Serum D-dimer, Albumin and Systemic Inflammatory Response Markers in Ovarian Clear Cell Carcinoma and Their Prognostic Implications

Wei Chen
Minhang hospital, Fudan University https://orcid.org/0000-0002-8159-5514
Siyuan Zhong
Fudan University Shanghai Cancer Center
Boer Shan
Fudan University Shanghai Cancer Center
Shuling Zhou
Fudan University Shanghai Cancer Center
Xiaohua Wu
Fudan University Shanghai Cancer Center
Huijuan Yang (huijuanyang@hotmail.com)
Fudan University Shanghai Cancer Center
Shuang Ye (mendy_ye@126.com)
Fudan University Shanghai Cancer Center

Research

Keywords: Ovarian Neoplasms; Clear Cell Carcinoma; D-dimer; Albumin; Neutrophil to lymphocyte ratio; Platinum resistance; Recurrence; Survival

Posted Date: March 9th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-16438/v1

Version of Record: A version of this preprint was published on August 8th, 2020. See the published version at https://doi.org/10.1186/s13048-020-00693-w.

Abstract

Background The study aims to evaluate whether preoperative systemic inflammatory response (SIR) markers or other hematologic variables, such as albumin, D-dimer, carbohydrate antigen 125 play a role in predicting chemotherapy response and survival outcome in patients with ovarian clear cell carcinoma (OCCC). Methods Preoperative leukocyte differential counts, platelet, serum albumin, plasma D-dimer and CA-125 levels were measured in patients with FIGO IC-IV ovarian clear cell cancer. The correlations of these hematologic biomarkers with clinicopathological features, chemotherapy response, and survival outcomes were further analyzed. Survival time was estimated using the Kaplan-Meier model, whereas Cox regression was conducted for multivariate analysis.

Results Among the 84 patients, 28.6% were classified as platinum-resistant and 69.0% as platinum sensitive. Preoperative CA125, albumin, D-dimer, and neutrophil to lymphocyte ratio (NLR), monocyte to lymphocyte ratio were significantly correlated with FIGO stage, residual tumor, and platinum response. Platelet to lymphocyte ratio was not related to platinum response (P =0.060). The median follow-up time was 28 months (range, 1 to 128 months). Preoperative CA125, albumin, and D-dimer were significant prognostic factors for overall survival (OS) and progression-free survival (PFS). In the univariate analysis, only NLR had prognostic significance for PFS (P =0.007). Multivariate analysis indicated that D-dimer > 3.27 (P = 0.001 for OS; P = 0.040 for PFS) and albumin <39.6 (P = 0.005 for OS and P = 0.041 for PFS) retained significance.

Conclusions Preoperative NLR has some predictive value for platinum resistance in patients with IC-IV stage OCCC, but has little predictive effect on prognosis. Elevated D-dimer and reduced albumin might be potential biomarkers for worse response to first-line platinum-based chemotherapy and poor clinical outcomes.

Background

Epithelial ovarian cancer (EOC) is the eighth commonest cause of female cancer death worldwide [1]. Ovarian clear cell carcinoma (OCCC) is a distinct histologic subtype that accounts for 5–25% of all EOC and is more commonly seen in Asian women [2, 3]. Although the prognosis for patients with stage I OCCC is relatively good, patients with stage IC-IV OCCC presents much poorer prognoses than patients with serous carcinoma due to its disease aggressiveness and chemotherapy resistance [3, 4]. The factors, such as FIGO stage, residual tumor and platinum response, known to influence treatment outcomes in OCCC [5] are limited to be confirmed after surgery or chemotherapy. The current standard treatment for EOC remains surgery and platinum-based cytotoxic chemotherapy. Generally, OCCC patients receive routine treatment, while the platinum-resistant patients derive little benefit from it but increase morbidity and costs. Clinically useful preoperative prognostic factors for early identification of chemotherapeutic responses are needed to improve clinical outcomes and decrease toxicity in stage IC-IV OCCC.

Albumin, D-dimer and systemic inflammatory response (SIR) markers, such as neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR) and platelets-to-lymphocyte ratio (PLR), are easily available and inexpensive to evaluate before initial treatment. Albumin was considered to be significant prognostic factors for overall survival of ovarian cancer [6]. The plasma D-dimer level, which significantly elevates in patients with OCCC, was associated with the incidence of deep venous thrombosis [7] as well as clinical progression and poor prognosis in malignancies including ovarian cancer [8, 9]. Plenty of studies have shown that elevated NLR is linked to poor prognosis among patients with solid tumors including gynecologic cancers [10, 11], and markers of systemic inflammatory response could provide useful prognostic information of overall survival in patients with OCCC [12, 13].

However, the evidence for the use of biomarkers available preoperatively as predictors of outcome in patients with OCCC receiving chemotherapy is lacking. The purpose of the current study was to determine whether preoperative hematologic biomarkers, such as albumin, D-dimer, carbohydrate antigen 125 (CA125) or SIR markers could play a role in predicting response to chemotherapy and survival outcome.

Materials And Methods

Patients

The study was approved by the institutional review board and the requirement for written informed consent was waived due to its retrospective design. We searched the Electronic Medical Record system to include all the patients who received initial surgery and were diagnosed with OCCC at our institution from 2008 to 2018. The inclusion criteria were listed as follows: 1) A pathology confirmed diagnosis of OCCC; 2) No preoperative treatment, including chemotherapy; 3) No significant past medical histology such as autoimmune diseases; 4) Without any sign of infection.

Early-stage patients received comprehensive staging surgery, while advanced patients underwent debulking surgery. All patients received paclitaxel and carboplatin-based chemotherapy. Platinum resistance was identified as progression within six months after the last platinum treatment, while platinum-refractory was defined as progression during chemotherapy. Overall survival (OS) was calculated as the time interval from initial surgery to death or last contact. Progression-free survival (PFS) was defined as the time interval from initial surgery to the date of first recurrence.

The time interval from blood collection to surgery is usually less than seven days. Preoperative leukocyte differential counts (neutrophils, monocyte, and lymphocyte), platelet, serum albumin, plasma D-dimer and CA-125 were retrospectively abstracted from the medical records. NLR was defined as absolute neutrophil count divided by absolute lymphocyte count, MLR was the ratio of absolute monocyte count and absolute lymphocyte count, and PLR was defined as absolute platelet count divided by absolute lymphocyte count.

Statistical analysis

Descriptive statistics were used in presenting clinicopathological variables. Medians and ranges are reported for continuous variables, while proportions are used for categorical data. The receiver operating characteristic (ROC) curves were used to obtain optimal albumin, D-dimer, CA125 and SIR marks cutoff values for predicting platinum response. Baseline characteristics were compared using Mann-Whitney U test for skewed data. Survival time was estimated using the Kaplan-Meier model, whereas Cox regression was conducted for multivariate analysis. Variables with statistical significance of univariate analysis were included in the multivariate one. All P values reported were two-tailed, and $P<0.05$ was considered statistically significant.

ROC curves and Kaplan-Meier curves were plotted using GraphPad Prism (Version 6.0, GraphPad Software, Inc., La Jolla, CA, USA). All other statistical analyses were performed with Statistical Package for Social Science (SPSS) (Version 20.0, SPSS, Inc., Chicago, IL, USA).

Result

Relations between preoperative hematologic biomarkers and clinicopathologic characteristics

A total of 91 OCCC participants who received initial surgery in our institution were involved and seven were excluded for FIGO IA-IB stage. Eighty-four cases were enrolled in the analysis. The median age of the patients was 52 years (range, 26 to 83 years). 44.0% (37/84) of the patients presented with late-stage tumors (FIGO III+IV). Optimal debulking was

achieved in 91.7% (77/84) patients. Eighty-two cases were available for platinum response assessment, and 2 patients were lost to follow-up during chemotherapy. In terms of chemotherapy response, 29.3% (24/82) patients were classified as platinum-resistant and 70.7% (58/82) as platinum sensitive. The median follow-up time was 28 months (range, 1 to 128 months).

Table 1 shows the median and range for leukocyte differential counts, CA125, albumin, D-dimer and SIR marks by tumor characteristics. Generally, preoperative CA125, albumin, D-dimer and SIR marks were significantly associated with FIGO stage, residual tumor, and platinum response. Neutrophilia, monocytosis, lymphopenia, elevated NLR, MLR, PLR, CA-125 levels, and decreased albumin were associated with advanced-stage disease and suboptimal debulking. The preoperative D-dimer level was not directly linked to the availability of optimal debulking. Elevated CA125, D-dimer, NLR, MLR and low level of albumin were associated with platinum resistance (P<0.05). Interestingly, platelet count was independent of FIGO stage, residual tumor, and platinum resistance. Lymphocyte count was also independent of platinum resistance. Therefore, PLR showed no difference in platinum sensitivity patients and platinum resistance ones (P=0.060).

ROC curves for platinum-based chemotherapy outcome prediction were generated to verify the optimal cut-off point for CA125, albumin, D-dimer and NLR, MLR. The area under the curve (AUC) and the best cut-off values were established by plotting ROC curves (Table 2 and Figure 1). The AUC of them were from the lowest of 0.676 (albumin) to the highest of 0.761(D-dimer). The cut-off value, sensitivity, specificity of albumin to predict platinum resistance were: ≤39.6g/l, 58.3%, and 74.1%. The corresponding values of D-dimer and NLR were: >3.27mg/l, 58.3%, 84.5% and >2.28, 87.5%, 48.3% respectively.

Prognostic factors influencing long-term survival with platinum-based chemotherapy

We found that preoperative CA125, albumin, and D-dimer were significant prognostic indicators for OS and PFS. CA125>135.2U/ml, albumin<39.6g/l and D-dimer>3.27mg/l were associated with shorter PFS and OS (P<0.05). In the univariate analysis, only NLR in SIR marks had prognostic significance for PFS (P=0.007). Multivariate analysis was performed on all these factors to eliminate the confounding effect. On multivariate analysis, patients with D-dimer >3.27 mg/l (P = 0.001 for OS and P = 0.040 for PFS) and albumin <39.6 g/l (P = 0.005 for OS and P = 0.041 for PFS) retained significance, respectively (Table 3 and Figure 2A, B). CA125 was not highly correlated with OS (P = 0.078) and PFS (P = 0.054), while NLR (P = 0.103) was not found to be related to PFS after adjusting for confounding variables.

Then, we further stratified patients into three groups by the cut-off value of albumin (ALB) and D-dimer (D2). The grouping basis is as follows: group 1, ALB-high and D2-low; group 2, ALB-low or D2-high; group 3, ALB-low and D2-high. The survival curves for the three groups are shown in Figure 2C. COX regression analysis showed that the risk of disease progression was 2.766 (95%CI, 1.362~5.615) times and 4.395 (95%CI, 1.906~10.132) times higher in group 2 and group 3 than in group 1. While the risk of death was 4.264 (95%CI, 1.648~11.032) time and 12.029 (95%CI, 4.158~34.796) time, respectively (Figure 3).

Discussion

Inflammation may play an important part in cancer progression. It has been reported that increased neutrophils could promote tumor proliferation, angiogenesis, and invasion [14], while lymphocytes decrease was always considered as immune deficiency [15]. Therefore, the NLR can represent both inflammation and the immune system. A high pretreatment NLR was considered to be an adverse prognostic indicator for both the early and advanced stages of several malignancies [10,16]. Emerging evidence showed that SIR markers, such as NLR, PLR, and MLR, were associated with the prognosis of ovarian cancer patients [17,18]. To date, few reliable preoperative biomarkers which could predict

resistance or prognosis in OCCC have been identified. There are four studies on the effectiveness of SIR markers in OCCC patients in the last five years, as shown in Table 4. Concerning NLR, most of the previous reports suggested that NLR was a prognostic indicator for PFS and/or OS [13,19,20]. There are some conflicting results regarding PLR, with one study suggesting that high PLR was associated with unfavorable outcomes, advanced stage, resistance to primary treatment and decreased survival [19], while others did not. One of the studies found that the lymphocyte-to-monocyte ratio, but not NLR or PLR, was an independent predictor of OS [21].

In the present study, we conducted a comprehensive analysis of blood cells and biochemical indicators, not only SIR markers, which might be related to the survival of OCCC patients. The most interesting finding was that although there was a significant increase in preoperative platelets in OCCC patients, it was not associated with staging, availability of optimal surgery, or platinum resistance. There was likewise no correlation between platinum resistance and preoperative lymphocyte count. So, PLR has nothing to do with resistance, and it is not related to survival which is consistent with most of the relevant studies[12,13,20]. Preoperative NLR level was associated with postoperative indicators such as FIGO stage, residual tumor and platinum resistance which are known prognostic factors in OCCC [5]. The difference was that although univariate analysis showed NLR was significantly associated with PFS, the relation was not supported by multivariate analysis, which means that it is not an independent predictor of survival. This discrepancy might have been due to sample size differences and the different cut-off values used. In the present study, the proportion of patients with advanced-stage and platinum-resistant was the highest, and the NLR cut-off value was determined by whether platinum-sensitive or resistant. The original intention of the design is to address the major obstacle in the treatment of OCCC, which remains the resistance to platinum-based chemotherapy. The finding suggests that a high NLR caused by an increased level of neutrophil, reduce the response to adjuvant chemotherapy. However, its effect on PFS is influenced by additional factors.

By stepwise comparison of prognostic values among the potential markers, we sought to identify the most dominant markers related to chemotherapy resistance and clinical outcomes in IC-IV OCCC. We found that preoperative D-dimer and albumin levels in OCCC patients were significantly correlated with platinum resistance and were independent predictors of PFS and OS. Patients with cancer often underlie a state of hypercoagulation and exaggerated fibrinolysis [22]. D-dimer, as an end-product of fibrinogen, is a signal of the activated coagulation system in numerous cancer types especially in the advanced stage [23,24]. Emerging studies also suggest that a high pre-treatment plasma D-dimer level was recently identified as a poor prognostic factor in EOC [8,25]. Regarding OCCC patients, in which D-dimer levels are generally elevated and are more pronounced than in other EOC patients, much attention has been paid to the relationship between D-dimer and venous thromboembolism [7,26]. The present study reported D-dimer cut-off value of 3.27 is a useful predictor of chemoresistance and can be used as an independent predictor of PFS and OS in clear cell ovarian cancer patients. On the other hand, pretreatment hypoalbuminemia, which is the outcome of malnutrition and cachexia in cancer patients due to the host responses to the tumor, also provides prognostic significance in OCCC [20]. Consistently with previous studies, we found out that hypoalbuminemia (albumin cut-off point of 39.6) acted as an independent predictor of PFS and OS, which is as well as D-dimer. Moreover, as long as either albumin or D-dimer had a cut-off value, the risk of disease progression and death significantly increased. The corresponding risks of patients who reached both the cut-off value were 4 times and 12 times higher than that of those who did not achieve one. Thus, D-dimer and albumin may have an important role in selecting patients for adjuvant anti-cancer therapy. For OCCC patients with a high possibility of platinum resistance, high recurrence rate, and mortality, it is worth discussing whether the early intervention of other anti-tumor therapies such as targeted drugs should be considered.

The present study presents several limitations. Firstly, selection and surveillance biases in our analysis could not be controlled due to the retrospective study design of only 84 samples from a single academic institution. Secondly,

though we excluded patients with any inflammatory condition, some hematologic biomarkers may have been affected by the presence of unrecognized systemic inflammatory diseases. Thirdly, some possible confounders affecting SIR and coagulation function were not assessed.

Conclusion

Elevated levels of preoperative D-dimer and low level of albumin might be the most useful biomarkers of worse response to first-line platinum-based chemotherapy and poor clinical outcomes. Elevated NLR has some predictive value for platinum resistance, but its predictive effect on prognosis needs further large prospective investigation.

Abbreviations

EOC: Epithelial ovarian cancer; OCCC: Ovarian clear cell carcinoma; FIGO: The International Federation of Gynecology and Obstetrics; SIR: Systemic inflammatory response; NLR: neutrophil-to-lymphocyte ratio; MLR monocyte-to-lymphocyte ratio CA125: Carbohydrate antigen 125; PLR platelets to lymphocyte ratio ROC: Receiver operating characteristic; PFS: Progression-free survival; OS: Overall survival; AUC: Area under the curve; CI: Confidence Interval;

Declarations

Ethics approval and consent to participate:

The study was approved by the Fudan University Shanghai Cancer Center review board and the requirement for written informed consent was waived due to its retrospective design.

Consent for publication:

Not applicable.

Availability of data and material:

The dataset supporting the conclusions of this article is available upon request. Please contact Dr. Shuang Ye (mendy_ye@126.com).

Competing interests:

The authors declare that they have no competing interests.

Funding:

The study was supported by grants from National Natural Science Foundation of China (81702558) and Fudan University Shanghai Cancer Center (YJ201603). The funding bodies didn't participate in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

Authors' contributions:

All the authors contributed to the contraception and design of the study.

Data curation: Shuang Ye, Wei Chen

Formal analysis: Wei Chen, Siyuan Zhong, Boer Shan

Funding acquisition: Shuang Ye

Investigation: Shuang Ye, Wei Chen, Shuling Zhou, Boer Shan, Xiaohua Wu, Huijuan Yang

Methodology: Boer Shan, Xiaohua Wu, Huijuan Yang

Project administration: Shuang Ye, Wei Chen, Siyuan Zhong, Boer Shan

Resources: Shuang Ye, Shuling Zhou, Siyuan Zhong, Boer Shan, Xiaohua Wu, Huijuan Yang

Software: Shuang Ye, Wei Chen

Supervision: Shuang Ye, Xiaohua Wu, Huijuan Yang

Validation: Shuang Ye, Wei Chen, Siyuan Zhong, Boer Shan Shuling Zhou

Visualization: Xiaohua Wu, Huijuan Yang

Roles/Writing - original draft: Wei Chen

Writing - review & editing: Shuang Ye, Xiaohua Wu, Huijuan Yang

All authors read and approved the final manuscript.

Acknowledgments:

Not applicable

References

[1] Siegel RL, Miller KD and Jemal A. Cancer statistics, 2018. CA Cancer J Clin. 2018;68:7-30.

[2] Anglesio MS, Carey MS, Köbel M, et al. Clear cell carcinoma of the ovary: a report from the first Ovarian Clear Cell Symposium, June 24th, 2010. Gynecologic oncology. 2011;121:407-415.

[3] Glasspool RMand McNeish IA. Clear cell carcinoma of ovary and uterus. Curr Oncol Rep. 2013;15:566-572.

[4] del Carmen MG, Birrer Mand Schorge JO. Clear cell carcinoma of the ovary: a review of the literature. Gynecologic oncology. 2012;126:481-490.

[5] Bennett JA, Dong F, Young RH, et al. Clear cell carcinoma of the ovary: evaluation of prognostic parameters based on a clinicopathological analysis of 100 cases. Histopathology. 2015;66:808-815.

[6] Clark TG, Stewart ME, Altman DG, et al. A prognostic model for ovarian cancer. British journal of cancer. 2001;85:944-952.

[7] Ebina Y, Uchiyama M, Imafuku H, et al. Risk factors for deep venous thrombosis in women with ovarian cancer. Medicine. 2018;97:e11009.

[8] Liu P, Wang Y, Tong L, et al. Elevated preoperative plasma D-dimer level is a useful predictor of chemoresistance and poor disease outcome for serous ovarian cancer patients. Cancer chemotherapy and pharmacology. 2015;76:1163-1171.

[9] Wu J, Fu Z, Liu G, et al. Clinical significance of plasma D-dimer in ovarian cancer: A meta-analysis. Medicine. 2017;96:e7062.

[10] Templeton AJ, McNamara MG, Šeruga B, et al. Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. J Natl Cancer Inst. 2014;106:dju124.

[11] Ethier JL, Desautels DN, Templeton AJ, et al. Is the neutrophil-to-lymphocyte ratio prognostic of survival outcomes in gynecologic cancers? A systematic review and meta-analysis. Gynecol Oncol. 2017;145:584-594.

[12] Kwon BS, Jeong DH, Byun JM, et al. Prognostic value of preoperative lymphocyte-monocyte ratio in patients with ovarian clear cell carcinoma. Journal of Cancer. 2018;9:1127-1134.

[13] Yoshida K, Yoshikawa N, Shirakawa A, et al. Prognostic value of neutrophil-to-lymphocyte ratio in early-stage ovarian clear-cell carcinoma. Journal of gynecologic oncology. 2019;30:e85.

[14] Ocana A, Nieto-Jiménez C, Pandiella A, et al. Neutrophils in cancer: prognostic role and therapeutic strategies. Mol Cancer. 2017;16:137.

[15] Dunn GP, Old LJ and Schreiber RD. The immunobiology of cancer immunosurveillance and immunoediting. Immunity. 2004;21:137-148.

[16] Mei Z, Shi L, Wang B, et al. Prognostic role of pretreatment blood neutrophil-to-lymphocyte ratio in advanced cancer survivors: A systematic review and meta-analysis of 66 cohort studies. Cancer Treat Rev. 2017;58:1-13.

[17] Zhao Z, Zhao X, Lu J, et al. Prognostic roles of neutrophil to lymphocyte ratio and platelet to lymphocyte ratio in ovarian cancer: a meta-analysis of retrospective studies. Archives of gynecology and obstetrics. 2018;297:849-857.

[18] Yang Z, Gu JH, Guo CS, et al. Preoperative neutrophil-to-lymphocyte ratio is a predictor of survival of epithelial ovarian cancer: a systematic review and meta-analysis of observational studies. Oncotarget. 2017;8:46414-46424.

[19] Kim HS, Choi H-Y, Lee M, et al. Systemic Inflammatory Response Markers and CA-125 Levels in Ovarian Clear Cell Carcinoma: A Two Center Cohort Study. Cancer research and treatment: official journal of Korean Cancer Association. 2016;48:250-258.

[20] Zhang H, Lu J, Lu Y, et al. Prognostic significance and predictors of the system inflammation score in ovarian clear cell carcinoma. PloS one. 2017;12:e0177520.

[21] Sierzega M, Lenart M, Rutkowska M, et al. Preoperative Neutrophil-Lymphocyte and Lymphocyte-Monocyte Ratios Reflect Immune Cell Population Rearrangement in Resectable Pancreatic Cancer. Ann Surg Oncol. 2017;24:808-815.

[22] Lin Y, Liu Z, Qiu Y, et al. Clinical significance of plasma D-dimer and fibrinogen in digestive cancer: A systematic review and meta-analysis. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology. 2018;44:1494-1503.

[23] Zhu LR, Li J, Chen P, et al. Clinical significance of plasma fibrinogen and D-dimer in predicting the chemotherapy efficacy and prognosis for small cell lung cancer patients. Clinical & translational oncology : official publication of the Federation of Spanish Oncology Societies and of the National Cancer Institute of Mexico. 2016;18:178-188.

[24] Li H, Zhao S, Jing Z, et al. Combination of D-dimer and carcinoembryonic antigen levels as a predictive and prognostic biomarker in advanced colorectal cancer patients. Journal of cellular biochemistry. 2018.

[25] Yamada Y, Kawaguchi R, Iwai K, et al. Preoperative plasma D-dimer level is a useful prognostic marker in ovarian cancer. Journal of obstetrics and gynaecology : the journal of the Institute of Obstetrics and Gynaecology. 2020;40:102-106.

[26] Uno K, Homma S, Satoh T, et al. Tissue factor expression as a possible determinant of thromboembolism in ovarian cancer. British journal of cancer. 2007;96:290-295.

Tables

Table 1. Patient characteristics in relation to preoperative blood parameters and SIR marks.

Characteristic	N[a] (%)	CA125[b] (U/ml)	Albumin[b] (g/l)	Leukocyte differential counts [b] (k/μl)			Platelet [b](k/μl)	D-dimer [b](mg/l)	Ratio [b]		
				Lymphocyte	Monocyte	Neutrophil			NLR	MLR	PLR
All cases	84	187.9 (6.5-5000*)	40.7 (25.9-52.1)	1.5 (0.4-2.9)	0.4 (0.03-1.6)	4.1 (1.9-15.2)	299 (124-608)	1.66 (0.19-55.20)	2.7 (1.1-20.3)	0.28 (0.03-2.00)	193.9 (77.5-955.0)
Age (years)											
≤52	42 (50)	188.0 (6.5-2854)	40.7 (33.1-49.4)	1.5 (0.6-2.9)	0.4 (0.2-1.0)	4.0 (1.9-12.2)	301 (124-500)	1.66 (0.19-55.20)	2.6 (1.1-20.3)	0.25 (0.12-0.83)	201.7 (77.5-615.0)
>52	42 (50)	165.0 (11.1-5000*)	40.4 (25.9-52.1)	1.5 (0.4-2.4)	0.4 (0.03-1.6)	4.4 (1.9-15.2)	296 (147-608)	1.66 (0.20-20.00)	2.8 (1.1-20.3)	0.32 (0.03-2.00)	191.0 (92.1-955.0)
P value		0.589	0.056	0.874	**0.039**	0.826	0.871	0.756	0.826	0.053	0.940
FIGO stage											
IC-II	47 (56.0)	70.5 (6.5-1930.0)	43.6 (29.6-52.1)	1.5 (0.9-2.9))	0.4 (0.03-1.0)	3.6 (1.9-10.7)	292 (124-500)	1.49 (0.19-55.20)	2.2 (1.1-7.1)	0.21 (0.03-0.67)	167.5 (77.5-500.0)
III-IV	37 (44.0)	276.9 (45.6-5000*)	39.2 (25.9-49.2)	1.4 (0.4-2.4)	0.4 (0.3-1.6)	4.6 (1.9-15.2)	311 (147-608)	2.61 (0.69-11.03)	3.2 (1.1-20.3)	0.33 (0.18-2.00)	230.0 (101.7-955.0)
P value		**<0.001**	**<0.001**	**0.031**	**0.002**	**0.009**	0.320	**0.001**	**0.001**	**<0.001**	**0.006**
Residual tumor (cm)											
0	63 (75.0)	157.4 (6.5-5000*)	41.7 (28.3-52.1)	1.5 (0.6-2.9)	0.4 (0.03-1.6)	3.8 (1.9-15.2))	292 (124-608)	1.66 (0.19-55.20)	2.4 (1.1-7.1)	0.25 (0.03-0.70)	173.5 (77.5-500)
≤1	14 (16.7)	371.4 (45.6-1845.3)	38.4 (29.0-43.7)	1.4 (0.9-2.4)	0.5 (0.3-0.9)	4.7 (2.7-6.6)	318 (202-593)	2.53 (0.69-9.30)	3.2 (1.3-5.7)	0.35 (0.19-0.82)	219.8 (107.1-539.1)
>1	7 (8.3)	475.1 (151.6-1866.0)	33.2 (25.9-49.2)	0.9 (0.4-1.8)	0.6 (0.3-1.4)	8.1 (2.7-12.2)	342 (253-382)	3.29 (0.75-6.06)	8.2 (2.8-20.3)	0.67 (0.39-2.00)	383.3 (190.0-955.0)
P value		**0.007**	**0.006**	**0.008**	**0.002**	**0.005**	0.314	0.064	**<0.001**	**<0.001**	**0.004**
Platinum response											
Sensitive	58 (69.0)	124.6 (6.47-5000*)	41.7 (29.0-52.1)	1.5 (0.6-2.9)	0.4 (0.03-1.0)	3.8 (1.9-10.7)	279 (124-500)	1.66 (0.19-20.00)	2.4 (1.1-7.1)	0.25 (0.03-0.70)	176.7 (77.5-500.0)
resistant	24 (28.6)	294.3 (38.21-1866.0)	39.2 (25.9-49.2)	1.5 (0.4-2.4)	0.5 (0.2-1.6)	4.9 (2.1-15.2)	316 (202-608)	3.82 (0.44-55.20)	3.2 (1.1-20.3)	0.35 (0.15-2.00)	214.3 (126.3-955.0)
P value		**0.002**	**0.012**	0.400	**0.011**	**0.003**	0.157	**<0.001**	**0.002**	**0.004**	0.060

Abbreviations: SIR, systemic inflammatory response. NLR, neutrophil to lymphocyte ratio; MLR, monocyte to lymphocyte ratio; PLR, platelet to lymphocyte ratio.

[a] Categorical data are shown in absolute value and proportion.

[b] Continuous variables are represented by median and range.

* The upper limit of CA125 detection is 5000.

P values with statistical significance were denoted.

Table 2. Predictive values of preoperative blood parameters and NLR, MLR for determination of platinum resistance.

Variables	AUC	*P*	95% CI	Cut-off value	Se%	Sp%	PPV%	NPV%
MLR	0.701	**0.004**	0.577-0.825	0.3	62.5	70.7	46.9	82.0
NLR	0.710	**0.003**	0.589-0.832	2.28	87.5	48.3	41.2	90.3
ALB	0.676	**0.013**	0.547-0.804	39.6	58.3	74.1	81.1	48.3
CA125	0.713	**0.003**	0.601-0.825	135.15	91.7	51.7	44.0	93.8
D2	0.761	**<0.001**	0.646-0.876	3.27	58.3	84.5	60.9	83.1

Abbreviations: MLR, monocyte to lymphocyte ratio; NLR, neutrophil to lymphocyte ratio; ALB, albumin; CA125, carbohydrate antigen 125; D2, D-dimer; AUC, area under the curve; CI, confidence interval; Se, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value;
P values with statistical significance were denoted.

Table 3. Univariate and multivariate cox proportional analysis regarding overall survival and progression free survival.

Variables	OS						PFS					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
MLR ≤0.30 vs. >0.30	/	/	0.061	/	/	0.882	/	/	0.079	/	/	0.943
NLR ≤2.28 vs. >2.28	/	/	0.121	/	/	0.854	2.767	1.320-5.800	**0.007**	/	/	0.103
CA125 ≤135.2 vs. >135.2	3.828	1.468-9.983	**0.006**	/	/	0.074	2.665	1.306-5.436	**0.007**	2.057	0.989-4.282	0.054
ALB ≤39.6 vs. >39.6	0.279	0.134-0.584	**0.001**	0.345	0.163-0.731	**0.005**	0.404	0.220-0.743	**0.004**	0.521	0.279-0.973	**0.041**
D2 ≤3.27 vs. >3.27	5.118	2.273-11.520	**<0.001**	4.092	1.809-9.254	**0.001**	2.552	1.365-4.773	**0.003**	1.959	1.032-3.717	**0.040**

Abbreviations: PFS, progression-free survival; OS, overall survival; MLR, monocyte to lymphocyte ratio; NLR, neutrophil to lymphocyte ratio; ALB, albumin; CA125, carbohydrate antigen 125; D2, D-dimer; HR: hazard ratio; CI, confidence interval.
P values with statistical significance were denoted.

Table 4. Summary of studies examining SIR as prognostic factors in OCCC patients.

	Kim 2016 [19]	Zhang 2017 [20]	Kwon 2018 [12]	Yoshida 2019 [13]	The present study
Sample size	109	155	109	83	84
Advanced-stage %	37.5	29	41.3	0	44
platinum resistance %	18.3	12.9	22	NA	28.6
Prognostic factor for PFS	NLR, PLR	NLR	None	None	None
Prognostic factor for OS	None	NLR	LMR	NLR	None
Cut-off value	4.44 for resistance 2.8 for survival	NA	NA	3.26 for OS	2.28 for resistance

Abbreviations: SIR, Systemic inflammatory response. NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; LMR, lymphocyte to monocyte ratio; PFS, progression-free survival; OS, overall survival; NA, not available.

Figures

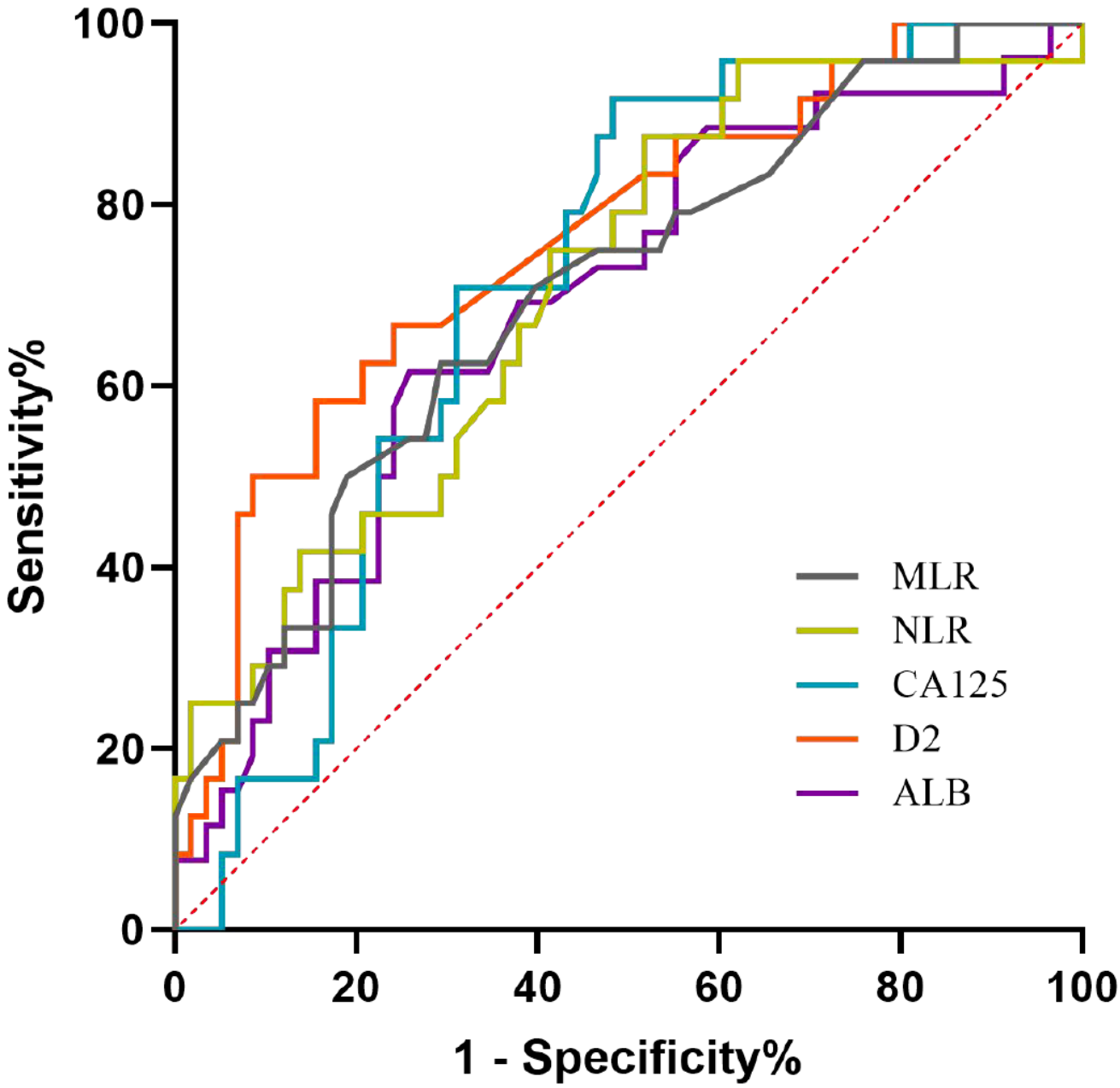

Figure 1

Receiver operating characteristic curve demonstrating the AUC of preoperative MLR, NLR, CA125, D2, and ALB for platinum resistance. (Abbreviations: AUC, area under the curve; MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil to lymphocyte ratio; CA125, carbohydrate antigen 125; D2, D-dimer; ALB, albumin.)

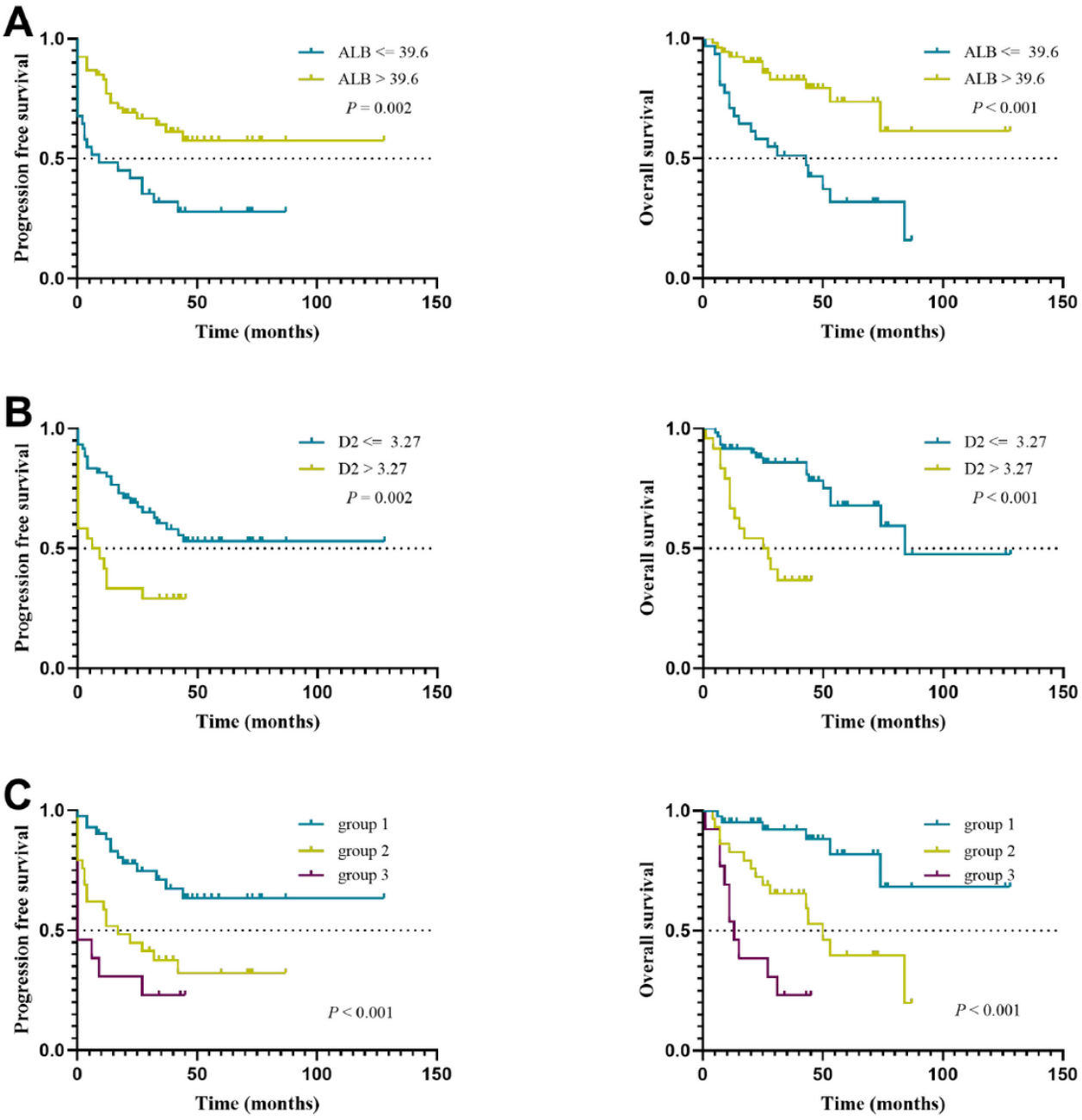

Figure 2

Kaplan-Meier curves showing PFS and OS stratified by preoperative ALB (A), D2 (B), and groups combining ALB and D2 (C). Group 1, ALB-high and D2-low; group 2, ALB-low or D2-high; group 3, ALB-low and D2-high. The p-values were calculated by log-rank test. (Abbreviations: ALB, albumin; D2, D-dimer; PFS, progression-free survival; OS, overall survival.)

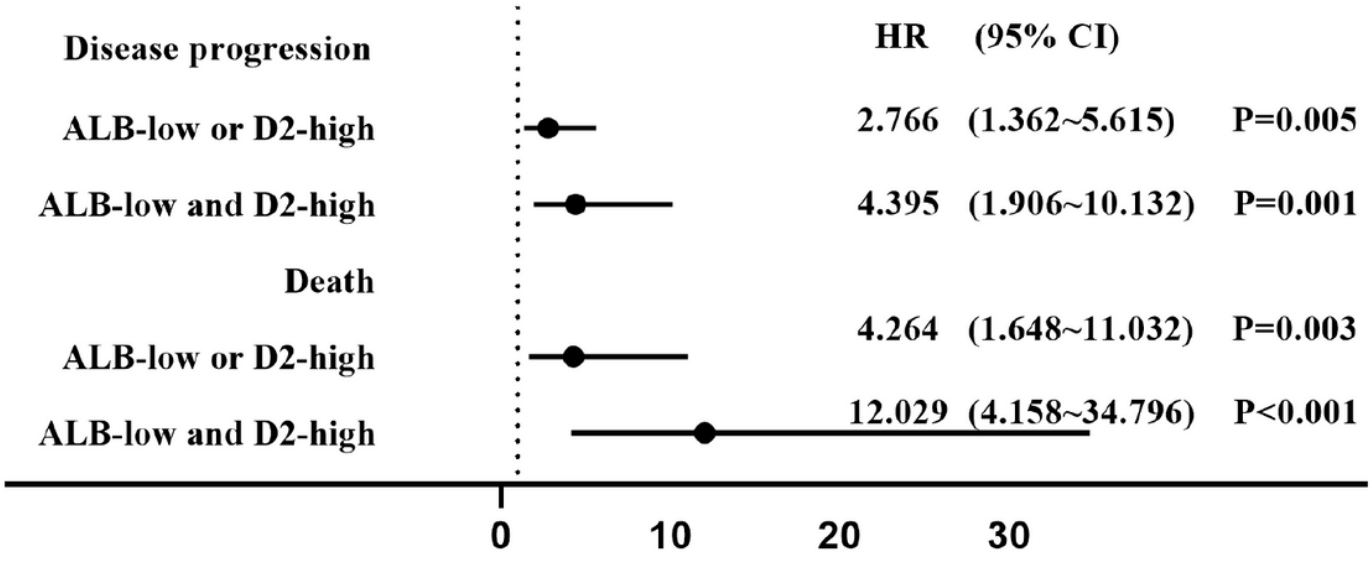

Figure 3

The risk of disease progression and death compared to ALB-high and D2-low. (Abbreviations: ALB, albumin; D2, D-dimer.)