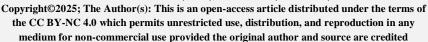


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REVIEW ARTICLE

THE CLINICAL VALUE OF D-DIMER LEVELS IN CERVICAL CANCER: IMPLICATIONS FOR EARLY DETECTION OF DISEASE PROGRESSION AND RECURRENCE

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Abstract

Cervical cancer continues to be a significant global health issue, especially in lowand middle-income nations, where late-stage diagnosis and elevated recurrence rates hinder treatment success. Thus, it is essential to identify trustworthy, accessible biomarkers to aid in the early detection of disease progression and recurrence. Among coagulation indicators, D-dimer a byproduct of fibrin breakdown has attracted growing interest for its possible clinical significance in cervical cancer. Increased D-dimer concentrations indicate hypercoagulability, tumor-related angiogenesis, and systemic inflammation, all of which are essential to cancer biology. This narrative review investigates the clinical significance of Ddimer in cervical cancer, assessing its function in risk stratification, tracking treatment response, and forecasting recurrence. We emphasize proof connecting high D-dimer levels to progressed disease stage, metastasis, and unfavorable prognosis, while also addressing its incorporation with imaging and additional hematological indicators to improve diagnostic precision. Issues like assay variability, absence of standardized cut-off values, and confounding factors influencing D-dimer levels are thoroughly assessed. Ultimately, we suggest future research avenues, such as validation studies, integration into predictive models, and investigation of D-dimer within multi-biomarker panels for precision oncology. Connecting coagulation science and oncology, D-dimer presents a potential supplementary marker to facilitate prompt interventions and enhance clinical results in cervical cancer.

Keywords: biomarkers, cervical cancer, D-Dimer, prognosis, treatment strategies.

INTRODUCTION

Cervical cancer poses a significant public health challenge globally, being the fourth most prevalent cancer in women, with around 604,000 new cases and nearly 342,000 deaths reported worldwide in 2020. The illness is mainly triggered by ongoing infection with high-risk human papillomavirus (HPV) types, resulting in the formation of precancerous lesions and, eventually, invasive cancer. In spite of progress in screening and vaccination, cervical cancer continues to be a major cause of illness and death, especially in lowand middle-income countries with restricted access to healthcare services¹⁻⁵. Established prognostic indicators in cervical cancer management incorporate tumor stage, histological subtype, and lymph node involvement. These elements are essential for shaping treatment and anticipating patient results⁶⁻⁸. strategies Nonetheless, they might not entirely reflect the intricacies of the disease, resulting in discrepancies in treatment outcomes and survival rates. Consequently,

there is an urgent requirement to discover more biomarkers that can improve prognostic precision and inform treatment strategies. D-dimer is a byproduct of fibrin degradation that enters the bloodstream during fibrinolysis, the process of dissolving blood clots^{9,10}. Several studies have reported a correlation between elevated D-dimer levels and advanced disease stages in cervical cancer^{11,12}. For instance, a study by Zhang et al. found that patients with higher D-dimer levels had significantly poorer overall survival and progressionfree survival rates compared to those with normal levels¹³. These findings suggest that D-dimer levels may provide valuable insights into tumor burden and the likelihood of metastasis, thus warranting further investigation into their role as prognostic indicators. In addition to their prognostic implications, D-dimer levels may also have therapeutic relevance in cervical cancer management¹³. Elevated D-dimer levels can signal an increased risk of venous thromboembolism (VTE), which is a common complication in cervical cancer patients. Managing VTE risk is essential, as it

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can impact treatment outcomes and overall survival. By monitoring D-dimer levels, clinicians can implement appropriate prophylactic measures to reduce VTE risk, thereby improving patient care and treatment efficacy^{14,15}. Furthermore, the integration of D-dimer levels into clinical practice can enhance risk stratification for cervical cancer patients ¹⁶. For example, patients with elevated D-dimer levels may warrant closer monitoring and more aggressive treatment regimens, while those with normal levels could be managed with standard care.

In cervical cancer, the quest for dependable biomarkers has traditionally concentrated on squamous cell carcinoma (SCC) antigen, which continues to be the most commonly utilized serum marker in clinical settings. Nevertheless, SCC antigen is constrained by its relatively low sensitivity in early-stage conditions and its limited relevance to squamous histological types. Conversely, D-dimer provides a dynamic assessment of tumor-related coagulopathy that can be tracked over time through different disease stages and treatment regimens. In contrast to SCC antigen, which more directly indicates tumor load, D-dimer offers understanding of the systemic biological processes induced by cancer, especially fibrinolysis and increased coagulability. Human papillomavirus (HPV), the primary cause of cervical cancer, also exacerbates this pro-thrombotic condition via chronic inflammation, activation of endothelial cells, and the secretion of cytokines that promote coagulation pathways. This interaction among viral oncogenesis, inflammatory responses, and hemostatic disturbances caused by tumors highlights D-dimer's potential as both a prognostic biomarker and a glimpse into the biological pathways that connect infection, immunity, and cancer advancement^{15,16}.

The aim of this review is to explore the role of D-dimer levels in the management of cervical cancer, specifically focusing on their prognostic implications and potential to inform treatment strategies.

The role of D-dimer in cervical cancer

Traditional prognostic factors such as tumor stage and histological type provide crucial information for treatment planning; however, they often fail to capture the complexity of the disease and its progression. In this context, D-dimer, a fibrin degradation product, has gained attention as a potential biomarker for assessing prognosis in cervical cancer patients¹⁷. D-dimer is produced during the breakdown of fibrin, a protein involved in blood clotting. Elevated levels of D-dimer in the bloodstream can indicate a hypercoagulable state, which is often associated with malignancies, including cervical cancer¹⁰. Research has shown that elevated Ddimer levels can correlate with advanced disease stages of cervical cancer, increased tumor burden, and poorer overall survival rates¹⁸. For example, studies have reported that cervical cancer patients with higher pretreatment D-dimer levels have worse clinical outcomes, highlighting the potential of D-dimer as a prognostic indicator. Several studies have explored the relationship between D-dimer levels and clinical characteristics in cervical cancer. Elevated D-dimer levels have been linked to lymph node involvement, metastasis, and

advanced tumor stages¹⁰. For instance, a study by Zhang *et al.* demonstrated that patients with higher D-dimer levels at diagnosis had a significantly higher risk of lymph node metastasis compared to those with normal levels¹³. This finding underscores the potential of D-dimer as a valuable marker for risk stratification in cervical cancer patients.

The prognostic value of D-dimer in cervical cancer extends beyond initial diagnosis. Monitoring D-dimer levels during treatment can provide insights into treatment response and disease progression. Studies have shown that a decrease in D-dimer levels during treatment may indicate a favorable response, while persistently elevated levels could signal treatment resistance or disease recurrence. This dynamic assessment can aid clinicians in making timely adjustments to treatment strategies, enhancing patient management¹⁷. Furthermore, D-dimer levels may play a role in understanding the coagulopathy associated with cervical cancer. Cervical cancer patients often experience a hypercoagulable state, which increases the risk of venous thromboembolism (VTE). Elevated Ddimer levels can indicate a higher risk for VTE, complicating treatment outcomes. By integrating Ddimer monitoring into cervical cancer management, clinicians can implement preventive measures to reduce VTE risk, thereby improving overall patient care. 19 While the potential role of D-dimer in cervical cancer is promising, there are still gaps in knowledge that need to be addressed. Standardized cut-off values for Ddimer levels specific to cervical cancer populations need to be established, and further research is needed to understand the underlying mechanisms driving elevated D-dimer levels in this context. Additionally, largescale, multicenter studies are required to validate the prognostic significance of D-dimer levels and to assess their clinical utility in guiding treatment decisions.

Pre-treatment prognostic value of D-dimer

Pre-treatment D-dimer levels have emerged as a powerful prognostic marker in cervical cancer, burden systemic reflecting both tumor and hypercoagulability. Numerous studies demonstrated that elevated baseline D-dimer correlates with advanced FIGO stage, lymph node metastasis, larger tumor volume, and aggressive histological features. Importantly, patients with high D-dimer at diagnosis consistently show worse progression-free survival (PFS) and overall survival (OS) compared to those with normal levels. These associations hold true even after adjusting for FIGO stage, suggesting that Ddimer provides incremental prognostic information beyond anatomic staging. Unlike FIGO staging, which is limited to structural and locoregional features, Ddimer captures the biological interplay between cancer, coagulation, and systemic inflammation. This ability to stratify patients within the same stage category highlights its value as a complementary biomarker for risk assessment at diagnosis¹⁹.

Post-treatment prognostic value of D-dimer

Post-treatment monitoring of D-dimer adds another layer of prognostic utility, offering insight into treatment response and recurrence risk. Patients whose D-dimer levels decline significantly following surgery,

radiotherapy, chemoradiotherapy or generally experience better outcomes, reflecting reduced tumor activity and normalization of coagulation pathways. In contrast, persistently elevated or rising D-dimer levels after therapy often precede radiologic or clinical evidence of recurrence, serving as an early warning signal of residual disease or metastatic progression. This dynamic monitoring capacity sets D-dimer apart from static tumor markers, allowing clinicians to track changes in real time. Importantly, evidence shows that post-treatment D-dimer trends provide incremental prognostic information beyond FIGO stage, as staging does not account for biological relapse risk once initial treatment is completed. Integrating D-dimer into posttreatment surveillance protocols could therefore improve early detection of recurrence, guide intensified follow-up, and inform timely intervention strategies²⁰.

D-Dimer as a tool for early detection of progression and recurrence

The clinical journey of cervical cancer, from diagnosis to treatment and post-therapeutic monitoring, demands vigilant follow-up to detect early signs of disease progression or recurrence. Traditionally, imaging modalities, tumor markers such as squamous cell carcinoma (SCC) antigen, and clinical evaluations have served as cornerstones in this process. However, these methods often detect recurrence at a stage when tumor burden is already significant. In recent years, D-dimer a fibrin degradation product widely known for its role in diagnosing thromboembolic events has garnered attention as a potential early biomarker for tumor progression and recurrence in cervical cancer^{20,21}. The biological rationale for using D-dimer in this context lies in the strong association between malignancy and hypercoagulability. Tumor cells can directly activate the coagulation cascade through the expression of procoagulant molecules, leading to increased fibrin formation and subsequent fibrinolysis, which elevates circulating D-dimer levels²². This systemic response reflects not only a prothrombotic state but also ongoing tumor activity and interaction with the vascular and immune systems. In cervical cancer, these mechanisms become particularly relevant due to the disease's for locoregional invasion lymphovascular spread^{23,24}. Numerous clinical studies have demonstrated that elevated pre-treatment D-dimer levels are associated with more advanced disease, greater tumor burden, and worse survival outcomes^{25,26}. More importantly, a growing body of evidence suggests that rising or persistently elevated D-dimer levels during or after treatment may signal occult progression or early recurrence^{27,28}. Unlike radiological imaging, which may miss small or asymptomatic lesions, or traditional tumor markers, which can lack sensitivity, D-dimer has the potential to provide an early systemic signal that pathological processes have resumed²⁹

Monitoring D-dimer levels serially throughout the course of treatment offers a dynamic perspective on disease activity. For instance, a patient whose D-dimer levels normalize following chemoradiation may be considered to have achieved a satisfactory response. However, if levels begin to rise again during follow-up, even in the absence of clinical symptoms or imaging

abnormalities, clinicians may be prompted investigate further through advanced imaging or biopsy^{30,31}. This preemptive approach could lead to earlier interventions, thereby improving clinical outcomes and survival chances³². Moreover, D-dimer testing is cost-effective, minimally invasive, and widely available in both primary and tertiary care settings³³. These attributes make it particularly useful in lowresource environments, where access to advanced diagnostic technologies may be limited. Incorporating D-dimer into the routine follow-up of cervical cancer patients may enable more tailored surveillance strategies, ensuring that high-risk individuals receive closer monitoring while minimizing unnecessary investigations for those with consistently low or stable D-dimer levels^{34,35}. Nevertheless, caution must be exercised in interpreting elevated D-dimer values. As a non-specific marker, D-dimer can rise in a variety of benign conditions, including infection, inflammation, trauma, or post-surgical states³⁶. Therefore, clinicians must contextualize these levels within the broader clinical picture, incorporating physical examination, patient history, and additional investigations to avoid false alarms or over-treatment³⁷.

Integration into clinical practice

To maximize the clinical utility of D-dimer in cervical cancer management, a tentative monitoring algorithm can be proposed^{38,39}. Baseline D-dimer should be measured at diagnosis to establish patient-specific risk profiles and guide initial prognostication 40,41. During treatment, D-dimer levels may be assessed at key intervals such as before each chemotherapy cycle, at completion of radiotherapy, and at 1-3-month posttreatment follow-up visits to evaluate therapeutic response^{42,43}. Following treatment, longitudinal monitoring at 3-6-month intervals may facilitate early detection of recurrence, particularly when combined with imaging modalities such as MRI or PET/CT for confirmation 44,45. Integrating D-dimer trends with clinical examination, imaging findings, and other biomarkers (e.g., SCC antigen or inflammatory markers) can enhance risk stratification and inform timely intervention⁴⁶.

Despite these potential benefits, several adoption barriers must be addressed. A primary limitation is the lack of standardized D-dimer cut-off values across studies, which complicates interpretation and reduces reproducibility in clinical practice⁴⁷. Additionally, posttreatment inflammation, infection, or thromboembolic events can lead to false-positive elevations, underscoring the need for contextualized assessment⁴⁸. Laboratory variability in D-dimer assays further challenges consistent implementation. Finally, clinician familiarity and acceptance may limit adoption, particularly in resource-limited settings where imaging and laboratory infrastructure are uneven. Addressing these barriers through prospective validation studies, standardization of assay protocols, and development of evidence-based guidelines will be essential for integrating D-dimer into routine cervical cancer management^{49,50}.

Comparative discussion with PET/CT and MRI

The prognostic and monitoring value of D-dimer in cervical cancer should be considered alongside advanced imaging modalities such as PET/CT and MRI, which remain the gold standards for staging and surveillance. PET/CT provides high sensitivity in detecting nodal and distant metastases, while MRI offers superior delineation of local tumor extent and treatment response. However, both imaging modalities are resource-intensive, costly, and not always accessible in low- and middle-income countries. In contrast, D-dimer testing is inexpensive, minimally invasive, and widely available, making it a practical adjunct in settings where advanced imaging is limited. Furthermore, while PET/CT and MRI primarily provide structural and metabolic information, D-dimer captures systemic biological processes such as tumordriven hypercoagulability and inflammation, thereby offering complementary insights into dynamics^{51,52}.

Nevertheless, the use of D-dimer as a standalone marker has limitations. A key challenge is its lack of specificity, particularly in the post-treatment setting. Radiation-induced inflammation, chemotherapy-related vascular injury, infection, or thromboembolic events can elevate D-dimer independently of tumor activity. This complicates the interpretation of elevated values after treatment and necessitates careful clinical correlation with imaging and other biomarkers. Compared to PET/CT and MRI, which directly visualize disease recurrence, D-dimer may yield false positives due to non-malignant causes. Thus, its optimal clinical role may lie in integrated approaches, where D-dimer is used for dynamic monitoring and risk stratification, while imaging is reserved confirmation localization and of suspected recurrence^{53,54}.

Tumor-induced hypercoagulability and confounding factors

One of the central biological underpinnings of elevated D-dimer levels in cervical cancer lies in the phenomenon of tumor-induced hypercoagulability. Malignant cells interact with the hemostatic system through multiple mechanisms, including the release of tissue factor, cancer procoagulant, and inflammatory cytokines that activate the coagulation cascade. This activation results in thrombin generation, fibrin deposition, and subsequent fibrinolysis, producing elevated circulating D-dimer. In cervical cancer, particularly those driven by persistent HPV infection, inflammation further amplifies by enhancing prothrombotic state endothelial dysfunction and upregulating procoagulant activity. The consequence is a sustained cycle of coagulation and fibrinolysis, making D-dimer not only a surrogate marker of thrombosis but also a potential indicator of tumor burden, invasion, and metastatic potential^{55,56}. However, interpretation of elevated D-dimer levels in

clinical practice must account for non-malignant

conditions that can also drive fibrin turnover. Acute

infections, common in cervical cancer patients with

immunosuppression or treatment-related complications, may independently increase D-dimer through systemic inflammation. Similarly, surgical interventions. particularly radical hysterectomy or lymphadenectomy, are associated with tissue injury and postoperative thromboembolic risk, which transiently D-dimer levels. Moreover, thromboembolism (VTE), a frequent comorbidity in cancer patients, remains a significant confounder that complicates the distinction between tumor-related and non-malignant causes of D-dimer elevation. Thus, while D-dimer is a valuable biomarker for monitoring disease progression and recurrence, its clinical interpretation must be contextualized within the broader spectrum of patient comorbidities and peritreatment events⁵⁷.

Treatment strategies informed by d-dimer levels in cervical cancer

The integration of D-dimer levels into cervical cancer management has significant implications for treatment strategies, enabling healthcare providers to tailor interventions based on individual patient profiles. As a biomarker associated with tumor burden, disease progression, and risk of complications, D-dimer levels can inform decision-making regarding treatment intensity, monitoring, and preventive measures¹². One of the primary treatment strategies informed by Ddimer levels involves risk stratification for therapy⁵¹. Patients presenting with elevated D-dimer levels may be at higher risk for advanced disease, necessitating more aggressive treatment approaches. For example, clinicians may consider upfront chemoradiotherapy for patients with high D-dimer levels instead of surgery alone, particularly in cases with significant lymph node involvement or larger tumor size. This approach aims to reduce the risk of recurrence and improve overall survival by addressing the disease comprehensively. Monitoring D-dimer levels during treatment can also guide the management of cervical cancer patients. Changes in D-dimer levels can provide insights into treatment response and disease progression. For instance, a decrease in D-dimer levels during therapy may indicate an effective response, prompting the continuation of the current treatment regimen. Conversely, persistently elevated D-dimer levels could signal treatment resistance or disease recurrence, warranting a reassessment of therapeutic strategy. In such cases, clinicians may consider switching to alternative treatments, such as second-line chemotherapy or targeted therapies, to improve patient outcomes 58,59.

Additionally, D-dimer levels can inform the management of venous thromboembolism (VTE) risk in cervical cancer patients. Cancer-related thrombosis is a common complication, and elevated D-dimer levels are indicative of increased VTE risk. Clinicians can use this information to implement prophylactic measures, such as anticoagulation therapy, particularly for patients undergoing surgery or those receiving chemotherapy, which may further elevate VTE risk. By addressing thrombosis risk, healthcare providers can enhance patient safety and potentially improve treatment outcomes⁵⁴.

Furthermore, D-dimer monitoring can play a role in the decision-making process for follow-up care. Patients

with elevated D-dimer levels at the end of treatment may require closer surveillance due to the increased risk of recurrence. This can lead to more frequent imaging studies and clinical evaluations to detect potential relapse at an earlier stage, allowing for timely intervention. On the other hand, patients with normalized D-dimer levels may be candidates for less intensive follow-up protocols, reducing the burden of unnecessary testing while still ensuring appropriate monitoring⁵⁴. While the prognostic implications of Ddimer levels are becoming clearer, further research is necessary to establish standardized protocols for incorporating D-dimer measurements into treatment strategies for cervical cancer. Determining the optimal cut-off values for D-dimer levels that guide treatment decisions will enhance the utility of this biomarker in clinical practice. Additionally, prospective studies examining the impact of D-dimer-informed treatment strategies on patient outcomes will be crucial in validating its role in cervical cancer management.

Future directions in cervical cancer research and management

While existing evidence supports the clinical potential of D-dimer in cervical cancer, several gaps must be addressed before routine implementation. Prospective, multicenter studies are needed to validate the prognostic and surveillance value of D-dimer, establish standardized assay protocols, and determine clinically relevant cut-off values. Future research should also explore the integration of D-dimer into multimodal biomarker panels, combining coagulation markers, tumor antigens (e.g., SCC), circulating tumor DNA, and imaging findings to enhance diagnostic accuracy and risk stratification ^{55,56}.

Additionally, longitudinal studies examining D-dimer dynamics across treatment phases can elucidate its role in monitoring response and predicting recurrence in real time. Investigating the use of predictive algorithms or risk models that incorporate D-dimer alongside clinical, pathological, and imaging data could further personalize follow-up strategies. Finally, evaluating cost-effectiveness, accessibility, and feasibility in low-resource settings will be crucial to ensure equitable adoption. By addressing these areas, future research can solidify D-dimer's role in precision oncology and improve patient outcomes in cervical cancer⁵⁷⁻⁵⁹.

CONCLUSIONS

D-dimer has been identified as a valuable biomarker in cervical cancer, indicating tumor-driven hyper-coagulability and overall inflammatory response. Data indicates its predictive significance both at initial assessment and in follow-up monitoring, with increased or rising levels linked to more advanced disease, inadequate treatment response, and higher recurrence risk. When combined with traditional staging systems like FIGO, D-dimer offers additional prognostic insights, serving as a dynamic and low-risk method for patient stratification and early identification of disease advancement.

Nonetheless, constraints such as assay variability, absence of standardized cut-off values, and

vulnerability to confounding elements like infection or postoperative inflammation demand interpretation. Although D-dimer cannot substitute for imaging techniques, it may act as an additional biomarker to inform prompt action and enhance followup approaches, especially in settings with limited resources. Future investigations ought to emphasize validating studies, standardized testing protocols, and incorporation into multimodal biomarker panels or predictive models. Through thorough assessment and meticulous clinical application, D-dimer can improve precision oncology methods, aiding in the early identification of recurrences and guiding personalized management plans in cervical cancer.

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AUTHOR'S CONTRIBUTION

Obeagu EI: conceived the idea, writing the manuscript, literature survey.

DATA AVAILABILITY

Data will be made available on request.

CONFLICT OF INTEREST

None to declare.

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