CD4+ and CD8+ Tumor-Infiltrating Lymphocytes (TILs) Biomarkers: Role in Predicting the Stadium and Prognosis of Cervical Cancer

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INTRODUCTION

Cervical cancer is one of the leading causes of cancer and is the fourth most common cancer in women worldwide, with an estimated 570,000 new cases in 2018 [1,2] with the highest incidence of cervical cancer (nearly 90% of 311,000 deaths worldwide in 2018) in low- and middle-income countries [1,3]. In contrast, cervical cancer and mortality incidence in countries with high resources is two to four times lower than in countries with lower resources [4–6]. Mortality rates vary among regions of the world, from less than 2 per 100,000 in West Asia, Western Europe, Australia, and New Zealand to more than 20 per 100,000 in Melanesia, Central, and East Africa [7,8].

More than 200 recognized types of Human papillomavirus (HPV) are associated with various clinical conditions ranging from harmless lesions to cancer. Most of these infections are non-oncogenic or benign [9,10]. Only a small proportion of infections with certain types of HPV can survive and develop into cancer, such as cervical cancer, the main cause of which is HPV infection by forming proliferative lesions on the cervix, like condylomas and papilloma in the squamous epithelium of the skin, mucosal tissue, head and neck, and anus [9–12]. Worldwide studies reveal that HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, and 73 are found in more than 0.5% of cervical cancers and identify that HPV 16 and 18 are the most common etiology [13–15]. It is usually transmitted by sexual contact causing squamous intraepithelial lesions. Long-term HPV infection can lead to the development of Cervical Intraepithelial Neoplasia (CIN) [14–17].

Cervical cancer can be caused by several factors, including sexual intercourse at a young age, frequent change of sexual partners, multiparity, smoking, long-term use of oral contraceptive pills, and suppression of the immune system, which can cause persistent HPV infection and play a role in the carcinogenic process [18–20]. HPV infection will produce protein products in
the form of oncoproteins (E6 and E7) formed due to the integration of the HPV genome into the host genome, which will induce uncontrolled cell growth. Mutations in the host genome accumulate are due to inhibition of the function of the retinoblastoma (Rb) and p53 genes [12,16,21,22].

Under normal circumstances, HPV infection will be destroyed by the immune response. The immune system is known as the innate immune system and adaptive (acquired) immunity. One of its functions is to prevent viral infections. The adaptive immune system reacts explicitly to certain HPV proteins, which have two defense systems, namely the type-1 helper T (Th1)-cell response and the type-2 Th1 response [23,24]. Several studies have shown that a decreased Th1 response and an increased Th2 response led to the suppression of cellular immunity and the development of cervical lesions [25,26]. Th1 cells promote cell-mediated immunity (CMI) by inducing cytotoxic T lymphocytes (CTLs) to kill virus-infected cells, whereas Th2 cells stimulate humoral immunity (stimulate B cells to produce antibodies) [27]. During the infection of HPV, Th1 immune system cells play an essential role in eliminating infection of HPV, especially in fighting the E6 and E7 proteins [12,28].

Despite the extraordinary nature of the human body’s defense system, HPV also has immune evasion mechanisms and facilitates cancer development [29,30]. HPV may remain undetected by the immune system for a long time. During the early stages of HPV infection, the innate immune system creates a pro-inflammatory microenvironment by recruiting innate immune cells to eliminate infected cells, initiating an effective immune response [31,32]. The specific immune response is essential for elimination because immunosuppression slows the eradication of HPV infection. However, virus eradication is slow, even in immunocompetent individuals, and the immunological mechanisms leading to viral clearance are not well understood [33,34].

Passively, HPV evades the immune system because of its expected life cycle outside the epithelial basement membrane and does not cause any danger signals. The immune system’s evasion is actively mediated intracellularly by altered gene expression and impaired protein function and extracellularly by disrupting the immune cell network from antigen-presenting cells to effector T cells. These strategies allow HPV to persist for a long time, which allows the virus to complete its life cycle and increases the risk of persistent lesions and early malignant transformation [35,36].

Recent studies, especially those focused on cancer immunotherapy treatment and prognosis, point to the body’s immune system being closely related to tumor regression. Th1 cells are one of the body’s cellular immunities that significantly suppress cancer progression. Migration of Th1 lymphocyte cells around the tumor, known as Tumor-Infiltrating Lymphocytes (TILs), has become an important issue as a biological marker in solid cancers, including squamous cell carcinoma of the cervix, especially in the early stages (cervical intraepithelial neoplasia grade 3), and the presence or expression of TILs in cervical cancer is related to the prognosis of these subtypes. The higher number of lymphocytes found around cancer cells indicates that the immunity of cancer patients is getting better and the prognosis (survival) of the patient is also increasing [12,26].

Many studies have been carried out on the role of TILs in solid cancer tissues other than the cervix, including carcinomas of the lung, gastrointestinal tract, genitourinary system, gynecological system, and head and neck, as well as primary brain tumors, mesothelioma, and melanoma [37,38]. This study examines the role of TILs in cervical cancer; the higher the expression of TILs, the better the patient’s prognosis. Tumor regression can be calculated, and immunotherapy treatment will be more easily applied to cancer patients. Tumors possess a variety of cell membrane-bound antigens, recognized as non-self by the immune system, which stimulate a cytotoxic immune response characterized by CD4+, CD8+, antigen-presenting cells, and other lymphoid elements’ infiltration. These infiltrating cells are immune surveillance mechanisms that inhibit tumor growth and spread. Tumor-infiltrating lymphocytes (TILs), mainly CD4+ and CD8+ T cells, have been extensively described in anti-tumor immunity, and knowledge of CD4+ and CD8+ T lymphocytes interplay in mediating the control of tumor growth exists [39].

Evidence has accumulated to support the prognostic and potential predictive impact of TILs in other solid tumors, both in triple-negative and HER2-positive cancers. The clinical utility of assessing TILs in breast cancer relates to risk prediction models, adjuvant and neoadjuvant chemotherapy decisions, and the growing potential of immunotherapy. However, the prominent lymphocytic infiltrate may be found in tumors not meeting the other strict criteria for medullary breast carcinoma. The induction of the Th1 immune response against HPV antigen plays an essential role in preventing the development of malignancy. This study will also explain the theory of how HPV evades the body’s immune response system and the choice of immunotherapy aimed at the benefits of TILs on the survival of cancer patients.

METHODS

Determining the review question

The scope of the topics to be reviewed is defined using the PICO formula: (1) Patient: cervical cancer patients; (2) Intervention: immunohistochemical examination with T CD4+ and CD8+ TILs and TILs immunotherapy; (3) Comparison: Available cervical
cancer chemotherapy; (4) Outcome: increased immunohistochemical expression of CD4+ and CD8+ T TILs and clinical improvement of cervical cancer patients.

**Determining eligibility criteria**

The eligibility criteria are determined by the inclusion and exclusion criteria. (1) Inclusion criteria were English articles relevant to cervical cancer tissue which underwent histopathological and immunohistochemical examination of Tumor-Infiltrating Lymphocytes (TILs) in the form of CD4+ and CD8+ as well as immunotherapy treatment with TILs and using clinical trials, cohort, retrospective, and cross-sectional research designs; (2) Exclusion criteria were articles relevant to cancer tissue from reproductive organs such as the uterus, ovaries, and fallopian tubes by examination of TILs and other methods such as Polymerase Chain Reaction/FISH, duplication articles, non-English language articles, and review articles.

**Study search**

Indexed articles from the last 5 years are systematically searched on the following databases: PubMed, SCOPUS, and ProQuest. The search terms used included (“TILs” [MeSH Terms] OR “Tumor-Infiltrating Lymphocytes” [All Fields]) AND (“cervical cancer”) [All Fields]) AND (“Human Papillomavirus” [All Fields] OR “HPV” [MeSH Terms]) AND (“CD4”) [MeSH Terms]) AND (“CD8”) [MeSH Terms]) AND (“immunohistochemistry” [All Fields]). All selected articles are in English.

**Study selection**

Study selection was carried out using Mendeley bibliography software. The first step is to do abstract screening followed by full-text screening. Articles or studies that are not relevant are excluded by considering their relevance and suitability for the research objectives. Study quality was assessed based on the Jadad scale.

Out of 469 articles, 19 articles were deleted due to repetition. Of the 450 articles, four were excluded because they were not in English. Based on the evaluation of titles and abstracts, 375 articles were excluded because the research topics were irrelevant. The remaining 71 free and complete access articles were examined by full-text review, using exclusion and inclusion criteria. Twenty-four studies did not meet the study design we were interested in, 13 articles did not address our desired results, 22 articles studied different types of cancer cells, and two articles detected antigen expression of TILs using methods other than immunohistochemical staining. Finally, ten articles were selected for a systematic review—the studies were searched and selected in detail using the PRISMA flow diagram (Figure 1).

**RESULT**

**Study Characteristics**

It was found that ten articles that matched the inclusion and exclusion criteria were then analyzed. Ten studies were published between 2017 and 2020. Most of the studies were reported in China. The following data is generated from the ten most relevant studies for a systematic review, including author information, year, the number of patients or country sample, participants, study design, extracted methodology, and summarized conclusions. The conclusions of the ten articles reviewed are made from scientific reviews and studies in the form of article designs by the research objectives, as shown in Table 1.

A study analyzed CD103C cell infiltration by immunohistochemistry (IHC) in an independent cohort of 630 cervical cancer patients. Patients were included...
Table 1. Characteristics of the study included in this systematic review

<table>
<thead>
<tr>
<th>No</th>
<th>Author</th>
<th>Year</th>
<th>Sample</th>
<th>Country</th>
<th>Participants</th>
<th>Research Studies</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cao et al. [40]</td>
<td>2020</td>
<td>62</td>
<td>China</td>
<td>Cervical cancer patient</td>
<td>Cohort</td>
<td>Patients with higher CD8+ TIL values have better survival rates</td>
</tr>
<tr>
<td>2</td>
<td>Ohno et al. [41]</td>
<td>2020</td>
<td>55</td>
<td>Japan</td>
<td>Cervical squamous cell cancer patient</td>
<td>Retrospective study</td>
<td>Abundant infiltration by CD3+, CD4+, CD8+, CD206+, and FOXP3+ TIL was statistically significant as an independent indicator of better progression and overall survival</td>
</tr>
<tr>
<td>3</td>
<td>Chen et al. [42]</td>
<td>2019</td>
<td>96</td>
<td>China</td>
<td>Cervical cancer patient</td>
<td>Cohort</td>
<td>CD45RO+ TILs and FOXP3+ TIL are probably useful biomarkers for risk stratification in cervical cancer patients</td>
</tr>
<tr>
<td>4</td>
<td>Wu et al. [43]</td>
<td>2020</td>
<td>44</td>
<td>China</td>
<td>Cervical cancer patient</td>
<td>Cohort</td>
<td>CD4+ cells and CD8+ cells, and the ratio of CD4+/CD8+ cells were related to clinicopathological and prognostic parameters</td>
</tr>
<tr>
<td>5</td>
<td>Maskey et al. [39]</td>
<td>2019</td>
<td>72</td>
<td>China</td>
<td>Cervical cancer patient</td>
<td>Cohort</td>
<td>The infiltration rate of CD4+ILs and CD8ILs has the potential to play a role in eliminating HPV-infected cervical epithelial cells.</td>
</tr>
<tr>
<td>6</td>
<td>Stevanovic et al. [44]</td>
<td>2019</td>
<td>58</td>
<td>Maryland</td>
<td>Cervical cancer patients and non-cervical cancer patients</td>
<td>Cohort</td>
<td>No significant differences were detected between cervical and non-cervical cancer patients in the total number of administered T cells, CD4+ T cells, and CD8+ T cells</td>
</tr>
<tr>
<td>7</td>
<td>Komdeur et al. [45]</td>
<td>2017</td>
<td>630</td>
<td>Dutch</td>
<td>Cervical cancer patient</td>
<td>Cohort</td>
<td>CD103+ TILs are promising markers for rapid assessment of tumour-reactive T-cell infiltration of cervical cancer and a promising response biomarker for E6/E7-targeted immunotherapy</td>
</tr>
<tr>
<td>8</td>
<td>Rossetti et al. [46]</td>
<td>2018</td>
<td>26</td>
<td>Brazil</td>
<td>Samples of cervical cancer patients and healthy donors to be induced into female mice</td>
<td>Cohort</td>
<td>Anti-CD40-activated B lymphocytes can elicit a T-cell response, and B lymphocytes can be used as a tool for cancer treatment immunotherapy</td>
</tr>
<tr>
<td>10</td>
<td>Miyasaka et al. [48]</td>
<td>2020</td>
<td>71</td>
<td>Japan</td>
<td>Cervical Cancer Patient</td>
<td>Retrospective study</td>
<td>The presence of CD8+TIL can be an independent favourable prognostic factor.</td>
</tr>
</tbody>
</table>
for CD103C TILs quantification if the Tissue Microarrays (TMA) used contained at least two nuclei with at least 20% tumor. Most patients in the surgery group were diagnosed with FIGO stage IB. Most patients in the R(C) T group were diagnosed with FIGO stage IIb. Of the surgery and RCT cohort, 64.2% of tumors were squamous cell carcinoma (SCC), and 17.9% were adenocarcinoma (AC). Komdeur et al. [45] reported that based on a positive staining result for CD103C, TILs were equally present in SCC, adenocarcinoma (ADC), and other subtypes. Interestingly, the median CD103C TILs cell infiltration in patients receiving radiotherapy (chemo) was significantly lower than in patients receiving surgery alone. Lower TILs CD103C cell counts were found in patients with higher FIGO stages.

Based on the correlation analysis of the subset of lymphocytes in peripheral blood, Wu et al. [43] revealed that most baseline characteristics, such as age (≤ 47 years vs > 47 years), stage (FIGO I vs FIGO II), tumor size (≤ 4 cm vs > 4 cm), and stromal invasion (≤ 1/2 vs > 1/2) did not show a significant difference, but histology (SCC vs ADC), lymph node (LN) metastatic status (negative vs positive), and lymphovascular space invasion (LVSI) status (negative vs positive) showed a significant difference. When comparing low levels with high levels of the lymphocyte subset (the median value of the lymphocyte subset was used as the limit value), the researchers found that most of the lymphocyte subsets did not show significant differences; however, the difference in the CD4+ or CD8+ cell ratio was significant.

Miyasaka et al. [48], reported that patients with FIGO stage IB-II disease had significantly better overall survival (OS) and progression-free survival (PFS) than patients with FIGO III-IV disease. Compared with a maximum tumor diameter (MTD) of 40 mm, MTD > 40 mm tended to be associated with worse OS. However, this difference did not reach statistical significance (44.9 vs 68.6%, p = 0.079). MTD > 40 mm was significantly associated with worse PFS (27.6 vs 63.5%, p = 0.018). In the immunohistochemical analysis, positive TILs for CD8 (CD8+ TILs) in tumor nests were observed in 83.1% of patient biopsy samples. Patients with CD8+ TILs had better OS rates than patients without CD8+ TILs; there was no significant difference. This study can also be supported based on a study conducted by Chen et al. [42]. They grouped patients based on lymph node status, a significant difference from FIGO stage, status LVI, CD3+ TILs in the central tumor area, CD45RO+ TILs in the central tumor area, and CD45RO+ TILs in the invasive margin area observed. Only lymph node metastatic status and tumor size were significantly different between patients with early-stage cervical cancer and patients with the advanced stage. However, no significant difference in tumor-infiltrating immune cells was observed.

**DISCUSSION**

Cervical cancer is known as HPV induced by forming proliferative lesions in the cervix, which plays a vital role in the progression of CIN to cervical cancer. Maskey et al. [39] whose research focused on determining the quantity of CD4+ T and CD8+ T cells in HPV normal cervix, normal HPV + cervix, and HPV + CIN with different degrees. It was found that Infiltration Lymphocytes (IL) were low in normal cervix and high IL in CIN, where IL increased with increasing grade of CIN.

HPV-TILs therapy is a personalized treatment in which the characteristics of self-transferred T cells can serve as mechanism-driven biomarkers to predict treatment response. It was reported by Stevanovic et al. [44], and these results are like those of a previous study where HPV reactivity from TILs could be associated with clinical response. A study conducted by Rossetti et al. [43] found that the administration of B lymphocytes can be used as an alternative therapy that will promote the anti-tumor response of T cells if appropriately stimulated. These actions can be combined with ablative actions such as chemotheraphy or radiotherapy before lymphocyte transfer to release tumor antigens and create appropriate niches for T-cell expansion. The data suggest that B lymphocytes can be considered a tool to promote anti-tumor T cell responses if properly stimulated.

While many clinical studies have demonstrated a long-term survival benefit of immunotherapy in various cancer entities, little is known about whether this therapy is effective against cervical cancer. Patients with metastatic HPV-associated carcinoma taking TILs therapy have shown modest responses to treatment. However, effective immunotherapy for the treatment of metastatic cervical cancer was limited by low microsatellite instability (MSI) expression and harmful to the Programmed death-ligand 1 (PD-L1). The study exploring the efficacy of adopting TILs and anti-PD1 antibody transfer in patients with metastatic cervical cancer was conducted by Yin et al. [47] showing low MSI expression that was harmful to PD-L1. Interestingly, their findings suggest that combination therapy of TILs and anti-PD1 has the potential to modulate metastatic cervical cancer growth in patients with low MSI expression and is negative for PD-L1. TILs mediate the anti-PD1 therapeutic effect in the tumor microenvironment; therefore, combining anti-PD1 with TILs therapy may provide a more effective anti-tumor effect in metastatic cervical cancer.

Cao et al. [40] analyzed patient survival based on TILs values and the relationship between TILs and HPV viral loads. Meanwhile, HPV viral load is the main factor influencing the composition and distribution of TILs; the higher the HPV viral load, the more active the tumor cell proliferation, and the tumor microenvironment tend to be more immunosuppressed. Patients with high viral
load values have a poorer prognosis because viral load leads to a predominance of inhibitory immune responses (FoxP3 TILs). In patients with low viral loads, the CD8+ TILs values were higher, which means that the survival of these patients was higher, in contrast to patients who have a low viral load.

A study conducted by Ohno et al [41], examined the association between the prognosis of cervical cancers II and III treated with concurrent chemoradiotherapy (CCRT) and TILs counts. In their study, they found that better survival was associated with a high density of CD3+, CD4+, CD8+, CD206+, and FOXP3+ T cells. This is positively correlated in cervical cancer patients where the more T cell density or TILs are found, the better the patient’s prognostication.

The study that assessed the patient’s prognostic regarding the stage of the disease conducted by Miyasaka et al. [48] reported that OS and PFS rates were significantly better in patients with stage IB-II FIGO than in patients with FIGO III-IVA. The presence of CD8+ TILs is a prognostic factor associated with better OS. It correlates with better PFS, suggesting that tumor-reactive T-cell infiltration of tumor tissue leads to a favorable prognosis. In addition, their results support further consideration of adding adjuvant immunotherapy to radiotherapy (RT) for AC. Currently, many clinical trials are investigating the effects of RT combined with immunotherapy for various types of malignancies. Therefore, the combination of RT with immunotherapy may improve the prognosis of patients with AC and CD8+ TILs in tumor nests.

Regarding the response to combination therapy with TILs and anti-PD1, Yin et al. [47] showed that patients with higher TILs and CD8+ infusion showed better PFS and OS. In contrast, higher infusions of CD8+ PD1+ TILs and CD4+ FoxP3+ TILs resulted in poor PFS and OS. The expression of PD1 by TILs is considered one of the factors attenuating the anti-tumor immune response.

One possible reason is that HPV-positive tumors may have enhanced sensitivity to treatment due to mutant TP53, allowing an apoptotic response of cancer cells to radiation and chemoradiation. Another potential explanation is that HPV-positive HNSCC might express HPV-encoded peptides recognizable by the host immunity. It has been reported that Cytotoxic T-lymphocytes (CTLs) recognize the HPV-specific peptides for tumor elimination [3,11]. The co-inhibitory receptors CTLA-4 and PD-1, which down-modulate CTL response in chronic antigen stimulation and decrease anti-tumor immunology, have been extensively investigated [44,46].

A plausible explanation for the differences in survival between HPV-positive and HPV-negative patients is that virally driven tumors provoke an adaptive immune response directed against tumor-expressed viral antigens: immune responses against the foreign viral antigen are less likely to be suppressed; there is no central immunological tolerance to confound the immune system’s attempts to control cancer. HPV-16-specific CD8+ T cell responses have been detected in the blood of HPV-positive cancer patients and, more recently, isolated from tumors, implicating a role in the anti-tumor response. Several recent studies have further demonstrated anti-tumor immunity in HPV-positive. Stevanovic et al. [50] found better survival in HPV-positive patients with seropositivity to E6/E7. Furthermore, infiltration of HPV-positive by PD-1-expressing T lymphocytes is a favorable prognostic factor.

In several solid tumors, quantification of densities of various T-cell subpopulations, including CD8+, CD4+ TILs cells (FoxP3+ CD4+), or subset ratios, has been suggested to improve the predictive power over that of absolute T-cell number (CD3+). Cytotoxic CD8+ T cells are the principal anti-tumor effector cells, and their abundance is a predictor of positive outcomes in several tumor types, particularly colorectal cancer, suggesting that the adaptive immune system has a role in suppressing tumor progression. Our analysis of a publicly available cancer microarray data set showed enrichment of genes associated with CD8+ T-cell effector function in patients with improved survival, arguing that the T cells are not simply ‘innocent bystanders’ of the biological events in the tumor but take an active role in tumor recognition [50].

Other studies examine the effects of HPV status and TILs levels on survival in tumors. Like other large studies, HPV-positive tumors were associated with significantly improved survival (3-year survival; HPV-positive 82% vs HPV-negative 56%, P < 0.001); pathological and clinical features of HPV-positive tumors were consistent with these series. The HPV-positive tumor was generally late-stage and was poorly differentiated (both P < 0.001). HPV positivity is inversely correlated with smoking and EGFR expression [all P < 0.005] [44,49].

TILs levels are also correlated significantly with HPV status (P < 0.001), with around 85% of HPV-positive tumors containing high or moderate levels of TILs. Considering the array of data, this is likely to reflect an adaptive anti-tumor response as the mechanism for improved outcomes. TILs levels stratified HPV-positive patients into those with good and poor prognoses. The 3-year survival for HPV-positive/TILs high tumors was 96% compared with 76% for moderate HPV-positive/TILs and 59% for low HPV positive/TILs. The low HPV-positive/TILs low tumors had similar survival to HPV-negative tumors (3-year survival, 56%) [50].

The limitation of the study is that we have found a limited number of articles discussing HPV infection with the role of TILs to the extent that we figuratively found another article discussing TILs’ role in other solid tumors. Future studies could expand the results by
examining the molecular characteristics of HPV infection distinctively. Meta-analysis about this topic is highly encouraged for research in the future to give further understanding of TILs’ role in predicting the stadium and prognosis of cervical cancer.

CONCLUSIONS

From 10 works of the literature analyzed, it can be concluded that HPV has been shown to affect the expression of TILs in cervical neoplastic lesions. There is a positive and significant correlation between TILs and the development of NIS into cervical cancer. There have been clinical trials of TILs therapy as immunotherapy and adjuvant immunotherapy for cervical cancer. There was found that TILs can be prognostic biomarkers and markers to predict the cervical cancer stage. T helper (CD4+) and cytotoxic T-cells (CD8+) were found in all the primary tumors without a recognizable distribution pattern within the individual tumors. The infiltrate ranged from one that was CD4+ predominant to one that was CD8+ predominant. There was a decline in the level of CD8+ T cells in regional lymph nodes, specifically found in the lymph nodes of cervical cancer patients. Recent studies have suggested that lymphatic flow in cancer patients may occur due to specific processes related to hosting immunity or non-specific suppression of NK and CD8+ T cells, which are responsible for the process of poor immunological activity. TILs levels also correlated significantly with the HPV status (P < 0.001), with around 85% of HPV-positive tumors containing high or moderate levels of TILs. Considering the array of data, this is likely to reflect an adaptive anti-tumor response as the mechanism for improved outcomes.

REFERENCES

