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# Different Significance of Platelets and Plateletcrit In Adenomyosis And Myoma

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**Abstract**

**Purpose:** The aim of our study was to investigate the differences of platelet and coagulation function parameters in adenomyosis, uterine leiomyomas and normal people to further explore the meanings of these differences in adenomyosis or uterine leiomyomas.

**Methods:** A retrospective case-control study was performed. The subjects were divided into adenomyosis group, uterine leiomyomas group and control group. Adenomyosis group included 217 women histological diagnosed after surgery between January 2017 and December 2019. Uterine leiomyomas group included 549 women confirmed by histopathologic examination in the same time and control group included 201 symptom-free women after medical examination. Clinical data, platelet parameters and coagulation function indicators were collected from all patients.

**Results:** platelet count (PC), mean platelet volume (MPV), platelet distribution width (PDW), plateletcrit (PCT), fibrinogen (FIB), D-Dimer and platelet maximum aggregation rate AA (AA:arachidonic acid reagent) were significantly differences among the three groups ($P$<0.05). PC, PCT, FIB, D-Dimer were significant higher in adenomyosis group compared with control group, while AA was lower in adenomyosis group ($P$<0.05). PC and PCT were significantly higher in the uterine leiomyomas group than in the control group ($P$<0.05). Bivariate logist regression analysis showed that PC, PCT, FIB, D-dimer and AA were not risk factors or protective factors for uterine adenomyosis, while PC and PCT were risk factors for uterine leiomyomas.

**Conclusion:** Our study found that elevated PC and PCT were independent risk factors for uterine leiomyomas, but were not associated with adenomyosis.

**Keywords:** adenomyosis; leiomyomas; platelet; coagulation function.

## Introduction

Adenomyosis refers to Endometrium Glands and stroma ectopic into the myometrium, accompanied by hyperplasia and hypertrophy of smooth muscle tissue (Donnez et al.,2018), adenomyosis can cause dysmenorrhea, menorrhagia, infertility and other symptoms, in addition, 1 / 3 of adenomyosis patients may be asymptomatic(Vannuccini and Petraglia, 2019). Uterine leiomyomas is a common benign tumor in gynecology. The incidence of uterine leiomyomas in women of childbearing age is 40% - 60% (Zhang et al.,2020). Adenomyosis and uterine leiomyomas are hormone dependent diseases. Abnormal estrogen and progesterone in vivo can play a role through pro-inflammatory factors, growth factors or inhibitor of apoptosis (L M et al.,2016). Chronic inflammation as the pathogenesis of adenomyosis and uterine leiomyomas has been confirmed by many studies. Vascular endothelial cell damage caused by inflammation can activate hemostatic system, cause platelet aggregation and release of coagulation factors.

Platelet parameters and coagulation function indicators are widely used in clinical practice. The purpose of this study was to investigate the differences of platelet parameters and coagulation function between patients with adenomyosis, patients with uterine leiomyomas and normal people, and to further study the significance of these differences in adenomyosis or uterine leiomyomas.

## 1. Materials and Methods

### 1.1 General Materials

The clinical data of adenomyosis and uterine leiomyomas patients confirmed by postoperative

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pathology in our hospital from January 2017 to December 2019 were retrospectively collected. Inclusion criteria: 1. All patients were treated with surgery, and the postoperative pathological examination results confirmed 2. The clinical data were complete. Exclusion criteria: 1. Anticoagulant drugs were used in the past 3 months; 2. Patients with arrhythmia indicated by ECG; 3. Abnormal liver and kidney function; 4. Severe endocrine abnormalities, blood system abnormalities and immune system abnormalities; 5. Patients with pregnancy or abortion history in recent 3 months; 6. patients with borderline or malignant tumors; 7. A family history of hemorrhagic diseases, hereditary diseases; 8. A history of thrombotic diseases; 9. patients with both adenomyosis and uterine leiomyomas. The control group was normal people who had physical examination in our hospital and had no medical diseases, and all patients underwent vaginal ultrasound examination without uterine lesions were found.

**1.2 Platelet and coagulation function indicators**

We retrospectively collected platelet and coagulation function indicators, including platelet count (PC), mean platelet volume (MPV), platelet distribution width (PDW), plateletcrit (PCT), plasma prothrombin time (PT), international standardized ratio (PT-INR), fibrinogen (FIB), activated partial thromboplastin time (APTT), thromboplastin time (TT), antithrombin III (AT-III), D-dimer, fibrinogen degradation product (FDP), platelet maximum aggregation rate (ADP: adenosine diphosphate, AA: arachidonic acid reagent).

In our hospital, each patient should be tested for blood routine (including platelet parameters) and coagulation function at admission, and surgery should be carried out within 1 week after admission. All operations were carried out in the proliferative phase of the menstrual cycle. Hemogram analysis is to collect 2ml of venous blood before the meeting and put it into the automatic blood analyzer (Huaxin Technology Co., Ltd., specification: xn-350; Haier Shi biomedical Co., Ltd., specification: dxh800). The coagulation function is to collect 4.5ml venous blood from patients before the meeting, centrifuged at 3800 rpm at 6 ℃ for 5 minutes in BD vacutainer, separate the bleeding plasma, put it in the corresponding kit and put it into BE automatic hemagglutination analyzer (Huaxin Technology Co., Ltd., specification: BE XRM, Germany) for analysis. In our hospital, APTT, PT, FIB and TT were determined by rapid solidification method, FDP was determined by immunoturbidimetry, ADP and AA were determined by optical turbidimetry, D-dimer was determined by latex enhanced immunoturbidimetry, and AT-III was by luminescence substrate method. Our hospital stipulates that coagulation function should be detected within 2 hours after blood collection. This study was approved by the Ethics Review Committee of Changzhou Maternity and Child Health Care Hospital Affiliated to Nanjing Medical University.

**1.3 Statistical analysis**

SPSS 25.0 software was used to analyze the data. The mean ± standard deviation (x ± s) was used to describe the continuous variables conforming to the normal distribution, the median (quartile) [M (Q)] was used for the description of continuous variables that did not conform to the normal distribution, and the percentage was used for the description of classified variables. Kruskal-Wallis Test followed by post-hoc Bonferroni was used for comparison of clinical characteristics, platelet indicators and coagulation function parameters across three groups. The variables with differences in the adenomyosis group, uterine leiomyomas group and the control group were respectively included in the bivariate logistic regression. P-value less than 0.05 was accepted as statistically significant.

**2. Results**

**2.1 Comparison results of clinical indicators**

A total of 967 Cases were included in this study, including 217 cases in adenomyosis group, 549 cases in uterine leiomyomas group and 201 cases in control group. The median age of adenomyosis group, uterine leiomyomas group and control group was 45 years old, 43 years old and 41 years old respectively, and the median body mass index was 23.59 Kg / m2, 22.72 Kg / m2 and 21.34 Kg / m2, respectively. In adenomyosis group, CA125 level was 62.10 (30.70-129.35) U / ml, and hemoglobin was 120 (99-131.50) g / L. The levels of CA125 and hemoglobin were 17 (11.60-24.05) U / ml and 126 (112-136) g / L in uterine leiomyomas group, and 12.60 (10-16.90) U / ml and 130 (124-137) g / L in control group. There were significant differences in age, BMI, CA125 and hemoglobin among the three groups ($P < 0.05$), as shown in Table 1.

**2.2 Comparison of platelet and coagulation function among the three groups**

According to Table 2, PC, MPV, PDW, PCT, FIB, D-dimer and AA were significantly different among

the three groups (P < 0.05), among which PC, PCT, FIB, D-dimer in adenomyosis group were significantly higher than those in control group (P < 0.05), and AA in adenomyosis group was significantly lower than that in control group (P < 0.05). PC and PCT in uterine leiomyomas group were significantly higher than those in control group (P < 0.05) (Table 3).

*Table 1.* **Nonparametric test results of clinical data of three groups M (Q)**

| | Adenomyosis group（n=217） | uterine leiomyomas group (n=549) | Control group(n=201) | *P* |
|---|---|---|---|---|
| Age (Years) | 45（41-48） | 43（38-48） | 41（34.50-48.50） | 0.000 |
| BMI（$Kg/m^2$） | 23.59（22.05-25.49） | 22.72（20.90-24.67） | 21.34（19.99-23.05） | 0.000 |
| CA125（U/mL） | 62.10（30.70-129.35） | 17（11.60-24.05） | 12.60（10-16.90） | 0.000 |
| Hb(g/L) | 120（99-131.50） | 126（112-136） | 130（124-137） | 0.000 |

P < 0.05 indicated that there was significant difference among the three groups.

*Table 2.* **Nonparametric test results of platelet and coagulation function between adenomyosis group, uterine leiomyomas group and control group M (Q)**

| | Adenomyosis group （n=201) | Uterine leiomyomas group （n=549) | Control group （n=201) | *P* |
|---|---|---|---|---|
| PC,109/L | 242（204-290.50） | 242（201-286.50） | 216（179-257） | 0.000 |
| MPV, fl | 9.42（8.53-10.40） | 9.65（8.76-10.60） | 9.83（8.77-10.50） | 0.025 |
| PCT, % | 0.22（0.19-0.27） | 0.23（0.19-0.27） | 0.21（0.17-0.25） | 0.000 |
| PDW, % | 16.65（15.40-17.16） | 16.46（13.25-16.98） | 16.49（13.10-17.07） | 0.048 |
| PT, s | 11.30（10.80-11.65） | 11.30（10.90-11.80） | 11.30（10.80-11.80） | 0.173 |
| PT-INR, % | 0.90（0.90-1.00） | 0.90（0.90-1.00） | 0.90（0.90-1.00） | 0.319 |
| FIB, g/L | 2.68（2.41-2.97） | 2.60（2.35-2.85） | 2.57（2.30-2.79） | 0.019 |
| APTT, s | 27.50（25.45-31.20） | 28.10（25.55-30.50） | 27.80（25.65-30.30） | 0.936 |
| TT, s | 10.30（9.70-10.85） | 10.30（9.80-11.20） | 10.30（9.70-10.90） | 0.054 |
| AT-III, s | 121.50（106.95-140.35） | 114.90（102.90-138.75） | 116.80（102.80-140.10） | 0.051 |
| D-Dimer, mg/L | 0.03（0.03-0.11） | 0.03（0.03-0.04） | 0.03(0.03-0.04) | 0.003 |
| FDP, mg/L | 1.98（1.34-2.62） | 1.98（1.39-2.49） | 1.92(1.33-2.52) | 0.714 |
| ADP, % | 77.70（67.20-85.25） | 79（71-86） | 81(71.15-86.70) | 0.089 |
| AA, % | 79（69.85-84） | 81.10（73.75-86.35） | 81(74.55-87) | 0.002 |

*Table 3.* **Post-hoc Bonferroni test of platelet and coagulation function in three groups (Bonferroni method)**

| | PC(□109/L) | MPV(fl) | PDW(%) | PCT(%) | FIB(g/L) | D-Dimer(mg/L) | AA（%） |
|---|---|---|---|---|---|---|---|
| ADM vs CG | 0.000* | 0.140 | 0.376 | 0.004* | 0.021* | 0.012* | 0.004* |
| ADM vs ULG | 1.000 | 0.023* | 0.041* | 0.842 | 0.961 | 0.004* | 0.005* |
| ULG vs CG | 0.000* | 1.000 | 1.000 | 0.000* | 0.071 | 1.000 | 1.000 |

ADM, Adenomyosis group; ULG, Uterine leiomyomas group; CG, Control group. P-value < 0.05 was accepted as statistically significant.

**2.3 Logistic regression results of platelet and coagulation function in adenomyosis group, uterine leiomyomas group and control group**

Since there were significant differences in age, BMI, CA125 and Hb among the three groups (P = 0.000), logistic regression analysis was used to analyze adenomyosis group, uterine leiomyomas group and control group. The variables with differences among each group were incorporated into the bivariate logistic regression. The Person analysis showed that the correlation between PC and PCT was r=0.884. PC and PCT were independently incorporated into the analysis during Logist regression. The results showed that PC and PCT were independent risk factors for uterine leiomyomas (P < 0.05). PC, PCT, FIB and AA were not independent risk factors or protective factors of adenomyosis (P> 0.05). In addition, age, BMI and CA125 were independent risk factors of adenomyosis and leiomyoma (P < 0.05). Hb was an independent protective factor for adenomyosis and leiomyoma (P < 0.05) (Table 4-5).

*Table 4.* **Bivariate logistic regression results of adenomyosis group and control group**

| | B | S.E. | Wald | df | *P* | Exp(B) | 95%C.I.for EXP(B) | |
|---|---|---|---|---|---|---|---|---|
| Age | 0.065 | 0.024 | 7.398 | 1 | 0.007 | 1.067 | 0.024 | 7.398 |
| BMI | 0.363 | 0.074 | 24.398 | 1 | 0.000 | 1.438 | 0.074 | 24.398 |
| CA125 | 0.195 | 0.027 | 50.404 | 1 | 0.000 | 1.215 | 0.027 | 50.404 |
| Hb | -0.047 | 0.014 | 10.562 | 1 | 0.001 | 0.954 | 0.014 | 10.562 |
| PC | -0.001 | 0.003 | 0.096 | 1 | 0.756 | 0.999 | 0.003 | 0.096 |
| PCT | -2.332 | 3.637 | 0.411 | 1 | 0.521 | 0.097 | 0.000 | 121.020 |
| FIB | -0.033 | 0.413 | 0.006 | 1 | 0.937 | 0.968 | 0.413 | 0.006 |
| D-Dimer | -0.677 | 1.047 | 0.418 | 1 | 0.518 | 0.508 | 1.047 | 0.418 |
| AA | -0.015 | 0.019 | 0.658 | 1 | 0.417 | 0.985 | 0.019 | 0.658 |

*Table 5.* **Bivariate logistic regression results of uterine leiomyomas and control group**

| | B | S.E. | Wald | df | *P* | Exp(B) | 95%C.I.for EXP(B) | |
|---|---|---|---|---|---|---|---|---|
| Age | 0.015 | 0.011 | 1.877 | 1 | 0.171 | 1.015 | 0.993 | 1.038 |
| BMI | 0.232 | 0.039 | 35.686 | 1 | 0.000 | 1.262 | 1.169 | 1.361 |
| CA125 | 0.084 | 0.014 | 36.021 | 1 | 0.000 | 1.088 | 1.058 | 1.118 |
| Hb | -0.035 | 0.007 | 26.403 | 1 | 0.000 | 0.965 | 0.953 | 0.978 |
| PC | 0.004 | 0.002 | 7.048 | 1 | 0.008 | 1.004 | 1.001 | 1.008 |
| PCT | 4.720 | 1.657 | 8.116 | 1 | 0.004 | 112.162 | 4.361 | 2884.505 |

## 3. Discussion

At present, it is believed that the change or deletion of endometrial myometrial junction (JZ), transfer of embryonic pluripotent stem cells or differentiation of adult stem cells, and Chronic uterine injury and tissue repair mechanisms are the main mechanisms leading to adenomyosis (Donnez et al.,2018； Pan et al.,2018). The pathogenesis of uterine leiomyoma is the change of hormone level, chronic inflammation, genetic and other causes of uterine smooth muscle hyperplasia and extracellular matrix deposition (Islam et al.,2018). Inflammation is closely related to the changes of platelets and coagulation factors. Many studies have found that platelets may participate in the fibrotic process of adenomyosis and leiomyomas. PDGF can increase the expression of collagen α and promote the proliferation of leiomyoma cells. TGF - β, activin A and TNF - α may increase the synthesis of extracellular matrix components in leiomyoma cells (Ciarmela et al.,2011). However, Liu, Shen et al.(Liu et al.,2016) found that CD42b positive platelet aggregation in adenomyosis lesions, and confirmed that activated platelets participate in the fibrosis process of adenomyosis by inducing the activation of TGF - β / Smad3 signaling pathway. Zhu, Chen et al. (Zhu et al., 2016) found that antiplatelet therapy can inhibit the myometrial infiltration of adenomyosis, improve dysmenorrhea, and reduce uterine hyperactivity and cortisol levels throughout the body. However, the drug treatment of adenomyosis and leiomyomas is still dominated by hormone therapy, and the research progress of non-hormone drugs such as antiplatelet drugs is slow (Vannuccini et al.,2018). According to our results, we found that platelet count and plateletcrit were independent risk factors of uterine leiomyomas, but not with adenomyosis. Therefore, we speculated that antiplatelet therapy for uterine leiomyomas may be more meaningful than adenomyosis.

At present, only two studies have analyzed whether platelet parameters were significant serological markers in adenomyosis, and the results of these two studies are opposite. Bodur, dundar et al. (Bodur et al., 2015) retrospectively analyzed the patients diagnosed as adenomyosis and non-adenomyosis after hysterectomy. On the basis of collecting the preoperative data of these patients, it was found that MPV had certain value in the preoperative diagnosis of adenomyosis. When the cutoff value of MPV was 8.5fl, the sensitivity and specificity of the diagnosis of adenomyosis were 56.6% and 82.6%, respectively. Coskun, Ince et al. (Coskun et al.,2019) discussed the diagnostic value of platelet count and mean platelet volume in endometriosis group, adenomyosis group and control group, and found that platelet count and mean platelet volume could not be used as useful hematological markers of endometriosis and adenomyosis. Our study found that the different platelet parameters are neither a risk factor nor a protective factor for adenomyosis, which was consistent with the latter study.

Our study also further explored the difference of coagulation function in adenomyosis group, leiomyomas group and control group. It was found

that D-dimer in adenomyosis group was significantly higher than that in uterine leiomyomas group and control group, and platelet aggregation rate AA was significantly lower than that in uterine leiomyomas group and control group. There was no significant difference in coagulation function between the two groups. Ding, Liu et al. (Ding et al.,2018) compared the coagulation function indexes between the patients with endometriosis and the control group before operation, and found that the platelet activation rate, platelet aggregation rate, D-dimer, FDP, fibrinogen in patients with endometriosis were higher than those in the control group, and TT was shortened, which indicated that patients with endometriosis had hypercoagulability. Yamanaka, Kimura et al. (Yamanaka et al., 2016) studied the changes of plasmin-α2-plasmin inhibitor complex (PIC), antithrombin complex (TAT), soluble fibrin (SF) and D-Dimer (DD) during menstrual period in 8 patients with adenomyosis. It was considered that patients with uterine volume $\geqslant$ 100 cubic cm were at risk of activation of coagulation system. Our study compared the difference of coagulation function between non-menstrual patients and normal people. These different indicators cannot explain the non-menstrual hypercoagulable state of patients with adenomyosis, and the different coagulation function indexes in adenomyosis group are not independent risk factors of adenomyosis. Therefore, we believe that there is insufficient evidence for anticoagulant therapy in patients with non-menstrual adenomyosis. In addition, we found that platelet aggregation rate AA in adenomyosis group was lower than that in uterine leiomyomas group and control group, which was contrary to the study of Ding, Liu et al. (Ding et al.,2018). Large platelets are more active in metabolism and enzyme activity than small platelets, they aggregate faster and release more mediators, such as thromboxane A2, serotonin and ATP (Sevuk et al., 2015). In our study, we can also see that the average platelet volume of adenomyosis group is lower than that of leiomyomas group and control group.

Our study had some limitations. First of all, our study was a retrospective study, it was difficult to collect the clinical data of patients completely, so we did not set up strict inter group control. We compared platelet and coagulation function indicators as preliminary screening for possible risk factors. Secondly, we concluded that PC and PCT were independent risk factors of uterine leiomyoma, which might change with the introduction of other risk factors. More prospective clinical studies are needed to provide evidence.

In conclusion, our study found that there may be differences in platelet and coagulation function in patients between adenomyosis, uterine leiomyomas and control group. Platelet count and plateletcrit were independent risk factors of uterine leiomyomas, which may provide basis for anti-platelet therapy in patients with uterine leiomyomas. However, in patients with adenomyosis, these differences were not significantly associated with adenomyosis. Therefore, more multicenter studies are needed to explore the significance of platelet and coagulation function changes in patients with adenomyosis.

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