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Preoperative platelet morphology parameters as prognostic predictors for endometrial malignant carcinoma stage and progesterone receptor

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Abstract

To investigate preoperative platelet morphology parameters and other whole blood cells in patients of malignant endometrial carcinoma compared with benign disease.

Retrospective analysis was performed through collecting patients' hematological parameters before performing total abdominal/vaginal hysterectomy and standard radical surgery due to benign and malignant endometrial disease between 2006 and 2017. Parameters required included white blood cell (WBC), hemoglobin, platelet count (PLT), platelet distribution width (PDW), mean platelet volume (MPV), and platelet thrombocytocrit (PCT). And neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were calculated. For malignant carcinoma, Ki-67 percentage and progesterone receptor (PR) status were further collected.

A total of 288 patients were included with 145 benign cases and 143 malignant cases. Patients of confirmed endometrial carcinoma showed a significant lower value of PDW (55.21 ± 4.72 vs 49.54 ± 5.89, $P < .001$), meanwhile significant higher values of MPV (7.12 ± 1.56 vs 8.89 ± 1.67, $P < .001$) and PCT (24.18 ± 6.89 vs 27.93 ± 8.93, $P = .003$). Further analysis of endometrial carcinoma patients showed that no significant difference in platelet parameters was found between patients with stage I to II and stage III to IV ($P > .05$), while increased value in PDW and reduced value in MPV was found in PR negative compared with positive patients.

Preoperative platelet morphology parameters seemed to be used as one kind of predictive factors to discriminate malignant and benign endometrial disease. Limited by present study design, further prospective studies are required to support this finding.

Abbreviations: EC = endometrial carcinoma, MPV = mean platelet volume, NLR = neutrophil-to-lymphocyte, PCT = platelet thrombocytocrit, PDW = platelet distribution width, PLR = platelet-to-lymphocyte, PLT = platelet count, PR = progesterone receptor, SD = standard deviation, WBC = white blood cell.

Keywords: endometrial disease, platelet indices, platelet morphology, predictive factors

1. Introduction

Endometrial carcinoma (EC) is the sixth most common cancer for females in the world, which was presented as the fourth most common and seventh most common gynecological cancer in the developed countries and developing countries.[1,2] It was estimated that about 319,600 new cases in 2012, and 53% of them occurred in developed countries.[2] And age adjusted incidence rate has increased to 4.7 per 100,000 person in the year of 2009.[3] In China, EC showed an estimated annual percentage change of 3.7% and for some more developed cities, the prevalence of EC was higher than cervical cancer.[4,5] Unopposed estrogen exposure was regard as one of the major factors induced increasing burden of EC incidence, which included obesity, activity lacking and hormone replacement and adjusted therapies.[5]

Same as other solid tumors, mechanism of EC also involved unbalanced estrogen and developed from a background of low-to-high degree hyperplasia due to persisted inflammation. Thus, inflammatory cell and cytokines and their changes had been focused on kinds of cancers, as well as precursor lesions and EC.[6,7] Among them, more and more studies revealed the immune function of platelets other than its basic coagulation function, which was easily available via a blood test.[8] A series of studies reported that platelet morphology and count parameters would be a prognostic predictors in colorectal cancer, laryngeal cancer, nasopharyngeal cancer, and non-small cell lung cancer.[9–13]

Although the difference of preoperative platelet parameters were compared in patients with different endometrial diseases in previous studies with small samples,[14,15] there was not a assessment of platelet parameters including platelet count (PLT), platelet distribution width (PDW), mean platelet volume (MPV), and platelet thrombocytocrit (PCT) together with cancer stage and progesterone receptor (PR) status yet (Fig. 1). In this study, we aimed to investigate the values of preoperative white blood

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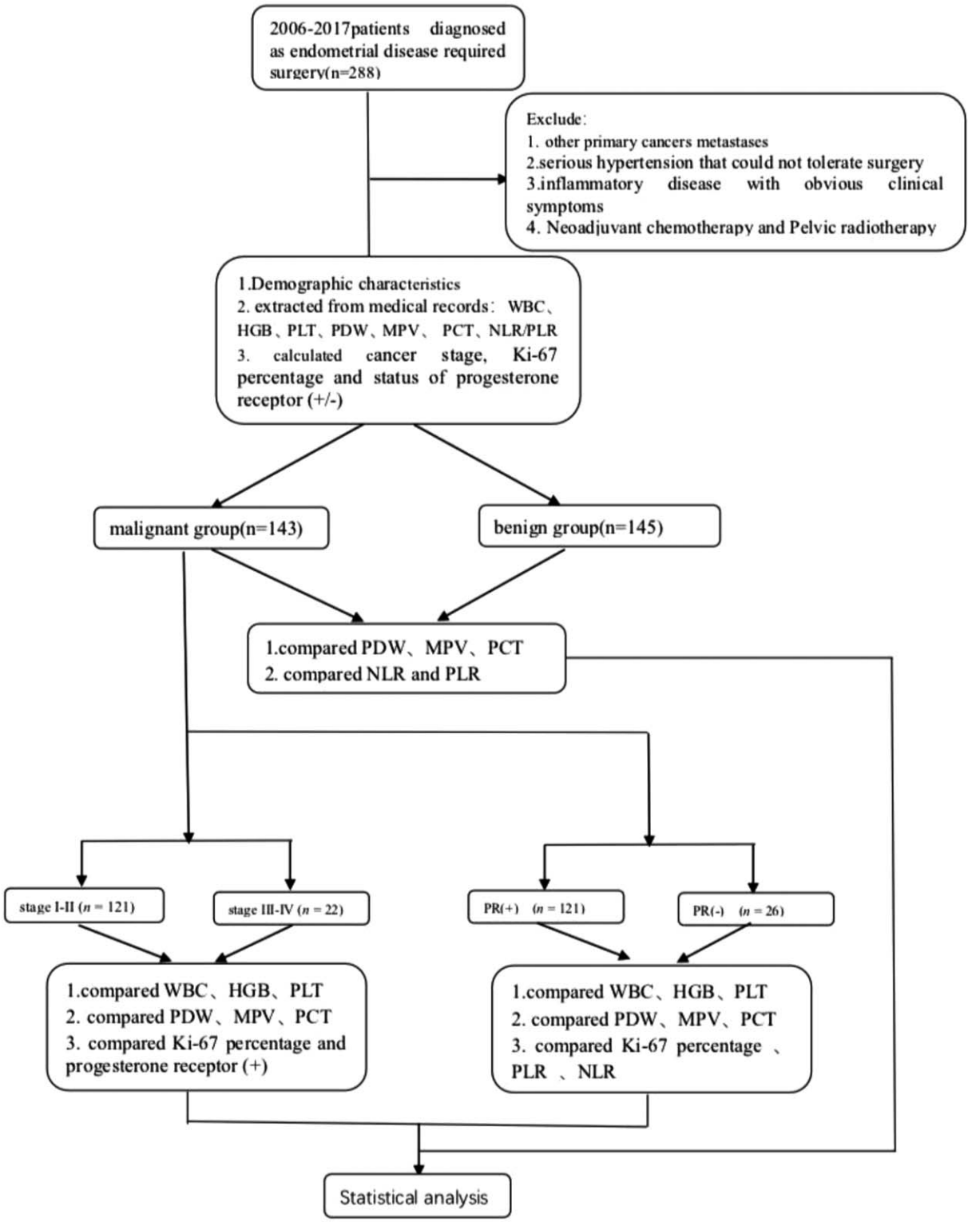

Figure 1. Flow diagram of the research process. Note: MPV = mean platelet volume, PCT = platelet thrombocytocrit, PDW = platelet distribution width, PLR = platelet count and lymphocyte count ratio, PLT = hemoglobin, platelet count, PR = progesterone receptor, NLR = neutrophil count and lymphocyte count ratio, WBC = white blood cell.

cell (WBC) and platelet parameters in patients of malignant EC with different stage and PR status.

2. Methods

2.1. Patients

Our study was a retrospective analysis of patients diagnosed with endometrial disease required surgery between January 2006 and June 2017 at Fujian Provincial Maternity and Children's Hospital. The main clinical symptom was vaginal bleeding, and routine ultrasonographic and gynecological examinations were performed for each patient after admission. Patients with pre-operatively benign diseases were scheduled to undergoing total abdominal or vaginal hysterectomy (such as patients without fertility requirements diagnosed as atypical endometrial hyperplasia, uterine fibroids with submucosal fibroids, abnormal uterine bleeding); whereas, intra-operative frozen pathological examination was used for suspicious malignant carcinoma, and confirmed patients adopted comprehensive surgery including total abdominal hysterectomy, bilateral salpingo-oophorectomy, and also pelvic or para-aortic lymph node dissection. Both of benign and malignant endometrial disease was confirmed by post-operative pathological examination.

All the patients adopted surgery within 2 weeks after admission, and hematological parameters before surgery were compared between different group of patients with pathology of benign disease and malignant disease. Patients missing such data were excluded, and also patients with other primary cancers metastases malignancies and hematological disease were excluded. Acute inflammatory disease with different severity would quickly and significantly affect the result of hematological text, and the treatment would further influence the stability of the results, so inflammatory disease with clear symptoms such as fever and abdominal pain were also excluded. As part of the malignancies clearly were diagnosed before surgery, patients adopted neoadjuvant chemotherapy or pelvic radiotherapy were also excluded. Some other factors which would significant influence the count of item in blood routine were also excluded.

Demographic characteristics were collected and compared to ensure the comparability of the patients. Hematological parameters before surgery including WBC, PLT, PDW, MPV, and PCT were extracted from medical records for all the patients. The neutrophil-to–lymphocyte (NLR) was calculated as the ratio of neutrophil count to lymphocyte count; the platelet-to-lymphocyte (PLR) was calculated as the ratio of PLT to lymphocyte count. Additional data including cancer stage, Ki-67 percentage and status of PR (+/−) were extracted from post-operative pathological examination reports. Cancer stage was judged according to the 2009 FIGO guidelines after the year of 2010 and 1988 FIGO guidelines before the year of 2010.

The study was approved by the local hospital Ethics Committee, and despite data used for analysis, no other information and privacy of the patients were involved.

2.2. Statistical analyses

Dichotomous parameters were analyzed using Fisher's Exact test. Continuous parameters were presented as mean ± standard deviation (SD) and compared using the Student's *t* test when variance analysis demonstrated the homogeneity. All statistical analyses were performed using the Statistical Package for Social Sciences software (SPSS Inc, version 12.0, Chicago, IL). Difference with $P < .05$ was set as statistically significant.

3. Results

3.1. Patient characteristics

A total of 288 patients diagnosed as endometrial disease required corresponding surgery were included in the analysis. Demographic characteristics were shown in Table 1. There were 145 females with an average age of 51.82 ± 8.54 years in the benign group, and there were 143 females with an average age of 55.87 ± 9.36 years in the malignant group, and no significant difference was found in aspects of age ($P = .56$). While, the prevalence of co-morbidities including mild-to-moderate hypertension (22.76% vs 42.66%, $P < .001$) and diabetes mellitus (24.14% vs 48.25%, $P < .001$) was found to be lower in the patients of benign group than it in the malignant group.

3.2. Comparison between patients with benign and malignant endometrial disease

In order to investigate the differences located in hematologic parameters, blood routine was test before surgery. No significant difference was found in the value of WBC (7.59 ± 2.78 vs 7.87 ± 3.13 * 10^3/mm^3), hemoglobin (10.82 ± 2.31 vs 10.52 ± 2.19 * 10^3/mm^3), and PLT (323.74 ± 89.97 vs 311.63 ± 92.38 * 10^3/mm^3) ($P > .05$).

Other parameters related to platelet morphology including PDW, MPV, and PCT were also compared. And the results showed that compared with benign endometrial disease patients, patients of malignant endometrial disease confirmed by pathological examination had a significantly lower value in average PDW (55.21 ± 4.72 vs 49.54 ± 5.89, $P < .001$), whereas a significantly higher value in average MPV (7.12 ± 1.56 vs 8.89 ± 1.67, $P < .001$) and PCT (24.18 ± 6.89 vs 27.93 ± 8.93, $P = .003$). Calculated NLR (2.19 ± 1.24 vs 2.38 ± 1.32) and PLR (137.96 ± 69.87 vs 128.87 ± 61.64) were not found to be statistical different between the groups ($P > .05$); as shown in Table 1.

Table 1

Demographic and clinic features of benign and malign endometrial patients.

Features	Benign group ($n = 145$)	Malign group ($n = 143$)	*P*
Age (years)	51.82 ± 8.54	55.87 ± 9.36	.56
Hypertension (%)	33 (22.76%)	61 (42.66%)	<.001
Diabetes mellitus (%)	35 (24.14%)	69 (48.25%)	<.001
WBC (10^3/mm^3)	7.59 ± 2.78	7.87 ± 3.13	.42
Hemoglobin (mg/dL)	10.82 ± 2.31	10.52 ± 2.19	.26
PLT (10^3/mm^3)	323.74 ± 89.97	311.63 ± 92.38	.34
PDW (%)	55.21 ± 4.72	49.54 ± 5.89	<.001
MPV (fL)	7.12 ± 1.56	8.89 ± 1.67	<.001
PCT (%)	24.18 ± 6.89	27.93 ± 8.93	.003
NLR	2.19 ± 1.24	2.38 ± 1.32	.21
PLR	137.96 ± 69.87	128.87 ± 61.64	.13

MPV = mean platelet volume, NLR = neutrophil count and lymphocyte count ratio, PCT = platelet thrombocytocrit, PDW = platelet distribution width, PLR = platelet count and lymphocyte count ratio, PLT = hemoglobin, platelet count, WBC = white blood cell.

Table 2

Comparison of hematologic parameters between early and advanced stage endometrial cancers.

Parameter	Stage I–II ($n=121$)	Stage III–IV ($n=22$)	P
WBC ($10^3/mm^3$)	7.79 ± 3.34	8.31 ± 2.89	.45
Hemoglobin (mg/dL)	10.59 ± 2.12	10.14 ± 2.31	.39
PLT ($10^3/mm^3$)	309.72 ± 91.87	322.14 ± 93.21	.56
PDW (%)	49.78 ± 6.24	48.22 ± 7.12	.34
MPV (fL)	8.79 ± 1.62	9.44 ± 1.96	.14
PCT (%)	27.11 ± 8.29	25.94 ± 9.11	.57
PLR	128.38 ± 67.87	131.57 ± 62.09	.83
NLR	2.41 ± 1.29	2.22 ± 1.31	.53
Ki-67 (%)	65.89 ± 19.65	80.68 ± 23.45	.005
PR (+)	106 (87.60%)	10 (45.45%)	<.001

MPV = mean platelet volume, NLR = neutrophil count and lymphocyte count ratio, PCT = platelet thrombocytocrit, PDW = platelet distribution width, PLR = platelet count and lymphocyte count ratio, PLT = hemoglobin, platelet count, PR = progesterone receptor, WBC = white blood cell.

3.3. Comparison between patients with different stage of endometrium carcinoma

In order to investigate the differences between different endometrium carcinoma stage, patients diagnose as malignant disease were divided into two groups: stage I to II (n = 121) and stage III to IV (n = 22); as shown in Table 2. There were no significant difference in the value of WBC (7.79 ± 3.34 vs 8.31 ± 2.89), hemoglobin (10.59 ± 2.12 vs 10.14 ± 2.31), and PLT (309.72 ± 91.87 vs 322.14 ± 93.21) ($P > .05$).

And also no significant difference was found in aspect of platelet morphology parameters including PDW, MPV, and PCT, and calculated NLR and PLR ($P > .05$). Data from postoperative pathological examination showed significant differences existing in Ki-67 percentage (65.89 ± 19.65 vs 80.68 ± 23.45, $P = .005$) and PR (+) (87.60% vs 45.45%, $P < .001$).

3.4. Comparison between patients with different status of progesterone receptor

In order to investigate the differences between two status of PR, patients diagnose as malignant disease were also divided into two groups: positive (n = 116) and negative (n = 21); as shown in Table 3. There were no significant differences in the value of WBC (7.83 ± 2.76 vs 8.04 ± 3.12), hemoglobin (10.48 ± 2.19 vs 10.85 ± 2.53), and PLT (312.62 ± 66.65 vs 307.38 ± 79.38) ($P > .05$).

Table 3

Comparison of hematologic parameters between groups with different type of progesterone receptor.

Parameter	Progesterone receptor (+) (n = 116)	Progesterone receptor (−) (n = 27)	P
WBC ($10^3/mm^3$)	7.83 ± 2.76	8.04 ± 3.12	.75
Hemoglobin (mg/dL)	10.48 ± 2.19	10.85 ± 2.53	.48
PLT ($10^3/mm^3$)	312.62 ± 66.65	307.38 ± 79.38	.77
PDW (%)	47.97 ± 16.97	56.29 ± 17.19	.02
MPV (fL)	9.19 ± 2.88	7.60 ± 3.01	.01
PCT (%)	26.99 ± 8.96	26.67 ± 9.18	.87
PLR	129.11 ± 61.09	127.84 ± 68.83	.93
NLR	2.37 ± 1.29	2.42 ± 1.43	.87
Ki-67 (%)	65.68 ± 19.54	78.84 ± 21.08	.003

MPV = mean platelet volume, NLR = neutrophil count and lymphocyte count ratio, PCT = platelet thrombocytocrit, PDW = platelet distribution width, PLR = platelet count and lymphocyte count ratio, PLT = hemoglobin, platelet count, WBC = white blood cell.

Statistical difference was found in aspects of PDW (47.97 ± 16.97 vs 56.29 ± 17.19, $P = .02$), MPV (9.19 ± 2.88 vs 7.60 ± 3.01, $P = .01$), and Ki-67 percentage (65.68 ± 19.54 vs 78.84 ± 21.08, $P = .003$), while no significant difference was found in PCT (26.99 ± 8.96 vs 26.67 ± 9.18), calculated PLR (129.11 ± 61.09 vs 127.84 ± 68.83) and NLR (2.37 ± 1.29 vs 2.42 ± 1.43; $P > .05$).

4. Discussion

Association among cancer and inflammation was certain.[6] Although specific mechanism remained unclear, whole blood elements including neutrophils, lymphocytes, and platelets played roles in tumor growth and invasion with some other molecules such as cytokines, growth factors, and local mediators.[16] Complete blood count was a repeatable, inexpensive and easily available laboratory test, and the parameters are also frequently changed along with many kinds of inflammatory processes and cancer occurrence.[17] EC has been less studies for this viewpoint. We aimed to investigate the preoperative alterations of the complete platelet parameters in EC compared with benign diseases such as chronic inflammation, hyperplasia, and bleeding, and the difference of early/advanced stage EC and different PR status.

Platelet parameters selected in this study included PLT, PDW, MPV, and PCT. The results showed that compared with benign disease, patients with EC had platelets with significantly smaller PDW, larger MPV and PCT. Among them, PDW represented the changes of morphological shape and reactivity of platelets. An increased PDW always indicated that platelets were activated by some factors, and they changed their shape and size though completing spherical transformation and pseudopodia formation.[18] MPV was the marker indicating platelet activity, and its increase in value mostly was associated with evaluated inflammatory process and malignancy. Platelets with larger MPV are supposed to carry more mediators and thus to some extent contribute to cancer development and progress.[19] PCT provided a direct value of volume percentage of platelet in routine whole blood counts, which is determined by PLT and MPV; and it did not have specific clinical meanings. In this study, different values were observed between EC and benign disease, which may be concluded as a correlation between platelet parameters and endometrial pathology. However, the results of PDW were not completely consistent with the other studies,[14,20] it supposed to be caused by different immune status as activation and tolerance balance in cell and humoral immunity. Nevertheless, significant abnormality in platelet parameters, especially MPV, can be regarded as an easy predictive factor on judging the severity of disease and selecting further options before endometrial biopsy and pathology result in high risk patients.

Besides, as markers of systemic inflammatory response despite of C-reactive protein, the ratios of NLR and PLR were found to be independent stratification indicators in EC in aspects of both survival and cervical stromal involvement.[21,22] These factors would be very useful for surgical patients to determine a optimal surgical procedure regarding radical surgery and lymphadenectomy. While, our study showed that NLR and PLR seemed to have little association with endometrial pathology as no significant difference was found between the groups. Although the role of active and mediator-secreting platelets in cancer development and progression was found, definite information on

the diagnosis and progression of a patient with EC was far away. Clear judgement of lymph node metastasis and cervical stromal involvement based on preoperative platelet parameters, NLR and PLR in different types of cancers including EC may be hard without imaging information such as magnetic resonance imaging.

In the present study, we further analyzed investigated the value of platelet parameters in EC according to the cancer stage and PR status. An increased percentage of Ki-67 reflected high degree of malignancy and metastasis.[23,24] Compared with Ki-67 percentage and PR status, both platelet parameters and ratios of NLR and PLR failed to discriminate the stage of EC. While, for different PR status, larger value PDW and smaller MPV of platelets were found in PR negative patients other than positive patients. PR positive patients was stated to have a better prognosis and response to endocrine therapy, and also PR positive patients was associated with lower risk of lymph node metastasis.[24,25] Thus, a combination of platelet parameters, Ki-67 percentage and PR status with cut-off value in different population may be more useful in clinic. Since there have been few reports on this topic, more studies are required to verify the assumptions (Table 4).

The major limitation of the present study is the small percentage in the comparison of the stage III to IV endometrium cancer when compared to the stage I to II group, and also in the comparison of PR status, so prospective large sample studies are always warranted to address the issue. Although the platelet parameters were not a certain diagnosis method as pathology, but as a easy and routine blood, it would be useful to provide primary judgement and limited information for clinical doctor before surgery. As a retrospective analysis, our study had certain limitation as them in all other such studies, as the most important bias of selection bias, it actually would sometime influence the stable results. Thus, further large scale and prospective studies may be warranted.

Table 4

The characteristics of patient population were described and compared between the 2 groups.

	Malign group		
FIGO stage (n)	I–II	III–IV	*P*
Number of patients	121	22	
Age (yrs)	54.28 ± 9.78	55.87 ± 8.36	.765
Hypertension (%)	52 (42.97%)	9 (40.9%)	.857
Diabetes mellitus (%)	58 (47.93%)	11 (50%)	.858
Histological type (n)			
Endometrioid carcinoma	62	11	.915
Mucinous carcinoma	31	6	.871
Serous carcinoma	15	4	.462
Clear cell carcinoma	16	2	.591
Neuroendocrine tumors	13	2	.816
Mixed cell adenocarcinoma	11	1	.419
Undifferentiated carcinoma and dedifferentiated carcinoma	4	1	.771
Differentiated grade			
G1	31	0	.007
G2	18	2	.472
G3	13	9	.001

5. Conclusion

Preoperative platelet morphology parameters seemed to be used as one kind of predictive factors to discriminate malignant and benign endometrial disease. Limited by present study design, further prospective studies are required to support this finding.

Author contributions

Conceptualization: Jianrong Song, Xiangqin Zheng.
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