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# Relationship between Comorbidity and Survival of Cervical Cancer: A Literature Review

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**ABSTRACT**

Cervical cancer is characterized as a tumor that forms in the lower section of the uterus, with persistent infection by high-risk HPV being the primary cause. Data from the WHO indicates that cervical cancer is the fourth most common cancer among women. In 2020, approximately 604,000 new cases were diagnosed, resulting in 342,000 deaths. Survival outcomes for cervical cancer patients vary based on several factors, including cancer stage, type, grade, age, recurrence, and the patient's overall health, particularly the presence of comorbidities. Comorbidity refers to the coexistence of an additional condition alongside a primary or index disease, which can either directly affect the prognosis of the primary condition or indirectly influence treatment decisions. In cancer patients, comorbidities can play a significant role in influencing disease progression, stage at diagnosis, treatment strategies, and clinical outcomes. Several studies have shown a significant relationship between comorbidities and survival in cervical cancer patients. However, other research has reported no significant association between comorbidities and cervical cancer survival. These differences in findings can be attributed to various factors, including variations in inclusion and exclusion criteria, differences in how comorbidities are measured, and variations in control variables such as age, treatment modalities, ethnicity, and cancer stage.

***Keywords:*** cervical cancer; survival; comorbidity.

## INTRODUCTION

According to data from the WHO, cervical cancer ranks as the fourth most common cancer in women. In 2020, an estimated 604,000 new cases were reported, with 342,000 deaths (World Health Organization, 2022). Cervical cancer is defined as a tumor that develops in the lower part of the uterus. The primary cause of cervical cancer is persistent infection with high-risk HPV. The HPV types most commonly associated with cervical cancer are HPV 16 and 18. HPV infection typically occurs through sexual contact [22].

According to the National Cancer Institute, the 5-year relative survival rate for cervical cancer diagnosed at an early stage can reach 91%. However, if the diagnosis occurs when the cancer has progressed to a locally advanced stage, the 5-year relative survival rate decreases to 60%. If the cancer has metastasized, the 5-year relative survival rate drops significantly to approximately 19%. The survival outcomes of cervical cancer patients vary for each individual and are influenced by various prognostic factors.

Key factors that can affect survival include the cancer stage, type of cancer, cancer grade, age, recurrence, and the patient's overall health condition, such as the presence or absence of comorbidities [11].

Comorbidity refers to the coexistence of an additional condition alongside a primary or index disease, which can either directly affect the prognosis of the primary condition or indirectly influence treatment decisions [4]. In cancer patients, comorbidities can play a significant role in influencing disease progression, stage at diagnosis, treatment strategies, and clinical outcomes [14]. Women with cervical cancer have been found to have a higher prevalence of comorbidities compared to the general female population [16]. Wassie et al. (2019) reported that cervical cancer patients with comorbidities exhibit reduced survival rates and face a 1.58 times higher risk of mortality compared to those without comorbid conditions [19]. Similarly, Diaz et al. (2018) observed that comorbidities play a significant role in affecting the survival outcomes of cervical cancer patients in Australia [6].

In contrast, Scambia et al. (2012) found no evidence suggesting that comorbidities have an impact on the survival of cervical cancer patients [15]. Given the differing findings regarding the impact of comorbidities on the survival of cervical cancer patients, a more in-depth investigation into this issue is necessary.

## REVIEW CONTENT

## 1. Cervical Cancer

### 1.1 *Definition of Cervical Cancer*

Cervical cancer is defined as a malignancy of the female reproductive system located in the cervix. Cervical cancer originates in the cells of the cervix, which is the lower, narrow part of the uterus that connects it to the vagina (birth canal). This type of cancer typically develops gradually over time. Before cancer develops, the cervical cells may undergo a process called dysplasia, where abnormal cells form within the cervical tissue. If these abnormal cells are not treated or removed, they can eventually turn into cancer and spread deeper into the cervix and nearby areas [10]. The primary cause is persistent infection with high-risk human papillomavirus (HPV), particularly HPV types 16 and 18. These two HPV types are the most carcinogenic, contributing to over 84.5% of cervical cancer cases [22].

### 1.2 *Pathophysiology of Cervical Cancer*

Cervical carcinoma originates at the squamocolumnar junction and may involve the squamous cells of the outer cervix, glandular cells of the inner cervix, or both. Its precursor lesions include dysplasia, such as cervical intraepithelial neoplasia (CIN) or adenocarcinoma in situ, which can progress to invasive cancer. This progression is typically slow. Longitudinal studies indicate that 30% to 70% of patients with untreated cervical carcinoma in situ will develop invasive carcinoma within 10 to 12 years. However, in approximately 10% of patients, lesions may progress from in situ to invasive carcinoma in less than one year. Once invasive, the tumor penetrates the basement membrane and invades the cervical stroma. Tumor expansion in the cervix can eventually manifest as ulceration, exophytic tumor growth, or extensive infiltration into underlying tissues, including the bladder or rectum [13].

Human Papillomavirus (HPV) is detected in 99.7% of cervical squamous cell carcinoma (SCC) and adenocarcinoma (AC), the most common types of cervical cancer. Among the 15 oncogenic HPV strains, types 16 and 18 are associated with 70% of cervical cancer cases. When HPV infection occurs in the cervical transformation zone or squamocolumnar junction (SCJ), it can lead to cellular dysplasia. Low-grade dysplasia, or cervical intraepithelial neoplasia 1 (CIN1), typically regresses; however, in some cases, it may progress to high-grade dysplasia (CIN2 or CIN3). Cervical cancer develops when high-grade lesions extend beyond the basal membrane of the cervical epithelium. It is estimated that 20% of women with untreated high-grade dysplasia will progress to invasive cervical cancer within five years [20].

### 1.3 *Staging of Cervical Cancer*

The stage of cervical cancer is the most prognostic factor, followed by nodal status, tumor volume, depth of cervical stromal invasion, and lymphovascular space invasion. Prognosis is poorer in women with pelvic or para-aortic lymph node involvement. The International Federation of Gynecology and Obstetrics (FIGO) staging system is the most commonly used classification for cervical cancer. Generally, cancers are classified into four stages, from stage I to IV. However, some cancers, such as cervical cancer, have an additional stage—stage 0—commonly referred to as the pre-cancer stage. Stage 0 is not included in the FIGO classification, as it does not yet qualify as cancer [8].

Stage 0 refers to abnormal cells found in the inner lining of the cervix, also known as carcinoma in situ. Stage I indicates that the cancer is confined to the cervix. Stage I is further subdivided into IA1, IA2, IB1, IB2, and IB3. Stage II is diagnosed when the carcinoma extends beyond the uterus but does not reach the pelvic wall or the lower third of the vagina. Stage II is further divided into IIA1, IIA2, and IIB. Stage III occurs when the tumor extends to the pelvic wall and/or involves the lower third of the vagina, and/or causes hydronephrosis or non-functioning kidneys, and/or involves pelvic and/or para-aortic lymph nodes. Stage III is subdivided into IIIA, IIIB, and IIIC. Finally, Stage IV is characterized by the tumor invading the bladder or rectal mucosa (confirmed by biopsy) and/or spreading beyond the true pelvis. Stage IV is divided into IVA and IVB [8].

### 1.4 *Management of Cervical Cancer*

Cervical cancer treatment is determined based on several factors, including the cancer stage, whether it has metastasized to other parts of the body, tumor size, and the patient's age and overall health. Treatment guidelines, recently updated by the National Comprehensive Cancer Network, include surgery, radiation, and chemotherapy either individually or in combination. If a woman is pregnant, treatment depends on the stage of pregnancy and the cervical cancer stage and should be determined in collaboration with the patient. If the cancer is in the third trimester or remains in an early stage without metastasis, treatment may be postponed until after delivery [8]. Women with advanced cervical cancer (stages IB2 to IVA) have higher recurrence rates and poorer survival outcomes. The standard of care for locally advanced cervical cancer is concurrent chemoradiation or definitive cisplatin-based chemotherapy, administered alongside radiation therapy, which includes both external beam radiation therapy and brachytherapy over 8 weeks [9].

### 1.5 *Prognosis of Cervical Cancer*

The prognosis of cervical cancer patients is highly influenced by the stage of the disease at the time of diagnosis. More than 90% of cervical cancer cases can be detected early through the use of Pap smear and HPV tests. However, these tests are not performed in approximately 33% of women diagnosed with cervical cancer, leading to higher

mortality rates than expected. The prognosis of cervical cancer is also influenced by various other factors, such as cancer stage, cancer type (adenocarcinoma or squamous cell carcinoma), age, overall health status, the presence of other health issues or immunocompromised conditions, and whether the cancer is newly diagnosed or recurrent [13].

## 2. Comorbidity

### 2.1 *Definition of Comorbid*

Several definitions have been proposed for comorbidity based on different conceptualizations of a core concept, which is the presence of more than one distinct condition in an individual. Although it is consistently used as an individual-level construct, four main types of distinctions are made: (1) the nature of the health conditions, (2) the relative importance of co-occurring conditions, (3) the chronology of condition presentation, and (4) the expanded conceptualization [17].

### 2.2 *Comorbidity in Cancer Patients*

Having one or more comorbidities can affect a patient's prognosis regarding the primary disease, such as cancer. Comorbidities can influence the timing of cancer diagnosis, either positively or negatively. For example, symptoms of comorbidities may prompt patients to seek medical care more promptly, potentially leading to earlier diagnosis or cancer symptoms may be mistakenly attributed to pre-existing health conditions, thereby delaying diagnosis. After diagnosis, the presence of comorbidities can also affect treatment timing, acceptance, or outcomes, with clear evidence that those with comorbidities are less likely to receive curative treatment than those without, although there is increasing evidence that many patients with comorbidities benefit from such treatment. While the coexistence of multiple health conditions is common, guidelines, funding, and primary healthcare structures may not support the care of more patients with various conditions, and care at secondary and tertiary centers is often highly specialized and isolated [7].

### 2.3 *Comorbidity Scale*

- *Charlson Comorbidity Index*

The Charlson Comorbidity Index (CCI) is one of the most frequently used methods for evaluating comorbid factors and predicting mortality. The CCI, which has been in use since 1987, considers numerous underlying conditions such as age, diabetes, kidney disease, malignancy, cerebrovascular disease, liver disease, HIV positivity, and many others [4]. The Charlson Comorbidity Index (CCI) has been adapted for use with various data sources, including ICD-9 and ICD-10 coding, and has shown consistent validity across multiple prognostic scales. It effectively predicts long-term mortality in a range of clinical populations, such as medical, surgical, ICU, trauma, and cancer patients. The CCI's sensitivity is evidenced by its correlation between higher scores and increased mortality, and its incremental validity enhances predictive accuracy when combined with other measures [3].

- *Elixhauser Score*

The Elixhauser comorbidity index consists of a comprehensive set of 30 comorbidities defined using ICD-9-CM codes from administrative data. It has been found to be a significant predictor of both hospital length of stay and hospital charges. While many of the individual comorbidities in the Elixhauser index were linked to in-hospital mortality, the overall association was not significant. A limitation of the original Elixhauser index is that it includes 30 binary variables for each comorbidity, without a weighting system to generate a single overall score [21].

- *ACE-27 (Adult Comorbidity Evaluation)*

The Adult Comorbidity Evaluation 27 (ACE-27) is a 26-item index that assesses the presence and severity of medical conditions by categorizing them into four classes: none, mild, moderate, or severe. Mild comorbidities are those that are controlled with or without medication, do not limit daily activities, and do not require hospitalization. Moderate comorbidities are those that necessitate treatment adjustments, cause some disability that affects daily activities, or require hospitalization or surgery. Severe comorbidities result in significant complications, irreversible organ damage, uncontrolled symptoms, and disabilities requiring full assistance with daily activities [1].

## 3. Relationship between Comorbidity and Survival Rate in Cervical Cancer

Comorbidities may influence survival rates both directly and indirectly. A comorbid condition can indirectly affect an individual's decision to undergo initial health screenings. Patients with chronic and severe comorbid conditions may focus more on managing their comorbidities and may neglect cancer screening, leading to a delayed diagnosis and ultimately worse prognosis [12]. In addition to its impact on cancer screening, comorbidities also affect the management of cancer therapy. The comorbid conditions of a patient can limit treatment options for cervical cancer, increase the risk of treatment complications, and potentially lead to the discontinuation of therapy [2]. Various comorbid diseases, such as obesity, diabetes, HIV/AIDS, and chronic viral hepatitis, also have a significant impact on immunity, as these conditions can impair immune function both locally and systemically [18]. Additionally, chronic depression and stress have been shown to affect immunity. These conditions can influence systemic immunity and the intratumoral immune environment through the activation of the hypothalamic-pituitary-adrenal (HPA) axis as a central stress response system [5].

Several studies have identified comorbidities as significant predictors of survival in cervical cancer patients. For example, a study by Wassie et al. (2019) showed that patients with comorbidities had a lower survival rate and 1.58 times higher mortality compared to patients without comorbidities. The presence or absence of comorbidities in this study was based on the Charlson Comorbidity Index, but the CCI score was not calculated for the patients.

Additionally, the study did not classify cervical cancer patients by stage or treatment [19]. Another study by Diaz et al. (2018) found that comorbidities impact the survival of cervical cancer patients in Australia. This study assessed comorbidities using the CCI and Elixhauser scores, classifying patients into three groups: those with a score of 0 (no comorbidities), those with a score of 1 (mild comorbidities), and those with a score of 2+ (severe comorbidities). The study also divided the population by ethnicity (indigenous and non-indigenous). The results indicated a decline in survival for the non-indigenous group with each increase in comorbidity score, as well as a higher mortality rate in the non-indigenous group as the comorbidity score increased [6].

However, another study by Ferrandina et al. (2012) found no significant relationship between survival rate and comorbidities in patients with locally advanced cervical cancer (stage IB2-IVA). This study used the CCI and ACE-27 index as measures of comorbidity. Patients were grouped into CCI=0 and CCI>0, as well as ACE-27=0 and ACE-27>0. The results showed no significant difference in Disease-Free Survival when measured using either the CCI or ACE-27 (p=0.9). Overall survival also did not show a significant difference based on categorization using either CCI or ACE-27 (p=0.8). The conflicting results from other studies may be partly explained by the use of different comorbidity scales, the occurrence of selection bias, and the quality of data selection [Ferrandina].

## CONCLUSION

Comorbidities may affect the survival rates of cervical cancer patients. However, discrepancies exist among studies, with some reporting a significant relationship while others find no such association. These differences in significance can be attributed to various factors, including differences in inclusion and exclusion criteria, variations in comorbidity measurement parameters, and differences in control variables such as age, treatment modalities, etnic, and cancer stage.

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