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A novel prognostic inflammation score predicts outcomes in patients with ovarian cancer

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ABSTRACT

Background: Systemic inflammation and host immunological nutritional status play important roles in the tumorigenesis of malignant cancer. A novel prognostic inflammation score (PIS) based on preoperative serum albumin and neutrophil to lymphocyte ratio (NLR) was designed. We explored its prognostic value in ovarian cancer.

Methods: 143 patients with ovarian cancer were enrolled in this retrospective study. The association of the PIS with clinicopathologic parameters was analyzed. The prognostic significance was determined by univariate and multivariate cox survival analyses.

Results: Both univariate and multivariate analyses showed that NLR and albumin were independent prognostic factors for overall survival (OS) and progression-free survival (PFS). An inverse correlation was observed between the NLR and serum albumin concentration. The novel prognostic inflammation score (PIS) was shown to be a significant predictor for OS and PFS (both $P < 0.001$) according to multivariate analysis. Additionally, low PIS was associated with advanced tumor stage ($P < 0.001$), metastasis ($P < 0.001$) and preoperative high PLR ($P < 0.001$).

Conclusions: The PIS is a novel but promising prognostic score in ovarian cancer. It is a significant prognostic marker adjusted for clinicopathologic characteristics to further identify patients' survival differences.

1. Introduction

Ovarian cancer is the fifth leading cause of cancer-related death [1] and the most fatal gynecologic malignancy in females due to the absence of sensitive and effective screening methods, as well as specific symptoms [2]. It is estimated by the American Cancer Society that there were 21,980 new cases and 14,270 deaths of ovarian cancer, accounting for 5% of the females' cancer-related mortality in the United States in 2014 [3]. Despite great improvements in treatment, the five-y overall survival rates did not change in the past decades. The identification of promising prognostic factors for ovarian cancer, in some ways could improve survival rates.

In addition to histopathological factors [4], systemic inflammation response and the patient's nutritional status, are believed to play important roles in the initiation and progression of various cancers [5–7]. Inflammation-based prognostic indicators, such as the platelet to lymphocyte ratio (PLR) [8], the neutrophil to lymphocyte ratio (NLR) [9,10], neutrophil counts [11] and C-reactive protein (CRP) [12,13] were reported as prognostic predictors in various cancers. Preoperative serum albumin concentration, reflecting host immunological nutritional status, was also investigated as a risk factor and prognostic variable in various cancers [14,15], including ovarian cancer [16]. However, the integration of the NLR and serum albumin was not yet investigated in ovarian cancer.

2. Materials and methods

2.1. Patients

This retrospective study reviewed the medical records of 143 patients with ovarian cancer who received operations at the Department of Gynecology in the First Affiliated Hospital of Wenzhou Medical University from 2006 to 2013. The study protocol was approved by the Ethics Committee of the First Affiliated Hospital at Wenzhou Medical University, and informed consent was obtained from all patients. The exclusion criteria included the presence of infection,

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trauma, coexisting hematological disease, or autoimmune disorders (these conditions could result in increased systematic inflammatory response components) or patients who failed to be followed up, or those without preoperative blood data available. All ovarian cancer patients followed up every 3 months for the first 2 y and every 6 months for the next 3 y. Gynecological examination, ultrasound, CT, chest-X ray and the serum concentration of CA-125 and CA-199 were evaluated at every visit. All the patients were staged according to guidelines of the International Federation of Gynecology and Obstetrics (FIGO2006). Clinical and pathological data including age, surgical stage, tumor subtype, distant metastasis, lymphovascular space invasion, pre-treatment complete blood counts (platelet, neutrophil, lymphocyte and monocyte counts), serum increased of albumin, and CA-125 were extracted from the retrospective medical records. NLR was defined as the absolute neutrophil count divided by the absolute lymphocyte count, and PLR was defined as the absolute platelet count divided by the absolute lymphocyte count. Serum CA-125 increased >35 U/ml was defined as abnormal, and a serum albumin increased ≤40 g/l was defined as hypoalbuminemia [17]. Moreover, we developed a novel prognostic inflammation score (PIS) defined as follows: patients with increased NLR and decreased serum albumin were assigned score 0; patients with either increased NLR or decreased serum albumin were assigned score 1; patients with decreased NLR and increased serum albumin were assigned score 2. Overall survival (OS) was defined as the time (months) from the date of primary surgery to the date of individual death of any cause. Progression-free survival (PFS) was defined as the time (months) from the date of primary surgery to the date of disease recurrence or disease progression. All patients were followed up until death or August, 2015.

2.2. Statistical analysis

SPSS 20.0 was used for the statistical analyses and the results were considered statistically significant with a $p < 0.05$. The best cutoff values of preoperative NLR, PLR were calculated by receiver operating characteristic (ROC) curve analysis and Youden's index [18,19]. Continuous data were expressed as mean ± standard deviation, and categorical data was compared using Chi-square or Fisher's exact tests. Survival analyses were performed using the Kaplan–Meier method and significant differences between groups were compared with the log-rank test. Univariable and multivariable survival analyses were performed using cox proportional hazards models. Hazard ratios (HRs) estimated from the cox-regression analysis were reported as relative risks with corresponding 95% confidence intervals [18]. Variables with statistical significance in the univariate cox regression analysis were progressed to a multivariate analysis by backward stepwise selection.

3. Results

3.1. Patients' characteristics

A total of 143 ovarian cancer patients were enrolled in this study, with a mean age of 52.27 ± 14.09 y, a mean serum albumin increased of 41.62 ± 5.47 g/l, a mean CA-125 concentration of 941.56 ± 1743.65 U/ml, a mean NLR of 3.61 ± 2.80, and a mean PLR of 200.66 ± 109.27. More than half of the patients (89 cases, 62%) were diagnosed at an advanced stage and 69% of the patients (98 cases) were found with metastasis. There were 51 (35.7%) deaths throughout the follow-up period. The estimated cumulative 5-y survival for this population was 63.2 ± 4.4% for OS and 54.2 ± 4.5% for PFS. The baseline patient characteristics were shown in Table 1. ROC curve analyses demonstrated the areas under the curve (AUC) for OS were 0.626 (95% confidence interval (CI) 0.531–0.722) and 0.603 (95% CI 0.506–0.699) for NLR, PLR, respectively. The optimal cut-off was 3.43 for NLR and 201 for PLR according to ROC curve determination. For the purpose of further analysis, patients were separated into 2 groups (NLR ≤3.43 and >3.43; PLR ≤201 and >201) according to the cutoff values of NLR and PLR. Patients were also divided into subgroups for age at diagnosis (≤40 vs. >40 y), albumin (≤40 vs. >40 g/l) and CA-125 (≤35 vs. >35 U/ml).

Table 1
The baseline patients' characteristics.

Parameter	N(143)	%(100)
Age (y)		
≤50	58	41
>50	85	59
Stage (FIGO)		
I–II	54	38
III–IV	89	62
Metastasis		
No	45	31
Yes	98	69
Tumor subtype		
Epithelial	122	85
Non-epithelial	21	15
Lymphovascular space invasion		
Negative	128	89
Positive	15	11
Albumin		
≤40	73	51
>40	70	49
CA125		
≤35	20	14
>35	123	86
NLR		
≤3.43	94	66
>3.43	49	34
PLR		
≤201	87	61
>201	56	39
PIS		
0	33	23
1	38	27
2	72	50

Abbreviations: N = number of patients; NLR = neutrophil to lymphocyte ratio; PLR = platelet to lymphocyte ratio; PIS = prognostic inflammation score.

3.2. Associations of NLR, serum albumin and PIS with OS and PFS

As shown in Table 2, the serum increased of albumin, CA-125, NLR, PLR and other clinicopathologic characteristics (including age, metastasis at presentation, tumor stage, lymphovascular space invasion and histological subtype) were subjected to a univariate analysis. Results from the univariate analysis indicated that age at diagnosis, tumor stage, metastasis, serum albumin, CA-125, pre-treatment NLR, and pre-treatment PLR were all associated with OS. These serum biological markers were significantly associated with PFS as well, except pretreatment PLR (Table 2).

Multivariable analyses suggested both serum albumin and NLR were independent prognostic factors for OS (Table 3) (HR, 0.36, 95% CI: 0.19–0.62, P = 0.002; HR, 3.37, 95% CI: 1.39–8.15, P = 0.007; respectively) and PFS (Table 4) (HR, 0.50, 95% CI: 0.29–0.87, P = 0.014; HR, 2.20, 95% CI: 1.03–4.70, P = 0.041; respectively), as well as metastasis and tumor subtype. Kaplan–Meier analysis for OS (Fig. 1A, C) and PFS (Fig. 1B, D) indicated that the increased serum albumin and decreased NLR were significantly correlated with favorable OS