Serum *Wnt10B/β-Catenin* in Early Diagnosis, Lymph Node Metastasis, and Prognosis in Cervical Cancer

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ABSTRACT

Objective: To assess the serum levels of *Wnt10B* and *β-catenin* for early diagnosis of the cervical cancer and their association with distant lymph node metastasis and prognosis.

Study Design: Observational study.

Place and Duration of the Study: Department of Gynaecology, Hunan Provincial People's Hospital, The First Hospital Affiliated with Hunan Normal University, Changsha, Hunan, China, from September 2019 to 2023.

Methodology: The cervical cancer group included 156 patients, while the control group comprised 96 healthy women. Serum samples were collected to compare the levels of *β-catenin* and *Wnt10B*. Univariate and multivariate analyses were used to explore the relationship between these biomarkers and clinical characteristics. The receiver Operating Characteristic (ROC) curve analysis was conducted to evaluate their diagnostic value.

Results: The cervical cancer group exhibited significantly higher serum levels of *β-catenin* and *Wnt10B* compared to the control group ($p < 0.001$). Univariate analysis revealed markedly elevated levels of *Wnt10B* and *β-catenin* ($p < 0.001$) in patients with poor prognosis, lymph node metastasis, and advanced stages (III–IV). Multivariate analysis identified prognosis ($p = 0.02$) and lymph node metastasis ($p < 0.001$) as independent risk factors for elevated *Wnt10B* and prognosis ($p = 0.006$) as a risk factor for increased *β-catenin*. According to ROC curve analysis, serum levels of *Wnt10B* (AUC = 0.77, $p = 0.0003$), *β-catenin* (AUC = 0.73, $p = 0.0021$), and the combined diagnostic approach (AUC = 0.79, $p = 0.0001$) could be used to predict the risk of postoperative recurrence.

Conclusion: Serum levels of *Wnt10B* and *β-catenin* are valuable biomarkers for early cervical cancer diagnosis, lymph node metastasis, and prognosis of cervical cancer.

Key Words: *Cervical cancer, Wnt10B, β-catenin, Early diagnosis, Prognostic biomarkers, Prognosis.*

How to cite this article: Wang J, Wu Y. Serum *Wnt10B/β-Catenin* in Early Diagnosis, Lymph Node Metastasis, and Prognosis in Cervical Cancer. *J Coll Physicians Surg Pak* 2025; **35(03)**:318-323.

INTRODUCTION

Three main types of cervical cancer (CC) that are recognised as serious global health issues related to gynaecology: Ninety percent of cases are squamous cell carcinomas, 10% are adenocarcinomas, and the remaining cases are adenosquamous carcinomas. After lung, colorectal, and breast cancers, CC ranks as the fourth most common cancer in women and the fourth leading cause of cancer-related mortality. The incidence and mortality rates of CC are particularly high in developing countries, with the prevalence continuing to rise globally, primarily due to inadequate disease prevention and control measures.[1,2]

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Received: August 15, 2024; Revised: January 16, 2025; Accepted: February 14, 2025
DOI: https://doi.org/10.29271/jcpsp.2025.03.318

Its occurrence and development involve a complex, multifactorial process. With the rapid advancement of molecular biology tools, research has increasingly focused on identifying novel molecular markers and understanding their roles in CC-related signalling pathways during initiation, progression, and metastasis. Among these, the *Wnt/β-catenin* signalling system has garnered great attention in research because of its involvement in a variety of malignancies.

The *Wnt*-signalling pathway, a highly conserved system, is essential for embryonic development, tissue regeneration, cell proliferation, and differentiation. The studies demonstrated that the *Wnt*-signalling pathway can be classified into two categories: The non-canonical *Wnt/β-catenin*-independent pathway, and the canonical *Wnt/β-catenin*-dependent pathway, depending on the mechanism involved. In the canonical *Wnt* pathway, the signal output is determined by the quantity of cytoplasmic *β-catenin*, which influences the expression of specific genes and regulates cell fate, cell cycle, and cancer progression. *Wnt10B*, a key ligand in the classical *Wnt/β-catenin*-dependent signalling pathway, plays a significant role in various cancers, including breast, stomach, and liver cancers.[3]

Wnt10B mRNA is also expressed in cervical cancer squamous cell lines, and the involvement of the *Wnt/β-catenin* pathway in cervical cancer tissues and cell lines has been extensively studied.[4] However, the relationship between the expression of *β-catenin* and *Wnt10B* in serum, and their roles in the early diagnosis of CC, distant lymph node metastasis, and prognosis remains underexplored. Further investigation on the relationship between the *Wnt10B* and the *Wnt/β-catenin*-signalling pathway in the progression of CC could provide new strategies for early diagnosis. Particularly in predicting distant lymph node metastasis, the combined detection of *Wnt10B* and *β-catenin* holds significant clinical value, providing a foundation for prognosis assessment and the development of new biomarkers in cervical cancer.

This study aimed to assess the expression levels of *Wnt10B* and *β-catenin* in the serum of cervical cancer patients and analyse their association with clinicopathological characteristics, such as tumour size, degree of differentiation, clinical stage, and distant lymph node metastasis. The potential application of serum *Wnt10B* and *β-catenin* in the early diagnosis of CC and in the evaluation of disease progression and prognosis, is also explored.

METHODOLOGY

Clinical information, including serum sample data, was obtained from 156 patients who were diagnosed with CC through biopsy and were treated at the Department of Gynaecology, Hunan Provincial People's Hospital, The First Hospital Affiliated with Hunan Normal University, Changsha, Hunan, China, from September 2019 to 2023. The data were retrieved from the Hospital's gynaecology department's medical records and pathology databases. Additionally, data from 96 healthy women who underwent physical examinations during the same period were included for the analysis. The participants were divided into the cervical cancer group (CC group) and the control group. The clinical data and serum expression levels of *Wnt10B* and *β-catenin* in both groups were analysed, with expression levels further examined based on the pathological data of the CC patients. Finally, the ROC curve for serum *Wnt10B* and *β-catenin* levels in diagnosing CC and predicting postoperative recurrence risk was assessed. The data from patients diagnosed with other types of cancer or those lacking information on tumour type and stage were excluded. All included patients were >18 years of age, had been diagnosed with cervical cancer, and voluntarily signed informed consent.

General patient data included age and weight. Diagnostic staging was performed according to the 2018 FIGO staging system. Treatment modalities consisted of surgery, chemotherapy, and radiotherapy.

Total RNA was isolated from the serum samples of CC patients using the TRIzol reagent. The high-capacity cDNA reverse transcription kit (Thermo-fisher scientific) was then used to reverse transcribe RNA (2μg) in accordance with the manufacturer's instructions. The following primers were used to identify *Wnt10B*: Upstream primer sequence: 5'-CCAGAGCCCCTTTAACCCTG-3'; downstream primer sequence: 5'-CAACTTCCCTAAGGGCCTGG-3'. For *β-catenin*: Upstream primer sequence: 5'-GTTGAGCACCTGTTTGCCTG-3'; downstream primer sequence: 5´-GTGTTCCAAGGGCTTTGCAG-3´. The $2^{-\Delta\Delta Ct}$ technique was used to measure the expression of *Wnt10B* and *β-catenin* after at least three repeated experiments.

Statistical analysis was performed by using IBM Corp.'s SPSS version 26.0. Two-tailed statistical tests were employed, with an alpha level of <0.05. Significance was determined if the p-value was less than <0.05. The normality of continuous data was assessed using the Shapiro-Wilk's test. Two-sample comparisons were conducted with t-tests, and normally distributed measures were expressed as mean ± standard deviation (SD). Univariate analysis of variance was used to examine the relationship between patients' clinical information (age, BMI, FIGO staging, lymphatic metastasis, muscle layer infiltration, vascular invasion, and prognosis), and serum levels of *Wnt10B* and *β-catenin*. The independent predictors were identified using binary multivariate logistic regression analysis. ROC curves were used to evaluate the clinical value of serum *Wnt10B* and *β-catenin* levels in predicting post-treatment relapse. Optimal cut-off values were determined using the Youden's index, which maximises the sum of sensitivity and specificity. The area under the curve (AUC) was also calculated to assess the diagnostic performance of each marker.

RESULTS

The primary objective of this study was to evaluate the serum levels of *Wnt10B* and *β-catenin* in CC patients and their potential role as diagnostic and prognostic markers. No significant differences in age or BMI were observed between the control and CC groups. The average age in the control group was 52.48 ± 6.78 years, and in the CC group, it was 53.19 ± 8.14 years ($t = 0.51$, $p = 0.61$). BMI values were 22.98 ± 1.45 in the control group and 22.50 ± 1.48 in the CC group ($t = 1.84$, $p = 0.07$). The serum levels of *Wnt10B* and *β-catenin* were significantly higher in the CC group compared to the control group. *Wnt10B* was 1.03 ± 0.18 in the control group and 1.59 ± 0.63 in the CC group ($t = 6.49$, $p < 0.001$). Similarly, *β-catenin* levels were 1.02 ± 0.12 in the control group and 1.39 ± 0.34 in the CC group ($t = 7.71$, $p < 0.001$).

Between patient age, BMI index, presence of myometrial invasion, and presence of vascular invasion, there were no significant associations found between serum *Wnt10B* and *β-catenin* levels ($p > 0.05$). The levels of serum *Wnt10B* and *β-catenin* in CC patients were correlated with the clinical stage (FIGO stage) and the presence of distant lymph node metastasis. Individuals with III–IV clinical phases, lymph node metastasis, and those with poor prognosis had higher expression rates of serum *Wnt10B* and *β-catenin* ($p < 0.05$, Table I).

Table I: Univariate analysis of pathological features and serum levels of *Wnt10B* and *β-catenin* in the CC group.

Factors		*Wnt10B*	t-value	p-value	*β-catenin*	t-value	p-value
Age	>53	2.19 ± 0.72	0.06	0.95	2.12 ± 0.64	0.54	0.59
	≤53	2.20 ± 0.75			2.21 ± 0.67		
BMI (kg/m^2)	>24	2.20 ± 0.73	0.01	0.99	2.18 ± 0.62	0.07	0.95
	≤24	2.19 ± 0.74			2.17 ± 0.69		
FIGO Staging	I-II	2.02 ± 0.68	2.41	0.02	1.92 ± 0.57	4.18	<0.001
	III-IV	2.44 ± 0.75			2.52 ± 0.61		
Lymphatic metastasis	Yes	2.62 ± 0.60	5.32	<0.001	2.48 ± 0.61	4.31	<0.001
	No	1.80 ± 0.39			1.88 ± 0.55		
Muscle layer	<1/2	2.24 ± 0.74	0.35	0.73	2.24 ± 0.59	0.67	0.51
Infiltration	≥1/2	2.17 ± 0.74			2.13 ± 0.68		
Vascular invasion	Yes	2.30 ± 0.74	0.93	0.35	2.23 ± 0.67	0.62	0.54
	No	2.13 ± 0.73			2.13 ± 0.65		
Prognosis	Good	1.96 ± 0.67	4.04	<0.001	1.98 ± 0.55	3.45	<0.001
	Poor	2.63 ± 0.64			2.51 ± 0.69		

t-test was applied.

Table II: Clinical data analysis of serum *Wnt10B* and *β-catenin* levels and patients with CC.

Factors	b	SE	Wald χ^2 value	p-value	OR
Wnt10B constant	-7.04	1.59	19.56	<0.001	0.001
Lymphatic metastasis	3.17	0.70	20.31	<0.001	23.86
Prognosis *β-catenin*	1.77	0.76	5.42	0.02	5.87
Constant	-2.02	0.78	6.76	0.009	0.13
Prognosis	1.56	0.56	7.67	0.006	4.77

Binary multivariate logistics regression was applied.

Table III: ROC curve analysis of serum *Wnt10B* and *β-catenin* levels for diagnostic and postoperative recurrence risk in cervical cancer.

Factors	AUC	Sensitivity %	Specificity %	Optimum Cut-off value
Wnt10B (diagnostic)	0.78	64.71	94.64	0.5935
β-catenin (diagnostic)	0.82	72.06	92.86	0.6492
Combined diagnosis (diagnostic)	0.83	75	92.84	10.50
Wnt10B (postoperative recurrence)	0.77	72.73%	75.00%	0.4773
β-catenin (postoperative recurrence)	0.73	84.09%	58.33%	0.4242
Combined diagnosis (postoperative recurrence)	0.79	100%	20.45%	1.205

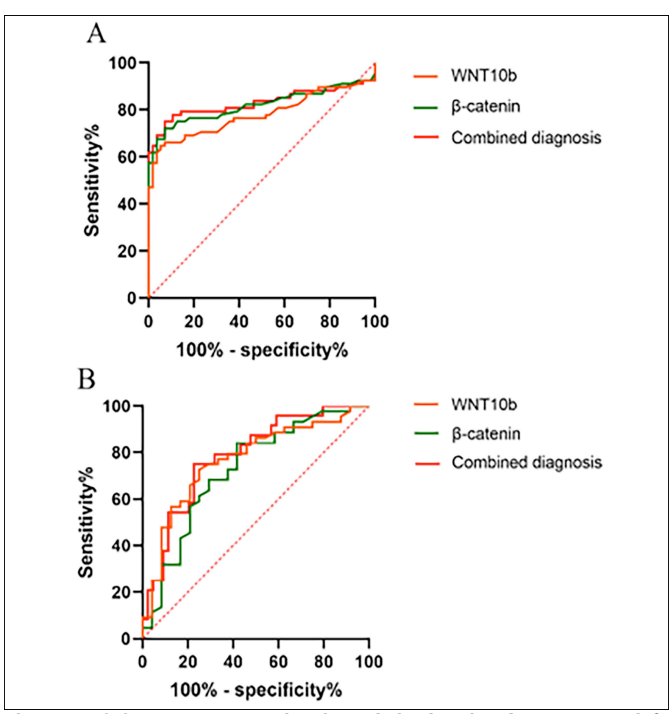

Figure 1: (A) ROC curve evaluation of the levels of *Wnt10B* and *β-catenin*'s CC diagnostic efficacy. (B) ROC curve analysis of serum *Wnt10B* and *β-catenin* levels and predictive value of postoperative recurrence risk.

The multivariate logistic regression analysis revealed that higher serum levels of *Wnt10B* are significantly associated with lymphatic metastasis (OR = 23.86, p <0.001) and a poor prognosis (OR = 5.87, p = 0.02). Similarly, *β-catenin* levels are also significantly linked to a poor prognosis (OR = 4.77, p = 0.006). These findings suggest that elevated levels of both markers are indicative of more severe disease progression in CC patients (Table II).

Table III showcases the diagnostic performance of *Wnt10B* and *β-catenin* for CC and postoperative recurrence. The combined diagnosis method shows the highest AUC of 0.83 and sensitivity of 75% for initial diagnosis, while *β-catenin* has the highest sensitivity of 84.09% for monitoring recurrence. *Wnt10B* demonstrates high specificity (94.64%) during the initial diagnosis and 75% for recurrence, compared to *β-catenin*'s (58.33%). The optimum cut-off values vary, with *Wnt10B* at 0.5935 for diagnosis and the combined approach significantly higher at 10.50. Overall, the combined diagnostic method enhances sensitivity and accuracy, while *Wnt10B* maintains high specificity in both contexts (Table III, Figure 1A, B).

DISCUSSION

CC is the fourth most common malignancy among women. While the incidence of CC has declined to some extent in

affluent nations,[5] the disease remains prevalent in lower-income countries and increasingly affects younger women.[1] Nearly 95% of CC cases are attributed to the human papillomavirus (HPV), the most common sexually-transmitted infection globally. High-risk HPV strains 16 and 18 are the cause of 70% of cases of CC. Approximately 70% of CC cases are discovered at an advanced stage, significantly contributing to these individuals' deaths.[6,7] Early detection and treatment are crucial, as cervical cancer is both preventable and curable when identified at an early stage.[8]

The World Health Organization has set a target of 70% lifetime screening coverage to achieve the goal of eradicating CC by 2030.[9] There are numerous CC screening techniques available now. Several CC screening methods are currently available.

The Papanicolaou (Pap) smear test was the first employed, and it has evolved into various screening techniques, including cytology-based screening (Pap test), next-generation sequencing (NGS), co-testing (HPV and cytology), and visual inspection with acetic acid (VIA). According to current screening guidelines, HPV testing is recommended as the primary screening method, either alone or in combination with cytology.[10]

A recent research indicated that the aberrant activation of the canonical *Wnt/β-catenin* signalling pathway has garnered increasing attention, as it may represent the second major contributing factor to cervical cancer development after HPV infection.[11] This pathway, centred on the core protein *β-catenin*, constitutes the classic *Wnt*-signalling system. Abnormal activation of the *Wnt/β-catenin* pathway affects the pathogenesis and metastasis of CC by disrupting cell differentiation and proliferation, ultimately leading to tumourigenesis.[12] Consequently, the *Wnt/β-catenin* pathway is considered a potential therapeutic target for the management of CC. Intervening and regulating the expression of target genes within this pathway may inhibit tumour progression and achieve therapeutic objectives.

Wnt10B, originally identified by the Leder group in 1995 in the mammary glands of mice,[13] has been shown to play a crucial role in the differentiation and proliferation of various cell types, including mesenchymal, mammary, prostate, cutaneous, haematological, dental pulp, and cancer stem cells.

Early diagnosis increases the chances of survival for patients with CC. According to this research, patients with early-stage CC have higher serum levels of *Wnt10B* and *β-catenin*, which may indicate that these molecules can be used as early diagnostic biomarkers. Previous studies have revealed a significant upregulation of *β-catenin* in the cervical epithelial tissues of individuals diagnosed with CC.[14] Although *Wnt10B* and *β-catenin* show potential as diagnostic biomarkers, their sensitivity and specificity in CC remain under investigation. As suggested by the present study, these markers should be viewed as supplementary diagnostic tools rather than standalone screening indicators, as their diagnostic capacity alone may not be sufficient to replace traditional methods such as HPV testing. Given the retrospective nature of the present study and the lack of dynamic monitoring of these markers, it is premature to recommend them as sole diagnostic tests. The authors propose their integration into screening protocols, particularly for high-risk HPV populations, with annual screenings. This approach may enhance diagnostic accuracy while maintaining the benefits of existing methods such as HPV testing and cytology.

Significant correlations were observed between CC stage, lymph node metastasis, and serum levels of *Wnt10B* and *β-catenin*, as well as between these biomarkers and the pathological characteristics of the CC group, through univariate and multivariate analyses. The Wnt/*β-catenin*-signalling pathway plays a critical role in tumour cell invasion and migration, as evidenced by the strong association between its activation and distant metastasis in CC. This may be due to the activation of the Wnt/*β-catenin* pathway, which promotes the expression of cell cycle-related genes (such as Cyclin D1),[15] thereby enhancing the cell proliferation and inhibiting apoptosis, contributing to tumour growth and spreading. Furthermore, the Wnt/*β-catenin*-signalling pathway can induce epithelial-mesenchymal transition (EMT), a key step in the acquisition of invasive and metastatic capacities by cancer cells. During EMT, cells acquire a mesenchymal phenotype, which enhances their ability to migrate and invade.[16] However, further studies with larger cohorts and longitudinal data are needed to fully assess the predictive value of these markers in this context.

Conventional treatments for CC include surgery, chemotherapy, and radiation, either alone or in combination. However, approximately 30-35% of advanced patients do not respond to these treatments, and chemotherapy often leads to drug resistance. Although the cure rate exceeds 80% in early-stage patients, about 20% still experience pelvic recurrence. The study found a significant association between these markers and patient outcomes by performing receiver operating characteristic (ROC) curve analysis to explore their relationship with the prognosis of CC patients. Inhibiting the expression of *β-catenin* can significantly suppress the carcinogenic process.[17,18] *Wnt10B* and *β-catenin* primarily promote cell division and inhibit apoptosis in tumour cells by regulating key cell cycle genes, such as Cyclin D.[15,19] Furthermore, the activation of the *Wnt/β-catenin* pathway induces EMT,[20] which is crucial for the invasion and migration of cancer cells. Therefore, *Wnt10B* and *β-catenin* may serve as potential therapeutic targets. However, the efficacy of targeting the *Wnt/β-catenin* signalling pathway requires further investigation. While inhibiting this pathway may suppress tumour growth, it can also adversely affect normal cells. To improve therapeutic outcomes, this pathway should be carefully regulated to

minimise side effects on normal tissues, with a focus on inhibitors that selectively target tumour cells without harming normal cells.

The limitations of this study include its retrospective design, relatively small sample size, and single-centre setting, which may reduce the generalisability of the results. Additionally, the study did not stratify patients by CC subtypes or other potential confounding factors. The short follow-up duration further limits the ability to assess the long-term prognostic value of serum *Wnt10B* and *β-catenin* levels. To address these limitations, future research should focus on multi-centre, large-scale studies with extended follow-up periods to validate and expand upon the current findings.

CONCLUSION

The *Wnt10B* and *β-catenin* are promising biomarkers for early diagnosis and prognosis of CC and could complement existing screening methods, especially for high-risk populations. They have the potential for monitoring tumours, but need to be further validated. At the same time, therapies targeting these pathways are of concern, but the impact on normal tissue should be considered. Future studies are needed to confirm its clinical application and explore treatment options.

FUNDING:
This study was supported by the Hunan Provincial Health Commission Scientific Research Project (B20180720).

ETHICAL APPROVAL:
This study was exempted by the Ethics Committee of Hunan Provincial People's Hospital, (The First Hospital Affiliated with Hunan Normal University, Changsha, Hunan, China).

PATIENTS' CONSENT:
The informed consent of the patients or their family members has been obtained prior to the publication of data related to this case.

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
JW: Designed the study and wrote the paper.
YW: Collected, analysed the data, and wrote the paper.
Both authors approved the final version of the manuscript to be published.

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