MEDS Clinical Medicine (2023)
Clausius Scientific Press, Canada

DOI: 10.23977/medsc.2023.040119
ISSN 2616-1907 Vol. 4 Num. 1

Research progress on the relationship between common hematological indicators and endometrial carcinoma

Yicheng Hu, Zhuoying Hu*

Department of Gynecology, The First Affiliated Hospital of Chongqing Medical University, Chongqing, 400016, China
**Corresponding author: huzhuoying@sina.com*

Keywords: Endometrial carcinoma, Endometrial hyperplasia, Hematological indicators, Diagnosis and prognosis

Abstract: Endometrial carcinoma (EC) is one of the most common malignant tumors in female reproductive tract, which mainly occurs in perimenopausal and postmenopausal women and has a good prognosis. Due to the increase of life expectancy and the change of living habits, the incidence of cervical cancer has been rising continuously in recent years, and patients are getting younger and younger. In some developed cities in China, the incidence of EC has reached the first place in gynecological malignant tumors. From the point of view of secondary prevention, making early screening strategy is the fundamental way to reduce the incidence of EC. Studies show that the hematological indexes of normal endometrial patients and EC patients are different, which is of great significance for early diagnosis, treatment and improvement of prognosis of EC patients. In order to provide reference for the early diagnosis and treatment of EC, this paper reviews the research status of hematological indexes in the diagnosis and treatment of EC.

1. Introduction

Endometrial carcinoma (EC) is an epithelial malignant tumor occurring in endometrium, accounting for 7% of the total number of female malignant tumors, and EC ranks first among newly diagnosed female reproductive tract malignant tumors in developed countries. The early symptoms of EC are nonspecific, mainly manifested as vaginal bleeding or fluid outflow. Although many early diagnosed endometrial cancers can be cured, with the increase of stages, the 5-year survival rate decreased significantly. At present, the diagnostic methods of EC mainly include imaging examination and sectional curettage, but the specificity of imaging examination is poor, especially in differentiating early endometrial cancer from endometrial hyperplasia. Segmental curettage has been considered as the "gold standard" in the diagnosis of endometrial cancer, and the commonly used methods of endometrial biopsy include hysteroscopic biopsy and diagnostic curettage. Segmental curettage is an invasive examination method with the possibility of missed diagnosis. There are three main reasons for segmental scraping and missed diagnosis: 1) The reason for missed diagnosis is related to the limited location of tumor growth, or the tumor growth in the fundus or the corner of the uterus; 2) Inexperienced surgeons may obtain less endometrial tissue during diagnostic curettage, leading to missed diagnosis; 3) The cytological morphology of moderate or severe atypical

hyperplasia is sometimes difficult to distinguish from highly differentiated endometrial adenocarcinoma, which is easily diagnosed as endometrial atypical hyperplasia if the pathologist is inexperienced. The above reasons may result in that the final postoperative pathological diagnosis of some patients is not completely consistent with that of the preoperative diagnostic curettage. In recent years, there have been many studies on the relationship between hematological indicators and the occurrence, development and prognosis of malignant tumors. It is of certain significance to explore simple, easy to obtain, and valuable hematological indicators for improving the diagnostic accuracy of endometrial carcinoma.

2. Parameters associated with leukocytes

2.1 Neutrophil-to-Lymphocyte Ratio (NLR)

NLR is defined as absolute neutrophil count/absolute lymphocyte count. Neutrophils are the main components of white blood cells and the main responders to bacterial infections, environmental exposure and some cancers. Neutrophils promote the development and metastasis of tumor through various channels, including matrix remodeling, cell proliferation, tumor cell adhesion control, tumor angiogenesis stimulation and inhibition of anti-tumor effect of T lymphocytes.

Lymphocytes are effective anti-cancer active substances, while CD4+T cells and CD8+T cells are T lymphocytes with anti-tumor activity. Cytokines produced by CD4+T cells can mediate the apoptosis of tumor cells and promote the differentiation and proliferation of CD8+T cells, which then destroy tumor cells through direct cytotoxic effects. A reduced number of lymphocytes around tumor tissue suggests a diminished role in inhibiting tumor growth, and increased lymphocyte levels are associated with a better prognosis in a variety of tumors.

Previous studies have found changes in peripheral blood lymphocyte level and increased NLR in patients with ovarian cancer, and many studies have found that increased NLR is associated with poor prognosis in patients with cervical cancer, and NLR is of certain value in the diagnosis and prognosis of gynecological tumors. Pergialiotis et al. [1] summarized 11 studies involving 4,688 patients, have conducted a meta-analysis and found that peripheral blood NLR levels in the EC group were significantly higher than those in the benign lesion group. Bacanakgil et al. [2] have calculated that when the optimal threshold value of NLR was ≥4, the sensitivity and specificity for the diagnosis of endometrial cancer were 20.5% and 99%, and concluded that NLR may be a potential hematologic marker for endometrial cancer. In 2021, Muzykiewicz et al. [3] included 26 studies, including 10,530 patients, to explore whether the level of NLR had an impact on the prognosis of common gynecological tumors (cervical cancer, endometrial cancer, ovarian cancer), and found that greater than cut-off value of NLR was associated with poor event free survival (EFS) and overall survival (OS). NLR seems to be an effective and simple marker to distinguish endometrial cancer from benign endometrial lesions, and it is also associated with cervical interstitial involvement, lymph node involvement, and tumor staging, and can be used for prognostic evaluation of EC patients. A large number of studies have shown a significant increase in the level of NLR in patients with endometrial cancer, and NLR can be used as a potential hematologic marker for the early diagnosis of endometrial cancer, but there is no consensus on the optimal cut-off value to distinguish benign and malignant lesions of endometrial, which makes it not yet applied in clinical work.

2.2 Platelet-to-Lymphocyte ratio (PLR)

PLR is defined as absolute platelet count/absolute lymphocyte count. It was first proposed in 1872 that elevated platelets might be associated with malignant tumors and play an important role in cancer progression, metastasis and cancer-related thrombosis. On the one hand, thrombocytosis can cause

platelet aggregation and degranulation process, thus promoting tumor angiogenesis; On the other hand, the growth factors secreted by platelets can stimulate the proliferation of tumor cells and enhance the adhesion ability of tumor cells to other tissues, thus promoting the growth and metastasis of tumors.

A case-control study[4]have found that preoperative PLR levels in patients with normal endometrial pathology were significantly lower than those in patients with precancer and endometrial cancer, and PLR was significantly different between the EC and precancer groups. However, in the meta-analysis of Pergialiotis et al.[1], there was no significant difference in PLR values between EC patients and patients with endometrial hyperplasia. Whether PLR can be used to distinguish hyperplasia and cancer from pathologically normal patients remains controversial. However, a large number of studies have confirmed that PLR has a certain predictive value in the progression and prognosis of EC patients, and the increase of PLR is closely related to tumor staging, including muscle invasion, cervical involvement, lymph node involvement, lymphatic vascular space invasion and distant metastasis [5].Although the available studies do not support the use of PLR in the diagnosis of EC, it appears to be associated with late and distant metastases and is a promising hematologic parameter for evaluating the prognosis of EC.

2.3 Monocyte-to-lymphocyte ratio (MLR)

MLR is defined as absolute monocyte count/absolute lymphocyte count. Exovascular monocytes are recruited into Tumor cells and formed by integrin activation as tumor-associated macrophages (TAMs). Matrix metalloproteinases are proteases capable of destroying extracellular matrix and basement membrane molecules. TAMs promote tumor cell invasion and metastasis by secreting matrix metalloproteinases. The increased accumulation of TAMs at the site of uterine tumor is associated with aggressive tumor behavior (higher stage and grade, lymphovascular space invasion, deep muscle layer tumor invasion) and reduced survival outcome of patients with endometrial cancer.

In recent years, scholars have found that the increase of monocyte number and the invasion of endometrial cancer patients. The higher the lymphocyte count, the lower the risk of death[6]. The recurrence and cancer-related death of patients with high MLR increased significantly, which can be used to predict the existence of distant metastasis and evaluate the prognosis of patients with endometrial cancer. The characteristics of sexual tumors are related to poor survival outcomes. With the increase of monocyte number, the disease-free survival and overall survival of EC patients will decrease. Song et al[7]used multivariate COX regression model to analyze the prognostic factors of EC, and found that the higher the level of monocyte number, the greater the risk of disease recurrence.

3. Parameters related to platelets

It is well known that platelets play an important role in the pathophysiological process of tumor angiogenesis. Mean platelet volume (MPV) is a major parameter evaluating platelet activation, and larger platelets have higher metabolism and enzyme activity than smaller platelets. Platelet distribution width (PDW) is a measure of platelet volume and is usually affected by platelet synthesis. Therefore, increased MPV level and decreased PDW level may be related to the occurrence and development of tumors.

A large number of studies have reported that elevated MPV levels in peripheral blood are associated with the occurrence and development of various types of cancer, such as hepatocellular carcinoma, ovarian cancer and breast cancer. In recent years, some studies have also reported the relationship between MPV and PDW levels and endometrial cancer. Scholars[8] have found that the MPV of patients with EC was slightly higher than that of healthy people (p=0.048), and the MPV level of patients with advanced EC was significantly higher than that of patients with early stage and

healthy people when comparing the preoperative mean platelet volume level of patients with endometrial cancer with that of healthy people. In addition, One study has compared MPV and PDW levels in healthy people, patients with endometrial hyperplasia, and patients with endometrial cancer and found that peripheral blood MPV levels were significantly elevated and PDW levels significantly reduced in the EC group [9].In other words, MPV level is positively correlated with the severity of the lesion, while PDW level is negatively correlated with the severity of the lesion. Perhaps MPV and PDW can be used as a reference for early diagnosis and identification of advanced endometrial cancer. Recent studies[10] have found that high platelet count (PLT≥350×10^9/L), high mean platelet volume (MPV≥8.8fL), and low platelet distribution width (PDW <12.1%) were independent risk factors for poor relapse-free survival (RFS) and overall survival (OS). Platelet activation parameters are also valuable in evaluating prognosis in patients with EC. It is well known that platelet count is determined by the balance between platelet production and platelet consumption. Due to compensatory mechanisms, the hypercoagulable state and tumor-associated inflammatory state of a malignant tumor may be obscured by a completely normal platelet count. In the future, if clinicians combine MPV, PDW and PLT for early diagnosis of EC, It may help improve the accuracy of EC diagnosis.

4. Tumor markers

4.1 Human epididymal Protein 4 (HE4)

The HE4 gene was first extracted from human epididymal epithelial cells in 1991. Kirchhoff is a novel tumor marker, which plays an important role in cell growth, differentiation and body defense. In 2003, HE4 was designated as a serological marker for ovarian cancer. Further studies have found that HE4 is also highly expressed in the serum and tissues of EC patients, while almost no expression is found in normal tissues and benign endometrial lesions. Scholars have conducted extensive studies on the accuracy of detection for the diagnosis of HE4. Abdalla et al.[11], when differentiating benign and malignant lesions of endometrial, found that the sensitivity and specificity of detection of endometrial malignancies were 73.08% and 85.71%, respectively, when the cut-off value of HE4 was 70 pmol/L. In the study of Dewan et al.[12], HE4 truncation value of 69.7 pmol/l was used to detect malignant tumors, which increased the sensitivity to 86.7% and the specificity to 100%. HE4 is a reliable indicator to distinguish benign and malignant endometrial lesions. HE4 concentration is also associated with lymph involvement, deep muscle involvement, and lymph vascular space involvement in EC patients, which has important predictive value in the preoperative diagnosis of EC and the evaluation of intraoperative lymph node dissection, especially when HE4 is combined with other indicators, the diagnostic specificity and accuracy are significantly improved.

4.2 Carbohydrate Antigen 125 (CA125)

CA125 has a high sensitivity in the diagnosis of endometrial cancer, which can be changed at the early stage of lesions, but its specificity is low, and it is also increased to varying degrees in endometriosis, ovarian cancer, breast cancer and even healthy women. Panici et al.[13] measured preoperative CA125 levels in patients with endometrial hyperplasia and endometrial cancer in 1989, and found that CA125 levels increased in only one patient in the hyperplasia group and 43% of patients in the cancer group, and the higher the tumor stage, the higher the incidence of CA125 level increase (stage I :36%; Phase II: 66%; Phase III :100%). Domestic scholars[14] also found that compared with polyp group, CA125 in serum of patients with complex hyperplasia and endometrial cancer increased, and CA125 in cervical and vaginal secretions increased more significantly. The expression and levels of CA125 in serum, cervical and vaginal secretions can be used as potential biomarkers for the diagnosis of precancerous lesions and endometrial cancer. Since CA125 is not a

specific tumor marker for endometrial cancer, it may not be accurate to diagnose endometrial cancer by referring only to CA125 levels, but it shows good sensitivity and accuracy in the combined diagnosis of other tumor markers. The area under the working characteristic curve of CA125 combined with RDW and MPV in the diagnosis of endometrial cancer was 0.924 (95%CI: 0.881-0.955) [15]. In the combination of CA125, combined with HE4, CA724 and CA19-9, the sensitivity and positive predictive values reached 59.1% and 88%, respectively [16]. CA125 combined with other indicators can be used as a reliable indicator for early screening of endometrial cancer, and can improve the differential diagnosis accuracy of endometrial cancer and endometrial hyperplasia. In addition, CA125 levels are also positively correlated with histological grade, lymph node metastasis, muscular invasion, and cervical involvement, and increased significantly with the increase of FIGO stage, and it is currently the most widely used hematological indicator related to the diagnosis and prognosis of endometrial cancer in clinical work.

5. C-reactive protein (CRP)

There are several hypotheses have explained the relationship between the increase of CRP concentration and tumorigenesis: (1) tumor tissue can cause inflammation, which leads to the increase of serum CRP level; (2) tumor cells can produce various cytokines and chemokines to stimulate the production of CRP in the liver; (3) CRP is part of the host's immune response to tumor cells. (4) CRP is a marker of chronic inflammation and promotes carcinogenesis by creating an attractive environment.

Some studies have reported a significant increase in serum CRP levels in patients with endometrial carcinoma. The detection of hs-CRP can also distinguish patients with endometriosis, soft tissue sarcoma and possible endometrial carcinoma[17]. As we all know, obesity is related to the occurrence and development of EC, CRP seems to mediate the effect of high BMI on cancer risk to some extent, so there is still controversy about whether CRP is an independent risk factor for EC. CRP can also be used as a prognostic indicator for a variety of gynecological malignant tumors, including cervical cancer, ovarian cancer, endometrial cancer and vulvar cancer. A study [18] has found that women with CRP $\geq$ 5.5mg/L before treatment had a 68% increase in overall mortality and a twice higher risk of cancer-specific death than women with CRP < 5.5mg/L. High CRP is associated with increased morbidity and mortality of endometrial cancer, so its detection may be helpful for the diagnosis and prognosis of EC.

6. D-dimer

D-dimer is a fibrin degradation product, which can stimulate the growth of malignant tumor by promoting tumor cell proliferation, adhesion and formation of tumor blood vessels. At the same time, tumor cells can activate the clotting pathway in endothelial cells, leading to the secretion of coagulants, fibrinolysis, and secondary increase of D-dimer.

Many studies have reported that D-dimer levels are elevated in solid tumors (breast cancer, gastric cancer, colorectal cancer, lung cancer, nasopharyngeal cancer, etc.), and it is related to poor prognosis and reduced response to treatment. Ge Lili [19] has incorporated eight indicators, including HE4, CA125, D-dimer, etc., to establish a screening model for endometrial cancer, and found that HE4 was the most valuable diagnostic indicator for endometrial cancer, followed by D-dimer. The elevated level of D-dimer is positively correlated with the degree of endometrial cancer. Patients with advanced EC have more severe coagulation and fibrinolytic dysfunction than those with early EC, and high D-dimer level may lead to shorter overall survival of patients with endometrial cancer [20].Exploring the diagnostic efficacy of preoperative D-dimer levels in benign and malignant endometrial lesions will help to identify high-risk groups of EC. In addition, close monitoring of D-

dimer levels in patients with EC during treatment also has a certain significance to improve the prognosis of patients.

7. Conclusion

In a word, hematological indicators are more universal, repeatable and objective than diagnostic curettage in early screening of endometrial cancer. In clinical work, we have found that some patients with endometrial cancer were actually diagnosed with endometrial atypical hyperplasia by preoperative segmental-examination curettage. Due to wrong preoperative diagnosis, these patients may lose the best opportunity for treatment. SO if the hematological indicators are abnormal, we can further combine diagnostic curettage, hysteroscopy, imaging and other inspection methods to improve the diagnostic accuracy of EC, so as to achieve the purpose of early detection, diagnosis and treatment of endometrial cancer. In addition, accurate diagnosis of endometrial dysplasia and endometrial cancer can help clinicians choose appropriate treatment and determine the scope of surgery. However, the diagnostic value of various hematological indexes is still controversial, and even the evaluation of the same index is different in different studies. In the future, large sample and multi-center data are needed to further evaluate the clinical diagnostic efficacy of EC.

References

[1] V. Pergialiotis, M. Oikonomou, V. Damaskou, D. Kalantzis, C. Chrelias, A.E. Tsantes, I. Panayiotides, Platelet to lymphocyte and neutrophil to lymphocyte ratio as predictive indices of endometrial carcinoma: Findings from a retrospective series of patients and meta-analysis, J Gynecol Obstet Hum Reprod 47(10) (2018) 511-516.

[2] B.H. Bacanakgil, I. Kaban, F. Unal, R. Guven, E. Sahin, S.G. Yildirim, Predictive Value of Hematological Inflammatory Markers in Endometrial Neoplasia, Asian Pacific journal of cancer prevention : APJCP 19(6) (2018) 1529-1532.

[3] J.L. Ethier, D.N. Desautels, A.J. Templeton, A. Oza, E. Amir, S. Lheureux, Is the neutrophil-to-lymphocyte ratio prognostic of survival outcomes in gynecologic cancers? A systematic review and meta-analysis, Gynecol Oncol 145(3) (2017) 584-594.

[4] S. Selen, F. Kilic, G. Kimyon Comert, M. Unsal, C. Kilic, A. Karalok, O. Turkmen, T. Turan, Can preoperative inflammatory markers differentiate endometrial cancer from complex atypical hyperplasia/endometrial intraepithelial neoplasia?, J Obstet Gynaecol Res 46(7) (2020) 1148-1156.

[5] T. Muangto, K. Maireang, Y. Poomtavorn, Y. Thaweekul, A. Punyashthira, N. Chantawong, P. Wisarnsirirak, J. Pattaraarchachai, K. Suwannarurk, Study on Preoperative Neutrophil/Lymphocyte (NLR) and Platelet/Lymphocyte Ratio (PLR) as a Predictive Factor in Endometrial Cancer, Asian Pacific journal of cancer prevention : APJCP 23(10) (2022) 3317-3322.

[6] B. Burgess, B. Levine, R.N. Taylor, M.G. Kelly, Preoperative Circulating Lymphocyte and Monocyte Counts Correlate with Patient Outcomes in Type I and Type II Endometrial Cancer, Reprod Sci 27(1) (2020) 194-203.

[7] H. Song, M.J. Jeong, J. Cha, J.S. Lee, J.G. Yoo, M.J. Song, J.H. Kim, S.J. Lee, H.N. Lee, J.H. Yoon, D.C. Park, S.I. Kim, Preoperative neutrophil-to-lymphocyte, platelet-to-lymphocyte and monocyte-to-lymphocyte ratio as a prognostic factor in non-endometrioid endometrial cancer, Int J Med Sci 18(16) (2021) 3712-3717.

[8] T. Oge, O.T. Yalcin, S.S. Ozalp, T. Isikci, Platelet volume as a parameter for platelet activation in patients with endometrial cancer, J Obstet Gynaecol 33(3) (2013) 301-4.

[9] J. Song, X. Lai, Y. Zhang, X. Zheng, J. Su, Preoperative platelet morphology parameters as prognostic predictors for endometrial malignant carcinoma stage and progesterone receptor, Medicine (Baltimore) 98(47) (2019) e17818.

[10] H. Chen, Q. Wu, Y. Zhang, Q. Li, J. Ma, F. Kong, X. Ma, Nomograms based on the novel platelet index score predict postoperative prognosis in endometrial cancer, Gynecol Oncol 158(3) (2020) 689-697.

[11] N. Abdalla, M. Pazura, A. Słomka, R. Piórkowski, W. Sawicki, K. Cendrowski, The role of HE4 and CA125 in differentiation between malignant and non-malignant endometrial pathologies, Ginekol Pol 87(12) (2016) 781-786.

[12] R. Dewan, A. Dewan, S. Hare, M. Bhardwaj, K. Mehrotra, Diagnostic Performance of Serum Human Epididymis Protein 4 in Endometrial Carcinoma: A Pilot Study, Journal of clinical and diagnostic research : JCDR 11(7) (2017) Xc01-xc05.

[13] P.B. Panici, G. Scambia, G. Baiocchi, L. Perrone, S. Greggi, F. Battaglia, S. Mancuso, Multiple serum markers in patients with endometrial cancer, Gynecol Obstet Invest 27(4) (1989) 208-12.

[14] S.M. He, F. Xing, H. Sui, Y. Wu, Y. Wang, D. Wang, G. Chen, Z. Kong, S.F. Zhou, Determination of CA-125 levels in

the serum, cervical and vaginal secretions, and endometrium in Chinese women with precancerous disease or endometrial cancer, Medical science monitor : international medical journal of experimental and clinical research 17(11) (2011) Cr618-625.
[15] J.N. Liu, X.S. Kong, T. Huang, R. Wang, W. Li, Q.F. Chen, Clinical Implications of Aberrant PD-1 and CTLA4 Expression for Cancer Immunity and Prognosis: A Pan-Cancer Study, Frontiers in immunology 11 (2020) 2048.
[16] J. Bian, X. Sun, B. Li, L. Ming, Clinical Significance of Serum HE4, CA125, CA724, and CA19-9 in Patients With Endometrial Cancer, Technology in cancer research & treatment 16(4) (2017) 435-439.
[17] A.N. Petric, R. Živadinović, D. Mitić, M. Stanojević, A. Živadinović, I. Kostić, Hematological and biochemical markers in determining the diagnosis and stage prediction of endometrial cancer, Ginekol Pol (2022).
[18] K. Njoku, N.C. Ramchander, Y.L. Wan, C.E. Barr, E.J. Crosbie, Pre-treatment inflammatory parameters predict survival from endometrial cancer: A prospective database analysis, Gynecol Oncol 164(1) (2022) 146-153.
[19] L. Ge, G. Liu, K. Hu, K. Huang, M. Zhang, J. Zhou, F. Teng, J. Cao, C. Dai, X. Jia, A New Risk Index Combining d-Dimer, Fibrinogen, HE4, and CA199 Differentiates Suspecting Endometrial Cancer From Patients With Abnormal Vaginal Bleeding or Discharge, Technology in cancer research & treatment 19 (2020) 1533033819901117.
[20] K. Nakamura, K. Nakayama, M. Ishikawa, H. Katagiri, T. Minamoto, T. Ishibashi, N. Ishikawa, E. Sato, K. Sanuki, H. Yamashita, T. Komatsu-Fujii, S. Kyo, High pretreatment plasma D-dimer levels are related to shorter overall survival in endometrial carcinoma, Eur J Obstet Gynecol Reprod Biol 201 (2016) 89-93.