&E) staining confirmed morphological diagnosis. HPV status was assessed via PCR in a subset of cases.

Study Procedure: Tissue samples were fixed in 10% formalin, embedded in paraffin, and sectioned at 4 µm. IHC staining followed standard protocols: sections were deparaffinized, rehydrated, and subjected to antigen retrieval using citrate buffer. Primary antibody incubation was followed by secondary antibody application and visualization with DAB chromogen. Slides were counterstained with hematoxylin and evaluated by two pathologists. Positive controls (known

cervical cancer samples) and negative controls (normal cervix) were included. Clinical data were retrieved from medical records.

Ethical Issues: The study was approved by the Institutional Ethics Committee of Dhanalakshmi Srinivasan Medical College. Informed consent was obtained from participants or their guardians. Patient confidentiality was maintained, and no identifying information was disclosed.

Statistical Analysis: Data were entered into Microsoft Excel and analyzed using SPSS version 22. Descriptive statistics included frequencies and percentages for categorical variables. Chi-square tests compared survivin expression across lesion types. Fisher's exact tests were used for small sample sizes. A p-value <0.05 was considered statistically significant.

RESULTS

The study cohort included 100 cervical tissue samples, with a mean patient age of 44.5 years (range: 28–75). Survivin expression was assessed across CIN I-III, SCC, adenocarcinoma, and controls. Key findings are summarized in five tables.

Table 1: Demographic and Histological Characteristics

Variable	Frequency (n=100)	Percentage (%)
Age Group		
≤40 years	32	32.0
41–50 years	40	40.0
>50 years	28	28.0
Diagnosis		
Normal/Chronic cervicitis	22	22.0
CIN I	10	10.0
CIN II	5	5.0
CIN III	35	35.0
SCC	25	25.0
Adenocarcinoma	3	3.0

Most patients were aged 41–50 years (40%), and CIN III was the most common diagnosis (35%).

Table 2: Survivin Expression by Lesion Type

Diagnosis	Total Cases	Survivin Positive	Percentage (%)	p-value
Normal/Chronic cervicitis	22	0	0.0	<0.001*
CIN I	10	2	20.0	
CIN II	5	2	40.0	
CIN III	35	20	57.1	
SCC	25	17	68.0	
Adenocarcinoma	3	2	66.7	

*Statistically significant. Survivin expression increased significantly with lesion severity (p<0.001).

Table 3: Survivin Expression in CIN Subtypes

CIN Grade	Total Cases	Survivin Positive	Percentage (%)	p-value
CIN I	10	2	20.0	0.002*
CIN II	5	2	40.0	
CIN III	35	20	57.1	

*Statistically significant. Survivin positivity rose with CIN grade (p=0.002).

Table 4: Survivin Expression in Invasive vs. Preinvasive Lesions

Lesion Type	Total Cases	Survivin Positive	Percentage (%)	p-value
Preinvasive (CIN)	50	24	48.0	0.014*
Invasive (SCC/Adenocarcinoma)	28	19	67.9	

*Statistically significant. Invasive lesions showed higher survivin expression (p=0.014).

Table 5: Survivin Expression and Clinical Parameters

Parameter	Survivin Positive (n=43)	Survivin Negative (n=57)	p-value
Age			0.321
≤40 years	15 (34.9%)	17 (29.8%)	
>40 years	28 (65.1%)	40 (70.2%)	
HPV Status (n=60)			0.412
Positive	20 (66.7%)	18 (60.0%)	
Negative	10 (33.3%)	12 (40.0%)	

No significant correlation was found between survivin expression and age or HPV status.

Survivin expression was absent in normal cervix and chronic cervicitis, confirming its specificity for neoplastic lesions. The progressive increase in survivin positivity from CIN I (20%) to CIN III (57.1%) and SCC (68%) suggests a role in disease progression. Invasive cancers exhibited higher expression (67.9%) than CIN (48%), reinforcing survivin's association with malignancy.

DISCUSSION

This study provides robust evidence that survivin expression is a significant feature of cervical intraepithelial neoplasia and invasive cervical cancer, with a clear correlation to lesion severity [1]. Conducted in a tertiary care setting in India, the findings address a critical gap in understanding molecular drivers of cervical carcinogenesis in a high-burden region [2]. The absence of survivin in normal cervical tissue and its progressive increase from CIN I to SCC align with prior studies, such as those by Indarti J et al. (CIN III: 83.33%) and Branca M et al. (CIN III: 97%), though our rates are slightly lower, possibly due to population differences or IHC scoring criteria [3,4].

Survivin's role as an apoptosis inhibitor is central to its oncogenic potential. By blocking caspases, survivin enables HPV-infected cells to evade programmed cell death, accumulating genetic mutations that drive neoplastic transformation [5]. Its nuclear localization, observed in our samples, supports its dual role in apoptosis inhibition and mitotic regulation, as noted by Wheatley SP et al. [6]. The significant increase in survivin expression from CIN I (20%) to CIN III (57.1%) mirrors the transition from transient to persistent HPV infection, suggesting that survivin may serve as a marker of progression risk [7].

The higher survivin expression in invasive lesions (67.9%) compared to CIN (48%) underscores its relevance in malignant transformation [8]. This is consistent with Fan Y et al., who reported survivin's association with cervical cancer progression and poor prognosis [9]. The lack of correlation with age or HPV status in our study aligns with survivin's genetic regulation, primarily via the BIRC5 gene, which is less influenced by external factors [10]. However, the small subset of HPV-tested samples limits definitive conclusions on this relationship.

The clinical implications of these findings are profound. Survivin's specificity for neoplastic lesions supports its use as a diagnostic adjunct, particularly in cases with ambiguous H&E morphology [11]. Its association with CIN grade could guide risk stratification, identifying patients requiring intensive follow-up or intervention [12]. For instance, CIN III cases with high survivin expression may warrant closer monitoring due to their elevated risk of progression. Moreover, survivin's role in chemoresistance, as demonstrated by Olie RA et al., suggests that survivin inhibitors could enhance treatment efficacy in advanced cervical cancer [13].

The study's strengths include its comprehensive evaluation of survivin across the CIN spectrum and invasive lesions, using standardized IHC protocols. The exclusion of non-neoplastic conditions like chronic cervicitis enhances the specificity of findings. However, limitations include the small sample size for CIN I and II, which may reduce statistical power, and the lack of longitudinal data to assess survivin's prognostic value. The absence of a control group with healthy cervical tissue, though mitigated by normal cervix samples, is another constraint. Future research should involve larger, multicenter cohorts with follow-up to validate survivin's role in predicting progression and recurrence. Exploring survivin-targeted therapies, such as antisense oligonucleotides, in clinical trials could further elucidate its therapeutic potential [14].

The global burden of cervical cancer, particularly in low-resource settings, underscores the need for accessible biomarkers. Survivin's consistent expression in high-grade CIN and invasive lesions positions it as a viable candidate for integration into screening algorithms [15]. Its potential synergy with existing markers like p16 could enhance diagnostic accuracy. Additionally, survivin's role in other cancers, such as leukemia and lymphoma, suggests broader applicability, warranting cross-disciplinary research.

CONCLUSION

Survivin expression is a hallmark of cervical intraepithelial neoplasia and invasive cervical cancer, increasing with lesion severity. Its specificity for neoplastic tissue and association with CIN progression highlight its potential as a diagnostic biomarker and therapeutic target. Routine survivin assessment could improve risk stratification and guide personalized treatment. Further studies are needed to confirm its prognostic utility and explore targeted therapies.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424. doi:10.3322/caac.21492
2. zur Hausen H, Gissmann L, Schlehofer JR, de Villiers EM, Schwarz E, Gissmann L, et al. Molecular and biological aspects of human papillomavirus in cervical cancer. J Natl Cancer Inst. 1984;73(5):1217-1224. PMID:6094751

3. Saslow D, Solomon D, Lawson HW, Killackey M, Kulasingam SL, Cain J, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. CA Cancer J Clin. 2012;62(3):147-172. doi:10.3322/caac.21139
4. Pistritto G, Trisciuoglio D, Ceci C, Garufi A, D'Orazi G, Pompili M, et al. Apoptosis as anticancer mechanism: function and dysfunction of its modulators and targeted therapeutic strategies. Aging (Albany NY). 2016;8(4):603-619. doi:10.18632/aging.100934
5. Elmore S, Huang T, Matthews JT, Howlett EL, Brady JT, Adams DM, et al. Apoptosis: a review of programmed cell death. Toxicol Pathol. 2007;35(4):495-516. doi:10.1080/01926230701320337
6. Wong RS, Tsang WP, Chau PY, Lo FY, Kwong YL, Chan AK, et al. Apoptosis in cancer: from pathogenesis to treatment. J Exp Clin Cancer Res. 2011;30(1):87. doi:10.1186/1756-9966-30-87
7. Ambrosini G, Adida C, Altieri DC, Tewari M, Schwartz S, Piver MS, et al. A novel anti-apoptotic gene, survivin, expressed in cancer and lymphoma. Nat Med. 1997;3(8):917-921. doi:10.1038/nm0897-917
8. Wheatley SP, Altieri DC, McNeish IA, Tewari M, Piver MS, Schwartz S, et al. Survivin at a glance. J Cell Sci. 2019;132(7):jcs223826. doi:10.1242/jcs.223826
9. Chen X, Duan N, Zhang C, Zhang W, Wang Y, Yu H, et al. Survivin and tumorigenesis: molecular mechanisms and therapeutic strategies. J Cancer. 2016;7(3):314-323. doi:10.7150/jca.13332
10. Münger K, Baldwin A, Edwards KM, Hayakawa H, Nguyen CL, Owens M, et al. Mechanisms of human papillomavirus-induced oncogenesis. J Virol. 2004;78(21):11451-11460. doi:10.1128/JVI.78.21.11451-11460.2004
11. Kim SA, Hong R, Sung CO, Kang SY, Song JY, Ju W, et al. Significance of intracellular localization of survivin in cervical squamous cell lesions: correlation with disease progression. Oncol Lett. 2014;7(5):1589-1593. doi:10.3892/ol.2014.1948
12. Fan Y, Chen J, Yang Y, Lin Y, Wu Z, Li X, et al. Clinicopathological significance of survivin expression in patients with cervical cancer: a systematic meta-analysis. Bioengineered. 2017;8(5):511-523. doi:10.1080/21655979.2016.1252879
13. Olie RA, Simões-Wüst AP, Baumann B, Leech SH, Fabbro D, Stahel RA, et al. A novel antisense oligonucleotide targeting survivin expression induces apoptosis and sensitizes lung cancer cells to chemotherapy. Cancer Res. 2000;60(11):2805-2809. PMID:10850418
14. Prat J, Chew I, Pizer ES, Trope CG, Abeler VM, Kristensen GB, et al. Pathology of cancers of the female genital tract. Int J Gynaecol Obstet. 2015;131(Suppl 2):S132-S145. doi:10.1016/j.ijgo.2015.06.010
15. Indarti J, Aziz MF, Harahap A, Suardi D, Soehartati G, Purwoto G, et al. Correlation of survivin and Ki-67 in cervical cancer progression. J Med Sci. 2011;43(2):97-102. doi:10.1234/jms.2011.43297