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CA125 modified by PLT and NLR improves the predictive accuracy of adenomyosis-derived pelvic dense adhesion

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Abstract

To explore the value of serum levels of CA125, platelet count (PLT), neutrophil–lymphocyte ratio (NLR), and modified CA125 markers CA125a and CA125b in predicting pelvic dense adhesion (PDA) associated with adenomyosis, CA125a = lg(CA125 × PLT × 10^9), CA125b = lg(CA125 × NLR).

This retrospective study included 304 patients who underwent surgery for adenomyosis. Correlations of serum levels of CA125, PLT, NLR, and modified CA125 markers with adenomyosis-derived PDA were analyzed by Logistic regression. Receiver operating characteristic curve was applied to assess the utility of these parameters for predicting PDA.

All the parameters including CA125, PLT, NLR, and modified CA125 markers were positively correlated with PDA ($P < .05$ or $P < .01$). More importantly, CA125a was more specific (85.03% vs. 83.00%) and more sensitive (47.56% vs. 47.47%) than CA125 alone for the prediction of PDA, and CA125b could also improve the predictive specificity of PDA (53.13% vs. 47.47%).

Serum CA125, PLT, and NLR were all closely correlated with PDA in adenomyosis patients. CA125 modified by PLT and NLR could further improve the predictive accuracy of adenomyosis-derived PDA, thus providing more meaningful references for better-informed decisions about the mode of surgical access for the clinical treatment of adenomyosis.

Abbreviations: AUC = area under the curve, CI = confidence interval, NLR = neutrophil–lymphocyte ratio, OR = odds ratio, PBAC = pictorial blood loss assessment chart, PDA = pelvic dense adhesion, PLT = platelet count, ROC = receiver operating characteristic, VAS = visual analog scale.

Keywords: adenomyosis, CA125, neutrophil–lymphocyte ratio, pelvic dense adhesion, platelet count

1. Introduction

Adenomyosis is a common gynecologic condition that is characterized by the presence of heterotopic endometrial glands and stroma within the myometrium and is closely related to endometriosis. The mean occurrence of adenomyosis at hysterectomy is 20% to 30%. Dysmenorrhea, menorrhagia, and subfertility are the most commonly reported symptoms that heavily affect the quality of life in patients with adenomyosis.[1,2] Hysterectomy is the current standard treatment for symptomatic adenomyosis.[3] However, adenomyosis-derived pelvic dense adhesion (PDA) is correlated with the quality of the perioperative period directly.[4] Recent data from patients who underwent laparoscopic hysterectomy showed that patients who required extensive adhesiolysis had a significantly increased odds ratio (OR) of 2.22 for conversion to laparotomy, and 3.5 for short-term postoperative complications (pelvic peritonitis, hematoma requiring surgical intervention, postoperative bleeding, and reoperation due to adhesions) relative to patients without adhesiolysis.[5] The pathological changes in pelvic cavity of adenomyosis are so complicated and at high risk of suffering from tissue and organ damage that making an accurate preoperative assessment on the presence or absence of PDA in adenomyosis patients has positive guiding significance for gynecologic surgeons. It is therefore necessary to seek a noninvasive, effective, and mature alternative for the clinical diagnosis of PDA.

Serum CA125, platelet (PLT), neutrophil (NEU), and neutrophil–lymphocyte ratio (NLR) are the common blood parameters that have been used for the auxiliary diagnosis of endometriosis.[6,7] Many studies have found that PLT and NEU can be applied to the diagnosis of clinical stages and prediction of diseases prognosis in tumors and endometriosis, and that their combination with CA125 could improve the diagnostic and predictive value.[8–10] However, the data published so far are limited and there has been little discussion about the correlation of CA125, PLT, and NLR with adenomyosis-derived PDA.

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The aim of this retrospective study was to investigate the correlation of serum levels of CA125, PLT, NLR, and modified CA125 markers with adenomyosis-derived PDA, and explore their clinical value for the prediction of PDA in 304 patients who underwent surgery for adenomyosis.

2. Materials and methods

2.1. Ethics statement

The study was approved by the Institutional Review Board of the Yangpu Hospital, Tongji University School of Medicine, Shanghai, China. Written informed consent was obtained from all subjects participating in the study.

2.2. Participants

From January 1, 2010 to March 31, 2016, 304 consecutive patients who underwent either laparoscopic or laparotomic surgery for adenomyosis at the Gynecological Department of Yangpu Hospital were included in this study. The diagnosis was confirmed by histology. Before surgery, the patients were interviewed personally using a standard questionnaire with respect to the sociodemographic characteristics, menstrual and obstetrical histories, medical complications, histories of abdominal surgery, clinical symptoms and signs, and surgical data. Participants with regular menstrual cycles (28–32 days) were not administered any hormonal therapy including oral contraceptive pills, progestins, gonadotropin-releasing hormone agonist, or levonorgestrel intrauterine system (LNG-IUS) within recent 3 months. Patients with cancer, autoimmune diseases, pelvic inflammatory disease, and other infectious diseases were excluded.

2.3. Evaluation of clinical symptoms and signs

The severity of dysmenorrhea was assessed using the visual analog scale (VAS) system as follows: 0, no pain; 1 to 3, minimal pain; 4 to 6, moderate pain; 7 to 9, severe pain; 10, the worst pain imaginable. Menstrual blood loss was evaluated using the pictorial blood loss assessment chart (PBAC). Menorrhagia was defined as excessive menstrual blood loss > 80 mL (PBAC > 100) per period. The uterine volume was measured by transvaginal ultrasound and calculated by the prolate ellipse equation: uterine volume $= D1 \times D2 \times D3 \times \pi/6$, where D1, D2, and D3 represent the vertical, transverse, and anteroposterior diameter of the uterus, respectively.[11]

2.4. Surgical information

Perioperative information was recorded. Based on the literature data[5] and the intraoperative real-time observation, the adenomyosis-derived PDA was defined as follows: The adenomyosis lesion was invasively adhered to the surrounding tissue or organ, such as the rectum, sigmoid colon, utero-sacral ligament, cardinal ligament, and bladder, forming a dense adherent zone, from which some coffee-colored secretion flowed out when pelvic adhesiolysis was performed in most cases. Adenomyosis was complicated with chocolate cyst of ovary and peritoneal endometriosis, leading to adhesion between the cyst and the ovarian fossa. The following types of adhesion were excluded: Adhesions caused by previous pelvic and abdominal surgeries such as cesarean section and appendix surgery performed between the incision and the peritoneum or abdominal wall; these adhesions were usually thin and membranous. Adhesions caused by infectious diseases of the fallopian tube or ovary such as hydrosalpinx, thickening of the tubal wall, annex abscess, and pelvic fluid. Two surgeons responsible for the operation would complete a postoperative questionnaire about the presence or absence of PDA by visual inspection.

2.5. Determination of blood parameters

Surgery was performed during the proliferative phase of menstrual cycle in all patients, and all blood analyses were done during the early proliferative phase. Complete blood count parameters were measured by Sysmex XE-2100 Automated Hematology Analyzer (China Pharmaceutical Group Shanghai Medical Instrument Co, Ltd, Shanghai, China). The NLR was obtained by dividing the absolute neutrophil count by the absolute lymphocyte count. Serum CA125 levels were detected with CA125 diagnostic kit (Beckman Coulter Commercial Enterprise (China) Co, Ltd, Shanghai, China) using DxI UniCel 800 automated chemiluminescence immunoassay system, with the concentrations expressed as U/mL. Modified CA125 markers: $CA125a = \lg(CA125 \times PLT \times 10^9)$; $CA125b = \lg(CA125 \times NLR)$.

2.6. Statistical analysis

All statistical analyses were performed with SPSS version 16.0 for Windows (SPSS Inc, Chicago, IL). Group measures were presented as means $\pm$ standard deviations, and intragroup differences were investigated using Student *t* test. Categorical variables were expressed as the number of cases and percentages. Differences between categorical data were evaluated using the Chi-squared test or Fisher exact test when necessary. Correlations of variables for each group were determined using Pearson correlation coefficient or the nonconditional Logistic regression when necessary. The optimal cutoff points of CA125, PLT, NLR, and modified CA125 markers in predicting PDA were evaluated by receiver operating characteristic (ROC) analyses by calculating the area under the curve (AUC), giving the maximum sum of sensitivity and specificity for the significance test. A value of $P \leq .05$ (2-sided test) was considered statistically significant.

3. Results

3.1. Comparison of characteristics between the non-PDA group and PDA group

A total of 304 adenomyosis patients were enrolled in the study, and the mean history of adenomyosis was 13.69 ± 5.32 (1–240) months. The sociodemographic, clinical, and laboratory characteristics of the groups are given in Table 1. There were no statistically significant differences in age, body mass index, parity, abortion, medical complications, history of abdominal surgery, dysmenorrhea, menstrual capacity, volume of the uterus, and the surgical modality. The patients with PDA had significantly higher estimated blood loss, a higher rate of hysterectomy and hemorrhage ≥ 500 mL, and a longer postoperative hospital stay than non-PDA patients ($P < .05$ or $P < .05$). The mean serum levels of CA125, PLT, NLR, CA125a, and CA125b in PDA group were also significantly higher than those in non-PDA group ($P < .01$ or $P < .05$).

Other than ureteric injury (n = 2), bowel injury (n = 5), and bladder injury (n = 2) were the primary intraoperative complications in this study. No case was converted from laparoscopy to laparotomy. Common types of PDA found during operation were

Table 1

Comparison of characteristics between non-PDA and PDA groups.

	Non-PDA (n = 160)	PDA (n = 144)	P*
Age, y	43.47 ± 6.09	42.44 ± 5.70	.132
BMI, kg/m^2	23.32 ± 2.89	23.50 ± 2.28	.811
Parity (n)	1 (0–8)	1 (0–8)	.108
Abortion (n)	2 (0–8)	1 (0–8)	.191
Medical complication†, n (%)	20 (12.50)	17 (11.81)	.863
Previous abdominal surgery, n (%)			.908
General surgery	15 (9.38)	15 (10.42)	
Gynecological surgery	42 (26.25)	40 (27.78)	
Cesarean section	46 (28.75)	39 (27.08)	
Dysmenorrhea, n (%)			.396
Minimal	47 (29.38)	33 (22.92)	
Moderate	41 (25.63)	37 (25.69)	
Severe	72 (45.00)	74 (51.39)	
Menstrual capacity, n (%)			.730
Normal	84 (52.50)	79 (54.86)	
Menorrhagia	76 (47.50)	65 (45.14)	
Volume of uterus, cm^3	227.93 ± 193.51	234.64 ± 144.68	.735
Operation type, n (%)			.423
Laparoscopy	148 (92.50)	129 (89.58)	
Laparotomy	12 (7.50)	15 (10.42)	
Hysterectomy, n (%)	65 (40.63)	76 (52.78)	.038
Estimated blood loss, mL	109.81 ± 78.23	202.50 ± 256.12	.000
Hemorrhage ≥ 500 mL, n (%)	1 (0.63)	11 (7.64)	.002
Postoperative hospital stay, d	6.30 ± 2.62	8.67 ± 8.39	.001
CA125, U/mL	77.27 ± 83.26	136.90 ± 144.61	.000
PLT, $\times 10^9$/L	264.18 ± 84.39	285.86 ± 86.37	.028
NLR	2.06 ± 0.83	2.34 ± 1.18	.015
CA125a	13.06 ± 0.49	13.39 ± 0.46	.000
CA125b	10.95 ± 0.49	11.28 ± 0.44	.000

BMI = body mass index, CA125a = lg (CA125 × PLT × 10^9), CA125b = lg(CA125 × NLR), NLR = neutrophil–lymphocyte ratio, PDA = pelvic dense adhesion, PLT = platelet count.

* Student *t* test, chi-squared test, or Fisher exact test when necessary.

† Mainly hypertension and diabetes were included.

follows: adhesion of the posterior uterine wall and the rectum, or sigmoid colon, resulting in complete or partial closure of the Douglas pouch; fibrosis and thickening of the uterosacral ligament, cardinal ligament, and parametrial tissue; adhesion of the ovarian fossa and the ovary, or oviduct. Various types of PDA occurred in 144 (43.37%) of the 304 included cases of adenomyosis.

3.2. Correlations between the parameters and PDA

Data analysis revealed that all the parameters including CA125, PLT, NLR, CA125a, and CA125b were positively correlated with PDA ($P < .05$ or $P < .01$) (Table 2).

Table 2

Correlations between the parameters and PDA.

	β	OR	95% CI	P*
CA125	0.005	1.005	1.003–1.008	.000
PLT	0.003	1.003	1.000–1.006	.030
NLR	0.289	1.335	1.055–1.690	.024
CA125a	1.422	4.145	2.471–6.952	.000
CA125b	1.552	4.719	2.749–8.102	.000

CI = confidence interval, NLR = neutrophil–lymphocyte ratio, OR = odds ratio, PDA = pelvic dense adhesion, PLT = platelet count.

* Nonconditional logistic regression.

3.3. Correlations between CA125 and the other parameters

Further study was performed to determine whether CA125 was correlated with the other parameters. It was found that CA125 was positively correlated with PLT ($r = 0.216$, $P < .01$), but insignificantly correlated with NLR.

3.4. ROC analysis of CA125, PLT, NLR, and modified CA125 markers for PDA prediction

The optimal cut-off points for CA125, PLT, NLR, CA125a, and CA125b for PDA prediction were further evaluated by ROC analysis (Fig. 1). According to the highest Youden index, the cut-off value was found to be 41.45 U/mL for CA125 and 246.50 × 10^9/L for PLT. According to the ROC analysis performed for the predictive performance of CA125a for PDA, the AUC was 0.684 (95% confidence interval [CI]: 0.625–0.744) and the cut-off value for distinguishing the groups was 13.00 with 85.03% sensitivity and 47.56% specificity. For CA125b, the AUC was 0.700 (95% CI: 0.641–0.759) and the cut-off value was 10.96 with 81.94% sensitivity and 53.13% specificity (Table 3).

4. Discussion

As a common pathological change of the pelvic cavity, adenomyosis-derived PDA is closely related to dysmenorrhea, chronic pelvic pain, and subfertility of adenomyosis.[12] Of the 304 adenomyosis patients reviewed retrospectively in this study, 144 (47.37%) cases developed various types of PDA. Adenomyosis-derived PDA interferes with visualization of the surgical filed and identification of the anatomical structure, thus lowering the quality of the perioperative period, and increasing the risk of intraoperative complications such as injury to the pelvic vessel, bladder, ureter and bowel, and postoperative complications such as bowel obstruction, chronic pelvic pain, and PDA recurrence.[5] A large sample-size study[4] on gynecologic laparoscopy reported that pelvic adhesions occurred in 61.6% cases in conversion-to-laparotomy group versus 47.7% in nonconversion group, and that they were significantly associated with an increased risk of laparotomy (OR: 2.30, 95% CI: 1.37–3.76). Adhesions were

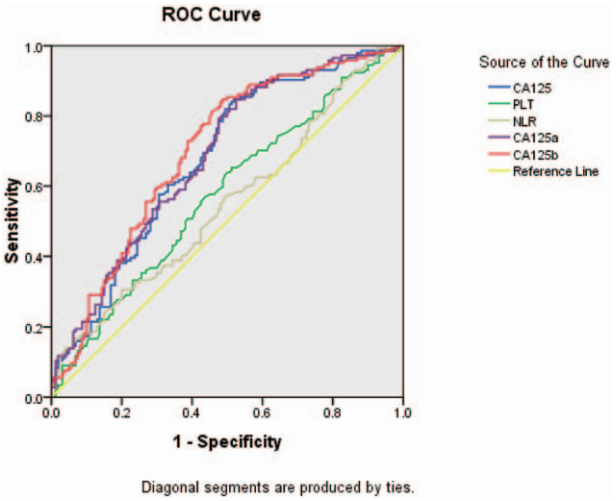

Figure 1. ROC analysis of CA125, PLT, NLR, and modified CA125 markers for prediction of PDA. NLR = neutrophil–lymphocyte ratio, PDA = pelvic dense adhesion, PLT = platelet count, ROC = receiver operating characteristic.

Table 3

SN, SP, PPV, NPV, and accuracy of CA125, PLT, NLR, and modified CA125 markers for prediction of PDA.

	AUC (95% CI)	SN, %	SP, %	PPV, %	NPV, %	Accuracy, %	Cut-off value	P^*
CA125	0.678 (0.618–0.738)	83.00	47.47	60.48	74.26	64.95	41.45	.000
PLT	0.574 (0.510–0.639)	64.71	48.10	54.70	58.46	56.27	246.50	.025
NLR	0.549 (0.484–0.614)	30.56	80.00	57.89	56.14	56.58	2.52	.138
CA125a	0.684 (0.625–0.744)	85.03	47.56	59.24	78.00	65.27	13.00	.000
CA125b	0.700 (0.641–0.759)	81.94	53.13	61.14	76.58	66.78	10.96	.000

AUC = area under the curve, CI = confidence interval, NLR = neutrophil–lymphocyte ratio, NPV = negative predictive value, PDA = pelvic dense adhesion, PLT = platelet count, PPV = positive predictive value, SN = sensitivity, SP = specificity.

* Receiver operating characteristic analyses.

cited as the primary reason for surgical conversion, accounting for 36.5%. Another study reported that PDA was the reason for conversion to laparotomy, accounting for 55.2%.[13] Our results showed that PDA patients had significantly higher estimated blood loss, a higher rate of hemorrhage ≥ 500 mL and a longer postoperative hospital stay than non-PDA patients, and that intraoperative complications requiring surgical intervention occurred in 9 (3.62%) cases, mainly involving injury to the gut, bladder, and ureter. The occurrence of hemorrhoea and intraoperative complications in the present study was closely related to PDA. So, making an accurate preoperative assessment on the presence or absence of PDA in adenomyosis patients has an important clinical value.

CA125 has been widely used for the diagnosis and follow-up of patients with adenomyosis.[6] Fundamental analysis studies in recent years demonstrated that CA125, PLT, and NEU may related to the development and progression of the inflammatory pathology of endometriosis via the inflammation-associated molecular mechanism.[14,15] It was reported that patients with preoperative CA125 levels higher than 65 IU/mL were at high risk for advanced-stage or severe pelvic adhesion.[16] Numerous studies demonstrated that both PLT and NEU were implicated in the pathogenesis of endometriosis and adenomyosis.[15,17,18] Cho et al[19] and Tokmak et al[7] reported that NLR was significantly positively correlated with the stage of endometriosis, and the combination of NLR and CA125 was more sensitive than CA125 alone for the differential diagnosis of endometriomas, which would be useful in identifying symptomatic patients with early-stage endometriosis. Therefore, we searched the probable relationship of these blood parameters with adenomyosis-derived PDA. To the best of our knowledge, no study has reported the use of CA125, PLT, and NLR to predict PDA.

In the present study, CA125a and CA125b were obtained by multiplying CA125 levels by PLT and NLR, respectively. The results showed that the mean serum levels of CA125, PLT, NLR, and modified CA125 markers (CA125a and CA125b) in PDA group were significantly higher than those in non-PDA group, and all the parameters were positively correlated with PDA. Kabawat et al[20] reported that the expression of CA125 was increased remarkably in the areas of inflammation and adhesion. The significant correlation between CA125 and PDA in our study is consistent with that reported in previous studies.[20] The significant correlations between PLT and NLR and PDA in this study suggest that both of PLT and NLR may be related to the inflammatory pathogenesis of adenomyosis.[14,18]

Furthermore, linear correlations between CA125 and the other parameters in adenomyosis patients were analyzed. Kim et al[21] reported that no significant correlation between CA125 and NLR in endometriosis patients, which is consistent with the result of the present study but contrary to the result reported by Cho et al[19] and Tokmak et al.[7] Therefore, further studies are needed to evaluate these findings.

In addition, ROC was applied to assess the utility of these parameters for predicting PDA in this study. It was found that either CA125 or PLT alone could be employed as an independent factor to predict PDA, but not NLR. CA125 modified by NLR was more specific (53.13%) than CA125 alone for the prediction of PDA, and CA125 modified by PLT could also improve the predictive accuracy of PDA with 85.03% sensitivity and 47.56% specificity.

Despite our important findings, there are some limitations in this study. First, a potential limitation of the study lies in its open, nonrandomized design, knowing that studies of this type are inevitably subject to potential patient and investigator biases (selection biases). In addition, only patient data during hospitalization were obtained for analysis, devoid of information about long-term postoperative complications. Finally, the menstrual dates in this study mainly depended on the medical records without histologic evaluation. Therefore, further studies with larger sample sizes are needed to avoid these limitations and verify the findings of the present study.

In summary, CA125, PLT, NLR, and modified CA125 markers (CA125a and CA125b) showed positive correlations with the adenomyosis-derived PDA, and CA125 modified by PLT and NLR could increase the predictive accuracy of PDA. These findings may help further improve the predictive accuracy of adenomyosis-derived PDA, thus providing more meaningful references for better-informed decisions about the mode of surgical access for the clinical treatment of adenomyosis.

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