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Observational Study

Haematology results, inflammatory haematological ratios, and inflammatory indices in cervical cancer: How is the difference between cancer stage?

Haematological laboratory results in cervical cancer

Abstract

BACKGROUND

Cervical cancer is a prevalent form of cancer affecting women worldwide and it is the second most prevalent cancer among women in Indonesia, accounting for 8.5% of all cancer-related deaths. Cervical cancer progression can be evaluated through laboratory tests to detect anaemia, an increased platelet count, and elevated inflammatory markers, therefore, effective laboratory examination is crucial for early detection and treatment of cervical cancer.

AIM

To evaluate the association between laboratory findings (haematology, haematology index, and inflammatory index) and the clinical stage of cervical cancer.

METHODS

This cross-sectional study analysed adult cervical cancer patients' data from medical records and central laboratory results including sociodemographic status, histopathological finding, clinical stage, and complete haematology examination. Numerical data was analysed by the one-way ANOVA (normal data distribution), while the Kruskal-Wallis test was used for non-parametric data (abnormal distribution), followed by appropriate post-hoc analysis. The categorical data was analysed by the Chi-square or Fisher Exact tests. The significance level was established at a *P value* < 0.05.

RESULTS

This study involved the data of 208 adult cervical cancer patients and found no association between age, marital history, parity history, hormonal contraceptive use and cervical cancer stages. There were significant differences in the clinical laboratory test results based on the clinical stage of cervical cancer, including haemoglobin levels ($P < 0.001$), leukocytes ($P < 0.001$), neutrophils ($P < 0.001$), monocytes ($P = 0.002$),

lymphocytes ($P = 0.006$), platelets ($P < 0.001$), neutrophil-lymphocyte ratio/NLR ($P < 0.001$), lymphocyte-monocyte ratio/LMR ($P < 0.001$), and platelet-lymphocyte ratio/PLR ($P < 0.001$). There were also significant differences in the systemic inflammatory index (SII) and systematic inflammatory response index (SIRI) between stage III+IV cervical cancer and stage II (SII $P < 0.001$; sSIRI $P = 0.001$) and stage I (SII $P < 0.001$; SIRI $P = 0.016$), associated with the shifts in previously mentioned complete haematological values with cancer advancement.

CONCLUSION

The haematological parameters, inflammatory haematological ratios, and inflammatory indices exhibited significant differences between cervical cancer stages, therefore these tests can be utilised to evaluate cervical cancer progression.

Key Words: Cervical cancer; Haematology; Haematology index; Inflammation; Malignancy

Core Tip: The current investigation of 208 adult cervical patients found that hematologic parameters such as leukocyte, neutrophil, monocyte, and platelet counts vary significantly depending on the cervical cancer clinical stage. There were significant changes in inflammatory haematological ratios (neutrophil-lymphocyte ratio/NLR, platelet-lymphocyte ratio/PLR, and lymphocyte-monocyte ratio/LMR) and inflammatory indices (systemic immune-inflammation index/SII and systemic inflammation response index/SIRI), particularly between patients with stage III+IV and those with stage II and I cervical cancer. The analysis revealed that the cervical cancer clinical stage is highly related to the hematologic parameters.

INTRODUCTION

Cervical cancer is characterised by the uncontrolled growth of aberrant cells in the cervix uteri[1]. This cancer is the fourth most prevalent form of cancer affecting women

worldwide[2] and is the second most prevalent cancer in Indonesian women with 36,964 new cervical cancer cases and 20,708 fatalities accounting for 8.5% of all cancer-related deaths[3]. Sexual contact is the primary factor contributing to disease transmission by exposure to the human papillomavirus (HPV). HPV is the primary oncogenic virus in women, responsible for around 90% of cervical cancer cases when there is a persistent high-risk HPV infection including HPV type 16 and 18[4].

Cervical cancer is frequently diagnosed at an advanced stage due to the lack of detection methods but is one of the most treatable forms of cancer if identified within the pre-cancerous stage[5]. A meta-analysis of 53,233 participants demonstrated that the incidence of late-stage cervical cancer patient presentation accounted for 60.66% of all cases worldwide, with Africa (62.60%) and Asia (69.30%) having higher rates than the global average[6]. This is primarily due to the individual's educational attainment, economic circumstance, geographical location, and pre-referral diagnosis by primary healthcare professionals[6,7]. This would undoubtedly exacerbate the death rate of cervical cancer, particularly in low-income nations, therefore, early identification is crucial in this case.

Various laboratory tests can be used to evaluate cervical cancer progression[8]. For instance, advanced cancer can cause chronic anaemia due to excessive cytokines directly and indirectly suppressing erythropoiesis[9]. Tumours also release cytokines that stimulate the formation of megakaryocytes and thrombopoiesis, resulting in an elevated platelet count[10]. Chronic inflammation also promotes the advancement of tumours and makes them more resistant to treatment. Therefore, cancer progression is linked to various inflammatory pathways, such as nuclear factor kappa B (NF-κB), Janus kinase/signal transducers and activators of transcription (JAK-STAT), toll-like receptor (TLR), and several proinflammatory cytokines [e.g., interleukin (IL), interferon (IFN), and tumour necrosis factor (TNF-α)][11]. Thus, there may be alterations in the leukocyte count and the composition of leukocytes including neutrophils, lymphocytes, and monocytes[12]. For example, there is a correlation between the neutrophil-lymphocyte ratio (NLR) and cancer severity with the NLR tending to increase as the

cancer progresses[13]. NLR is linked to increased cytokines [IL-1, IL-6, IL-7, IL-8, IL-12, IL-17, granulocyte colony-stimulating factor (G-CSF), and monocyte chemoattractant protein-1] that boost the function of tumour macrophages[14]. Furthermore, reduced lymphocytes during advanced cancer may impact immune surveillance, causing diminished CD4+ T cells and an altered CD4+/CD8+ ratio related to rapid tumour growth and lymph node infiltration which are associated with PLR elevation[15]. Moreover, there is evidence of elevated levels of inflammatory markers, such as the systemic inflammation index (SII) and systemic inflammatory response index (SIRI) in some cancers, including lung, pancreatic, and breast cancers [16–18]. However, SIRI prognostic significance has not been widely examined in cervical cancer, although nomogram creation utilizing SIRI, FIGO stage, and lymphovascular invasion could better predict cervical cancer prognosis than FIGO stage alone because it may indicate the dynamic tumour burden and immune response status in patients[19].

Therefore, this study aimed to evaluate the association between laboratory findings (haematology, inflammatory haematological ratios, and inflammatory indices) and the clinical stage of cervical cancer to facilitate early diagnosis of cervical cancer and ultimately enhance the prognosis of people living with cancer by utilising readily available biomarkers.

MATERIALS AND METHODS

This cross-sectional study collected data from cervical cancer patients from the Medical Records and Central Laboratory Installation of Dr Mohammad Hoesin General Hospital in Palembang, Indonesia (a tertiary-level facility). Cervical cancer patients aged ≥ 18 years and diagnosed from August 2022 to July 2023 were recruited using the total sampling technique considering a minimum sample size of 207, with an enrolment ratio of two, $\alpha = 0.05$, and $\beta = 80\%$. The study was approved by the medical and health research ethics committees of the Faculty of Medicine, Universitas Sriwijaya (Protocol No. 301-2023).

The data included information on the patient's sociodemographic status (such as age, marital status, parity, and hormonal contraceptive use), histopathological examinations, clinical stage of cervical cancer, and a comprehensive haematological examination (haemoglobin, leukocyte, neutrophil, monocyte, lymphocyte, and platelet counts). Additionally, haematological indices such as the NLR, PLR, and lymphocyte-monocyte ratio (LMR), as well as inflammatory indices, namely the SIRI and SII were also recorded[20].

The clinical stages of cervical cancer were classified according to the 2018 classification of The International Federation of Gynaecology and Obstetrics (FIGO), categorising the disease into four main stages: I, II, III, and IV[21]. The participants were categorised into three distinct stages: stage I, stage II, and stage III + IV due to the limited number of samples available in Stage IV. The NLR was determined by dividing the number of neutrophils by the number of lymphocytes, while the PLR was calculated by dividing the numbers of platelets and lymphocytes. LMR was determined by dividing the number of lymphocytes by the number of monocytes. SIRI was determined by multiplying the monocyte count by the neutrophil count and dividing it by the lymphocyte count. Meanwhile, the SII was obtained by multiplying the platelet count by the neutrophil count and then dividing it by the lymphocyte count. The haematological analysis was conducted using a Sysmex XN-1000 machine.

The statistical analysis was conducted using IBM SPSS software version 26.0 (Armonk, NY: IBM Corp), with a significance level set at $P\ value < 0.05$. The data normality was assessed using the Kolmogorov-Smirnov test on a sample size of more than 50 participants. A univariate analysis was conducted to examine the frequency distribution of each variable. Normally distributed data was analysed by one-way ANOVA and the Kruskal-Wallis test was applied to non-normally distributed data, followed by the appropriate post hoc test, either Tukey (homogenous sample), Games-Howell (non-homogenous sample) or Bonferroni correction test (non-parametric data). The Chi-square or Fisher Exact tests were employed for categorical data.

RESULTS

This analysis involved 208 cervical cancer patients with an average age of 48.5 years who were categorised into three groups: Stage I (n = 25), stage II (n = 51), and stage III + IV (n = 132). Most patients (98.5%) were married with multiparity and grand multiparity as the most common parity status and five patients had a prior record of hormonal contraception. Based on histopathological analysis, the most common type of cervical cancer was squamous cell carcinoma (68.6%), followed by adenocarcinoma, mixed types, and other types. There is no statistically significant association between age and the clinical stage of cervical cancer. Furthermore, there is no statistically significant association between marital status (P = 0.41), parity history (P = 0.34), and history of hormonal contraceptive usage (P = 0.39) and the clinical stage of cervical cancer. Similar findings apply to parity history, hormonal contraception use, and histological classification.

The hematologic results presented in Table 1 showed that several haematologic markers including haemoglobin ($P < 0.001$), leukocyte counts ($P < 0.001$) and platelet counts ($P < 0.001$) exhibited statistically significant variations depending on the clinical stage. Leukocyte counts, including neutrophils ($P < 0.001$), monocytes (P = 0.002), and lymphocytes (P = 0.006) exhibited comparable results. The progressive increase in leukocytes, platelets, neutrophils, and monocytes illustrated the association between cervical cancer stage and haematologic results. Concurrently, haemoglobin levels exhibited a progressive decline with the increasing severity of cancer stages and varied significantly between each stage ($P < 0.001$). The leukocyte counts were significantly different between stage III+IV and stage II (P = 0.042) and stage I ($P < 0.001$). Neutrophils exhibited a notable disparity between stage III+IV and stage II (P = 0.006) as well as stage I ($P < 0.001$). However, only significant differences between stage III+IV and stage II were observed for monocytes (P = 0.002) and lymphocytes (P = 0.005).

Furthermore, analysis of the haematological indices NLR ($P < 0.001$), PLR ($P < 0.001$), and LMR ($P < 0.001$) revealed notable variations depending on the clinical stage. The NLR and PLR results were comparable, with notable differences in the levels of these

indicators between patients with stage III+IV and stage II (NLR $P < 0.001$; PLR $P = 0.001$) and stage I (NLR $P < 0.001$; PLR $P < 0.001$). However, LMR was only different between stage I and stage II ($P = 0.004$) and stage III+IV ($P = 0.019$), suggesting that monocytes are not significantly elevated between these clinical stages. These changes are attributed to lower lymphocyte counts and elevated neutrophil and platelet counts along with disease progression.

There were significant differences in all inflammatory indexes based on the severity of cervical cancer ($P < 0.001$). Post-hoc analysis revealed significant differences in SII values between patients with stage III+IV and those with stage II ($P < 0.001$) and stage I ($P < 0.001$). Similarly, the SIRI was significantly different between stage III+IV and stage II ($P = 0.001$) and stage I ($P = 0.016$), demonstrating increased inflammation in patients with a more advanced cancer stage.

DISCUSSION

The present investigation evaluated the association between laboratory findings (haematology, haematology index, and inflammatory index) and the clinical stage of cervical cancer using data from 208 patients with an average age of 48.5 ± 10.25 years which is consistent with the global average age of cervical cancer diagnosis (53 years, range: 45 to 68 years)[22]. Moreover, the lack of an association between parity history and hormonal contraceptive use is consistent with findings from several earlier study [23–26].

There were significant differences in the laboratory findings among the various stages of cervical cancer. The haemoglobin levels decreased with cancer progression in line with the study of Kunos *et al.* which demonstrated a significant association ($P = 0.01$) between pre-therapy haemoglobin levels and the cervical cancer stage[27]. Another investigation conducted in Tianjin, China also demonstrated a notable association between the presence of anaemia and the cervical cancer stage ($P = 0.002$)[28]. The causes of anaemia in cervical cancer are multifaceted. It can arise from a haemorrhage associated with the vulnerability of the newly formed blood vessels or from cytokine

activation which inhibits the generation of erythropoietin (EPO), hindering the body's ability to use iron and decreasing the formation of erythroid precursors[9,29,30].

Non-haematopoietic cancers, including cervical cancers frequently exhibit leukemoid response, characterised by leucocytosis caused by factors external to the bone marrow[31]. This study demonstrated a notable disparity in leukocyte counts among the different cancer stages with the most substantial increase observed in stages III and IV. Prior studies have also demonstrated that individuals with advanced cervical cancer exhibited more leukocyte abnormalities. Moreover, the increased neutrophil and monocyte counts, and decreased lymphocytes observed in the present study correlated with the progressive nature of cervical cancer. Previously, neutrophilia was demonstrated to be the most reliable indication of tumour cell invasiveness, which is directly linked to the malignancy severity[32]. The precise mechanism of neutrophilia within the tumour remains uncertain but it involves many cytokines including granulocyte colony-stimulating factor (G-CSF), IL-1, and IL-6 produced by the tumour[14,33]. The present study observed a notable disparity in lymphocyte levels in advanced clinical stages (III-IV), in line with a previous study that reported an initial rise in lymphocytes during stages I and II, followed by a sharp decline at stage IV (a decrease of 22.8% compared to healthy individuals)[8]. The decreased lymphocytes are due to a decline in the immune system's capacity to combat and eradicate tumour cells, promoting tumour development[34]. The suppressive effect of neutrophils on lymphocytes is also an indicator of weakened immune system[35]. There was considerable variation in monocytes dependent on the cancer stage in the present study, contradictory to prior studies that found no association between monocytosis and different disease stages. Nevertheless, elevated monocytes are a negative prognostic indicator in patients with cervical cancer[36]. Monocytosis itself may be associated with several confounding factors including smoking and drinking history, as well as liver metastasis [37].

Elevation of platelet count in this study is consistent with an advanced cancer stage. Indeed, individuals with thrombocytosis were more commonly diagnosed with

advanced stages (IIB-IVB) of cervical cancer[38]. Elevated platelet counts can be initiated by the secretion of cytokines including vascular endothelial growth factor (VEGF) and transforming growth factor-beta (TGF-β)[39] as platelets function as a storage site that triggers the release of growth factors, which in turn stimulate the formation of new blood vessels, cell growth, movement, and enhancing tumour proliferation and growth[40].

As cervical cancer progresses, lymphocyte counts drop, resulting in higher NLR and PLR readings and lower LMR, as evidenced by the notable disparity in NLR [41,42] and PLR [43] across different cervical cancer clinical stages. A meta-analysis found a negative correlation between increased PLR and the prognosis of stage I and II cervical cancer patients (HR = 1.61; 95%CI = 1.21-2.15; P = 0.001) as well as stage I and IV patients (HR = 1.47; 95%CI = 1.19-1.81; P < 0.001)[43]. Prabawa *et al* demonstrated a notable disparity in PLR levels (P = 0.001) between the initial and later phases of cervical cancer[41]. Elevated NLR and PLR are indicative of impaired lymphocyte function since reduced lymphocyte count leads to diminished immune system efficacy in combating tumour cells, facilitating tumour progression[44]. Furthermore, both NLR and PLR had a substantial capability to predict patients with tumour stages IIB and above as well as lymph node metastasis[8]. The levels of these indicators rise in patients with more advanced or aggressive illness, as seen by a growth in tumour size, nodal stage, and number of metastatic lesions[15,43,45,46]. The study demonstrated a decline in LMR during the advanced stages of cervical cancer in line with a previous study which reported a correlation between LMR and tumour stage (P = 0.012), as well as parametrial involvement (P = 0.022) and adjuvant therapy (P < 0.001)[47]. A low LMR is significantly correlated with specific clinicopathological parameters that are suggestive of a poor prognosis and aggressive illness[48].

In the current study, the inflammatory indicators, namely SII and SIRI, exhibited substantial differences among different clinical stages. Essentially, increased inflammatory markers were observed as a protective reaction of the body against internal or external damage, such as the development of tumours[11]. A prior

investigation reported that elevated SII and SIRI are significantly linked to the likelihood of recurrence in individuals with early-stage cervical cancer. However, only a high SII relates to mortality[20]. SIRI strongly correlates with inflammatory haematological ratios, including NLR, PLR, and MLR, in matched and unmatched datasets ($P < 0.001$)[19]. Additionally, SII can differentiate the prognosis of patients in various FIGO stages, providing a valuable complement to the FIGO stage and increasing the sensitivity of screening for high-risk individuals to establish the most suitable personalised treatment[49]. Furthermore, a nomogram incorporating SIRI, FIGO stage, and lymphovascular invasion gave a better prognostic value with a c-index of 0.8, significantly higher than the FIGO stage alone ($P < 0.001$). Also, an increase in SIRI by > 75% at eight weeks after resection surgery was a risk factor for death and these patients had the worst prognosis (hazard ratio/HR = 3.30, 95%CI: 2.08–5.25, $P < 0.001$) [19]. The inhibition of lymphocytes and T cell responses, along with elevated neutrophils, can contribute to tumour advancement, angiogenesis, and metastasis[35,50], thereby creating an inflammatory milieu. Before therapy, alterations in neutrophils and lymphocytes can indicate the extent of systemic inflammation or stress[51].

This study has several limitations including insufficient medical record data for several cervical cancer patients. The problem involves a lack of laboratory and sociodemographic data including hormonal contraceptives, which is seldom communicated in the study population. In addition, the assessment of patient outcomes, such as survival, tumour regression, or recurrence, was not conducted per this study's cross-sectional design. Furthermore, a confounding analysis was not possible due to limited data availability.

CONCLUSION

There were notable variations in the haematological parameters (haemoglobin and leukocyte, platelet, neutrophil, monocyte, and lymphocyte counts), inflammatory haematological ratios (NLR, PLR, and LMR), and inflammatory indices (SII and SIRI)

across the different clinical stages of cervical cancer. Subsequent investigations should evaluate all blood-related measures and indicators, along with supplementary inflammatory markers to evaluate treatment effectiveness. Furthermore, these indicators could potentially be used to determine prognosis.

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