Preoperative platelet count improves the prognostic prediction of the FIGO staging system for operable cervical cancer patients

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ABSTRACT

Background: Increased platelet has been identified as an independent and unfavorable prognostic indicator in various cancers including cervical cancer. In our study, the prognostic value of preoperative platelet count combining with FIGO (International Federation of Gynecology and Obstetrics) stage in patients with operable cervical cancer was investigated.

Methods: A large cohort study including 800 operable cervical cancer patients was conducted from May 2005 to December 2012. Cancer-related biomarkers such as platelet count, hematocrit, hemoglobin, RDW was evaluated together with FIGO staging system in stage IA1–IIA2 cervical cancer patients. The prediction validity of platelet together with FIGO stage was then evaluated by receiver operating characteristic (ROC) curve, and the areas under the curve (AUCs) were compared by Z test.

Results: Univariate cox proportional hazard analysis demonstrated that hematocrit, platelet count, hemoglobin, FIGO stage, tumor differentiation, PLN (pelvic lymph node metastasis), LVSI (vascular lymph node invasion) were associated with overall survival (OS) and disease free survival (DFS), instead of RDW (red cell distribution width), age and histological subtype. Multivariate analysis demonstrated that preoperative platelet and FIGO stage were independent predictors for OS and DFS in cervical cancer. Furthermore, significant improvements were found after the combination of platelet count and FIGO stage in predicting OS and DFS for cervical cancer patients ($P = 0.0128$ and $P = 0.0385$, respectively).

Conclusions: Combination of platelet count and FIGO stage improved the prediction performance of FIGO staging and provide additional risk stratification for operable cervical cancer patients.

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1. Introduction

The incidence and mortality of invasive cervical cancer has decreased steadily, but it is still the second most common malignancy in females worldwide and the leading cause of cancer-related deaths among women in less developed countries. In the year of 2012, about 500,000 new cervical cancer cases were diagnosed, and 275,000 deaths were estimated to occur of this malignancy globally [1,2].

The FIGO (International Federation of Gynecology and Obstetrics) staging system for cervical cancer, revealing the extent and aggressiveness of tumor, is one of the known predictors for survivals, and determines patients' treatment plan [3]. Nevertheless, as it is based on clinical evaluation of the anatomic extent, the correlation between FIGO staging and final histopathologic classification is inevitably imperfect. The error rate is about 25% in patients with early stages (≤IIA) while 65% to 90% in patients with advanced stages (≥IIB) [4].

Hence, it is necessary to improve the FIGO staging system for more accurate and practical prognostication in cervical cancer patients, optimizing individualized treatment and the life quality of long-term survivals. Cancer-related inflammation responses play important roles at different stages of tumor development, including initiation, promotion, malignancy conversion, invasion, and metastasis [5,6]. And inflammatory biomarkers, such as platelet count [7,8], anemia (defined by hematocrit or hemoglobin) [9–11] and red cell distribution width (RDW) [12,13] had been well studied in various diseases as survival predictors. These biomarkers are cheap and easily accessible in clinical settings, which may provide additional information to evaluate the clinical outcomes for cancer patients.

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To the best of our knowledge, the association between these biomarkers and the FIGO staging classification was not fully investigated, providing no evidence of whether these biomarkers could be used together with the FIGO staging system to improve prognostic prediction in cervical cancer. Therefore, the current study was performed to investigate the prognostic roles of preoperative platelet count, anemia, RDW and FIGO staging system in stage IA1–IIA2 cervical cancer patients and to find out more accurate indicators for cervical cancer.

2. Materials and methods

2.1. Patients

From May 2005 and December 2012, 800 cervical cancer patients in stage IA1–IIA2 were enrolled in our retrospective study. Radical hysterectomy with additional chemotherapy or radiotherapy was carried out in our hospital. The exclusion criteria were as follows: perioperative mortality and preoperative routine laboratory tests unavailable, history of immunological or hematological system diseases, liver disease, previous anti-cancer therapies and other malignancies. The hospital ethics committee of the first affiliated hospital of Wenzhou Medical University approved our study protocol, and informed consent was obtained from each patient. The hematological and laboratory parameters, such as platelet, hematocrit, hemoglobin and RDW level were collected within one week before surgery. Clinical and pathological materials, including age at diagnosis, FIGO stage, pathological types, tumor differentiation, vascular lymph node invasion (LVSI), and pelvic lymph node metastasis (PLN) were also recorded.

2.2. Follow-up and prognosis evaluation

Out-patient medical records, telephone consultations, and social security death indices were adopted to calculate overall survival (OS) and disease free survival (DFS). OS and DFS were defined as the date from surgery to the date of death in spite of any cause and the first evidence of relapse. Patients alive (without recurrence) were censored on last follow-up date. Follow-up was every 3 months for the first two years, 6 months interval for the next three years, and annually thereafter. Follow-up evaluations including gynecological examinations, cervical cytology, trans-vaginal ultrasound scanning, computed tomography (CT) and/or magnetic resonance imaging (MRI) were carried out.

2.3. Statistical analysis

Categorical variables were compared by adopting the Chi-square or Fisher's exact test. Survival analysis was performed by adopting the cox proportional hazard regression and compared by Kaplan-Meier curves. Variables with statistical significance in the univariate cox regression analysis were then progressed to a multivariate analysis by backward stepwise selection. The best threshold values of platelet, hematocrit, hemoglobin, RDW were determined by receiver operating characteristic (ROC) curve analysis.

Platelet, hematocrit, hemoglobin, RDW were evaluated together with traditional clinicopathological variables in the univariate and multivariate analyses. Platelet count and FIGO staging were identified as independent prognostic indicators for OS and DFS through multivariate analysis. Accordingly, patients were categorized into 4 groups to analyze the prognostic significance of pretreatment platelet count ($<272 \times 10^9$/L and $\geq272 \times 10^9$/L) when stratified by FIGO staging classification (stage I and stage IIA). Furthermore, the predicted validity of platelet count together with FIGO staging (stage IA, IB and IIA) were evaluated by ROC curve, using the approaches of Hanley and McNeil [14,15], and the comparison of areas under the curve (AUCs) was carried out by Z test. All P values were 2-sided and a P value < 0.05 was defined to be statistically significant. Statistical analysis was performed

using the Statistical Package for Social Sciences version 22.0 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Patients' characteristics

800 patients with clinically and histologically confirmed cervical cancer were enrolled in the present analysis. These patients were diagnosed at a mean age of 49.5 ± 10.7 years, with a mean follow-up period of 62.2 ± 26.7 months. At the last follow-up time, 124 patients recurred, and 99 patients were dead. According to FIGO staging system, 105 (13.1%) of these patients were in stage IA, 359(44.9%) in IB, and the left 336 (42.0%) were in IIA.

3.2. Prognostic significance of variables

As presented in Table 1, univariate analysis suggested that platelet, hematocrit and hemoglobin were significant predictors for OS ($P =$ 0.002, $P =$ 0.031, and $P =$ 0.010, respectively) and DFS ($P =$ 0.002, $P =$ 0.048 and $P =$ 0.017, respectively) in cervical cancer patients as well as FIGO stage, tumor differentiation, PLN and LVSI ($P < 0.05$ for all), instead of RDW, age at diagnosis, and histological subtype ($P > 0.05$ for all).

To evaluate the independent prognostic factors for OS and DFS, multivariate cox proportional hazard analysis was therefore adopted. Multivariate analysis showed that platelet, FIGO stage, and PLN were independent factors for OS ($P < 0.05$ for all) and DFS ($P < 0.05$ for all) (Tables 2 and 3, respectively). Besides, hemoglobin was proved to be an independent predictor for OS ($P =$ 0.029), but not for DFS ($P =$ 0.070).

3.3. Cutoff value determination and correlations between platelet and clinicopathological parameters of cervical cancer

The best cutoff value for platelet corresponding to the maximum joint sensitivity and specificity judged by ROC curves were 272×10^9/L. The large cohort of patients were divided into high- and low-platelet ($<272 \times 10^9$/L vs. $\geq272 \times 10^9$/L). As shown in Table 4, increased platelet counts were associated with older age ($P < 0.001$) and the presence of both LVSI ($P =$ 0.011) and PLN ($P < 0.001$) significantly.

3.4. Combining the FIGO staging system and platelet count to provide additional stratification

To further investigate patients with different oncological outcomes, patients were stratified by platelet count and FIGO stage as follows: Group1, stage IA1–IB2 disease with platelet count $<272 \times 10^9$/L; Group 2, stage IA1–IB2 disease with platelet count $\geq272 \times 10^9$/L; Group 3, stage IIA disease with platelet count $<272 \times 10^9$/L; Group 4, stage IIA disease with platelet count $\geq272 \times 10^9$/L. Cumulative 5-year OS rate in the Group1 and Group 2 were 95.1% and 84.5% ($P < 0.001$), respectively, and 5-year DFS rate were 90.5% and 80.5% ($P =$ 0.006). Patients in Group 3 and Group 4 had 5-year OS rate of 87.8% and 76.5% ($P =$ 0.013), and 5-year DFS rate of 83.5% and 72.8% ($P =$ 0.033), respectively. However, no significance difference was found between Group 2 and Group 3 concerning both OS ($P =$ 0.411) and DFS ($P =$ 0.490) (Fig. 1A and B).

ROC curves were utilized to evaluate the prognostic prediction of combination of platelet count ($<272 \times 10^9$/L and $\geq272 \times 10^9$/L) and FIGO staging classification (stage IA, IB and IIA). As shown in Fig. 2A, conjoint analysis showed that the AUC of platelet combined with FIGO stage ($AUC_{platelet + FIGO stage} = 0.653$, 95%CI: 0.619–0.686) was better than FIGO stage alone ($AUC_{FIGO stage} = 0.611$, 95%CI: 0.576–0.645) in predicting OS for cervical cancer patients, with $P =$ 0.013. Significant improvement also found in predicting DFS for patients ($P =$ 0.039),