



Predictive value of the systemic immune-inflammation index for the efficacy of neoadjuvant chemotherapy and prognosis in patients with stage III ovarian cancer—a retrospective cohort study

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Background: The systemic immune-inflammation index (SII) has been proven to be related to the prognoses of multiple malignant tumors. However, there are still few studies on the relationship between the SII and the effect of neoadjuvant chemotherapy in patients with ovarian cancer. It is of great significance to predict the efficacy of neoadjuvant chemotherapy in patients with ovarian cancer. Our study was aimed at determining the predictive value of the SII for the efficacy of neoadjuvant chemotherapy and prognosis in patients with stage III ovarian cancer.

Methods: A total of 102 patients with stage III ovarian cancer treated in Tongji Hospital of Tongji University from January 2017 to January 2019 were retrospectively collected. According to the level of the SII before neoadjuvant chemotherapy, patients were divided into the high SII group and low SII group. We compared the effect of neoadjuvant chemotherapy between the 2 groups, and observed the progression-free survival and mortality of patients in the 2 groups after 3 years follow-up.

Results: Compared with patients in the low SII group, the complete response rate of patients in the high SII group decreased significantly after neoadjuvant chemotherapy (13.73% *vs.* 45.10%, $P=0.001$), and the progressive disease rate increased (19.61% *vs.* 1.96%, $P=0.011$). The SII had certain value in predicting the inefficacy of neoadjuvant chemotherapy in patients with stage III ovarian cancer, and the area under the curve was 0.655 (95% CI: 0.548–0.762, $P=0.007$). The progression-free survival of patients in the high SII group was shorter than that of patients in the low SII group ($P<0.001$), and the overall survival rate of patients in the high SII group was lower (47.06% *vs.* 70.59%, $P=0.016$). The SII had predicting value for the postoperative death of ovarian cancer patients after neoadjuvant chemotherapy, and the area under the curve was 0.646 (95% CI: 0.537–0.756, $P=0.012$). Multivariate regression analysis showed that higher SII was a risk factor for death in ovarian cancer patients after neoadjuvant chemotherapy (OR: 2.700, $P=0.017$).

Conclusions: A high SII was a predictor of inefficacy of neoadjuvant chemotherapy in patients with stage III ovarian cancer and was related to poor prognosis.

Keywords: Systemic immune-inflammation index; ovarian cancer; neoadjuvant chemotherapy; efficacy

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Introduction

Ovarian cancer is a common malignant tumor of the reproductive system in women. It was reported that the incidence rate of ovarian cancer was 3.6/100,000 to 9.7/100,000, and the 1-, 3-, and 5-year survival rates after diagnosis were 79.7%, 69.7%, and 61.4% respectively (1). Because early ovarian cancer cannot be detected by clinical symptoms, some patients have locally advanced disease at the first diagnosis. Stage III ovarian cancer is defined as a disease with abdominal cavity or retroperitoneal lymph nodes metastasis and liver surface metastasis accompanied by a poor prognosis. Hence, reducing the mortality of these patients is key to reducing the overall mortality of ovarian cancer patients. At present, patients with stage III ovarian cancer are often treated with neoadjuvant chemotherapy combined with interval debulking surgery (2-4). Chemotherapy has a significant curative effect on multiple malignant tumors (5,6), and patients who achieve complete response after neoadjuvant chemotherapy have better outcomes. Therefore, it is of great importance to predict the effectiveness of neoadjuvant chemotherapy in patients with ovarian cancer. CA125 is a common biomarker in patients with ovarian cancer, which is of certain significance in diagnosis and prognosis. However, recent research showed that there was no significant correlation between CA125 and the efficacy of neoadjuvant chemotherapy in patients with ovarian cancer (7), necessitating the identification of biomarkers to predict the efficacy of neoadjuvant chemotherapy in ovarian cancer. The systemic immune-inflammation index (SII), reflecting the immune and inflammatory status of patients with malignant tumors, has been used in the diagnosis and treatment of a variety of malignant tumors and has been found to be related to the prognosis of patients (8-10). Studies also confirmed that a high SII was associated with shortened progression-free survival and increased mortality in patients with ovarian cancer (11). The SII is a predictor of the efficacy of neoadjuvant chemotherapy in patients with gastric cancer, cervical cancer, and breast cancer (12-17). However, there are no studies on the correlation between the SII and the efficacy of neoadjuvant chemotherapy in patients with ovarian cancer. The purpose of our study was to explore the predictive value of the SII for the efficacy of neoadjuvant chemotherapy in patients with stage III ovarian cancer. We present the following article in accordance with the STARD reporting checklist (available at <https://gs.amegroups.com/article/view/10.21037/gs-22-459/rc>).

Methods

General information

A total of 102 patients with stage III ovarian cancer treated in Tongji Hospital of Tongji University from January 2017 to January 2019 were retrospectively collected (a retrospective cohort study). According to the level of the SII before neoadjuvant chemotherapy, patients were divided into the high SII group and low SII group. The inclusion criteria were as follows: (I) stage III epithelial ovarian cancer; (II) 18 to 75 years old; (III) patients received neoadjuvant chemotherapy with interval debulking surgery; (IV) Karnofsky performance status score ≥ 70 ; (V) patients with completed clinical materials; (VI) patients with measurable target lesions which could evaluate the efficacy of neoadjuvant chemotherapy. The exclusion criteria were as follows: (I) combined with other malignant tumors; (II) liver, kidney, heart, brain, lung, or other organ dysfunction; (III) metastatic ovarian cancer or postoperative recurrence of ovarian cancer; (IV) patients who received other special treatment, such as immunotherapy, anti-angiogenesis agents; (V) patients who dropped out during follow-up. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the ethics committee of Tongji Hospital of Tongji University (No. 2022-05-04-012). Individual consent for this retrospective analysis was waived.

Study variables

- (I) The Response Evaluation Criteria in Solid Tumors (RECIST 1.1): The efficacy of neoadjuvant chemotherapy was evaluated by RECIST 1.1, and was divided into complete response, partial response, stable disease, and progressive disease. Complete response was defined as the disappearance of all target lesions, and the short diameter of lymph nodes was < 10 mm pathologically. Partial response was defined as the total length of all target lesions decreasing by at least 30% compared with the baseline level. Stable disease was defined as the efficacy of neoadjuvant chemotherapy between partial response and progressive disease. Progressive disease was diagnosed when the total length of all target lesions increased by at least 20% compared with the baseline level and the absolute value increased by at least 5 mm, or new lesions appeared.

- (II) Classification of neoadjuvant chemotherapy efficacy. Efficacy included complete response and partial response, while ineffectiveness included stable disease and progressive disease.
- (III) Progression-free survival. After neoadjuvant chemotherapy, interval debulking surgery was performed. The time from the operation to tumor progression, recurrence, metastasis, or death was defined as progression-free survival.
- (IV) The rate of 3-year overall survival. All patients were followed up for 3 years after the operation, and the overall survival rate was observed.
- (V) Age, ascites, menopause status, serum CA125, histological grade, and Federation International of Gynecology and Obstetrics (FIGO) stage were also studied.

Therapeutic strategy

All patients received neoadjuvant chemotherapy with platinum and paclitaxel after admission every 21 days. After 6 cycles of treatment, interval debulking surgery was performed, and adjuvant chemotherapy was subsequently administered.

Statistical analysis

All statistical analyses were performed using SPSS 26.0. A two-tailed $P < 0.05$ was considered statistically significant. Measurement data were expressed as mean \pm standard deviation. The independent samples t -test was applied for the comparison of measurement data between 2 groups, and the Kruskal-Wallis test was used for multiple group comparisons. Enumeration data expressed as n (%) was analyzed by the Pearson χ^2 test in the comparison of measurement data between 2 groups. Kaplan-Meier analysis was performed to evaluate progression-free survival for the 2 groups. A receiver operating characteristic (ROC) curve was used to analyze the predictive value of the SII and CA125 for postoperative death in ovarian cancer patients. We used multivariate regression analysis to explore the risk factors of death after neoadjuvant chemotherapy in patients with ovarian cancer.

Results

Comparison of general information between the low SII group and high SII group

There was no significant difference between the 2 groups

in terms of age, menopause status, FIGO stage, histological grade, and ascites ($P > 0.05$). Compared with the low SII group, the serum CA125 level in the high SII group was significantly higher (914.84 ± 391.64 vs. 756.39 ± 396.21 U/mL, $P = 0.045$) and the SII level increased as well when compared with that of the low SII group (872.78 ± 191.55 vs. 457.87 ± 116.66 , $P < 0.001$) (Table 1).

Correlation between the SII and neoadjuvant chemotherapy efficacy

Compared with patients in the low SII group, the complete response rate of patients in the high SII group decreased significantly after neoadjuvant chemotherapy (13.73% vs. 45.10%, $P = 0.001$), and the progressive disease rate increased (19.61% vs. 1.96%, $P = 0.011$) (Table 2). Patients who achieved complete response after neoadjuvant chemotherapy had a lower SII, while patients with progressive disease had a higher SII ($P = 0.003$) (Figure 1). The SII had certain value in predicting the inefficacy of neoadjuvant chemotherapy in patients with stage III ovarian cancer, and the area under the curve was 0.655 (95% CI: 0.548–0.762, $P = 0.007$) (Figure 2).

Correlation between the SII and progression-free survival in stage III ovarian cancer patients after neoadjuvant chemotherapy

The progression-free survival of patients in the high SII group was shorter than that of patients in the low SII group ($P < 0.001$) (Figure 3).

Correlation between the SII and 3-year overall survival in stage III ovarian cancer patients after neoadjuvant chemotherapy

The overall survival rate of patients in the high SII group was lower than that of patients in the low SII group (47.06% vs. 70.59%, $P = 0.016$). The SII had diagnostic value for the postoperative death of ovarian cancer patients after neoadjuvant chemotherapy, and the area under the curve was 0.646 (95% CI: 0.537–0.756, $P = 0.012$). CA125 had no significant predictive value for the postoperative death of ovarian cancer patients after neoadjuvant chemotherapy ($P = 0.671$) (Table 3 and Figure 4). Compared with patients who survived for 3 years after the operation, the SII of patients who died within 3 years after the operation was significantly higher (739.75 ± 269.44 vs. 613.22 ± 244.70 ,

Table 1 Comparison of the general information of the 2 groups

Characteristics	High SII group (n=51)	Low SII group (n=51)	t/ χ^2	P value
Age (years) (mean \pm SD)	56.25 \pm 10.93	57.25 \pm 10.37	0.474	0.637
Menopause, n (%)			0.671	0.413
Yes	30 (58.82)	34 (66.67)		
No	21 (41.18)	17 (33.33)		
FIGO stage, n (%)			3.904	0.142
IIIA	21 (41.18)	12 (23.53)		
IIIB	15 (29.41)	22 (43.14)		
IIIC	15 (29.41)	17 (33.33)		
Histological grade, n (%)			0.039	0.843
Moderately and poorly	26 (50.98)	27 (52.94)		
Differentiated, n (%)				
Well-differentiated	25 (49.02)	24 (47.06)		
Ascites, n (%)			1.325	0.250
Yes	42 (82.35)	46 (90.20)		
No	9 (17.65)	5 (9.80)		
CA125 (U/mL) (mean \pm SD)	914.84 \pm 391.64	756.39 \pm 396.21	2.031	0.045
SII level (mean \pm SD)	872.78 \pm 191.55	457.87 \pm 116.66	13.212	<0.001

SII, systemic immune-inflammation index; FIGO, Federation International of Gynecology and Obstetrics.

Table 2 Correlation between the SII and neoadjuvant chemotherapy efficacy

Neoadjuvant chemotherapy efficacy	High SII group (n=51)	Low SII group (n=51)	χ^2	P value
Complete response, n (%)	7 (13.73)	23 (45.10)	16.769	0.001
Partial response, n (%)	15 (29.41)	11 (21.57)	–	–
Stable disease, n (%)	19 (37.25)	16 (31.37)	–	–
Progressive disease, n (%)	10 (19.61)	1 (1.96)	6.521	0.011

SII, systemic immune-inflammation index.

P=0.015) (*Figure 5*). Multivariate regression analysis showed that higher SII was a risk factor for death in ovarian cancer patients after neoadjuvant chemotherapy (OR: 2.700, P=0.017).

Correlation between neoadjuvant chemotherapy efficacy and progression-free survival

The progression-free survival of patients who achieved complete response after neoadjuvant chemotherapy tended to be longer, but the difference did not reach statistical

significance (P=0.302) (*Figure 6*).

Discussion

There are still few studies exploring the relationship between the SII and the efficacy of neoadjuvant chemotherapy in patients with ovarian cancer. We illustrated the correlation between the SII and the efficacy of neoadjuvant chemotherapy, progression-free survival, and overall survival in patients with ovarian cancer. The results showed that a high SII was associated with inefficacy

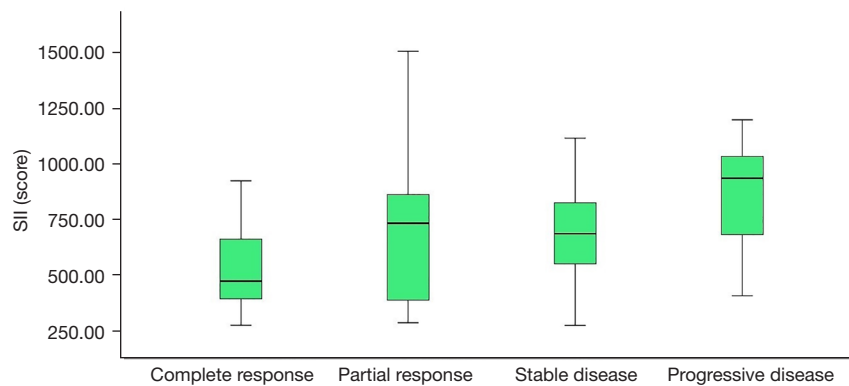


Figure 1 Correlation between the SII and neoadjuvant chemotherapy efficacy. SII, systemic immune-inflammation index.

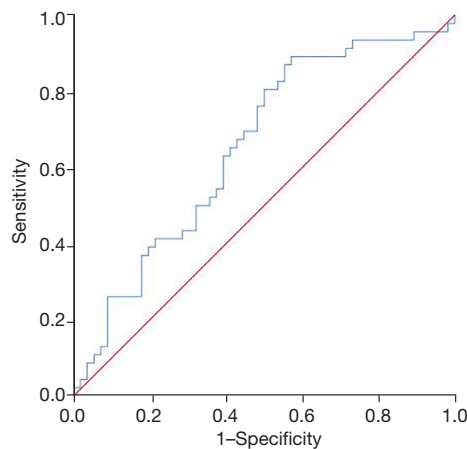


Figure 2 Diagnostic value of the SII for predicting neoadjuvant chemotherapy inefficacy in patients with stage III ovarian cancer. SII, systemic immune-inflammation index.

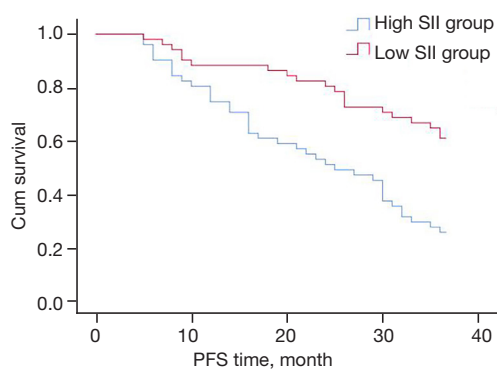


Figure 3 Correlation between the SII and progression-free survival in stage III ovarian cancer patients after neoadjuvant chemotherapy. SII, systemic immune-inflammation index; PFS, progression-free survival.

of neoadjuvant chemotherapy, shortened progression-free survival, and reduced overall survival in patients with ovarian cancer.

Ovarian cancer patients with advanced disease at the first diagnosis often have a poor prognosis. These patients often received neoadjuvant chemotherapy, which can help patients achieve better outcomes. However, some patients have a poor response to neoadjuvant chemotherapy, and even develop progressive disease. These patients then have to undergo intensive treatment. Therefore, it is of great significance to predict the efficacy of neoadjuvant chemotherapy in patients with ovarian cancer before neoadjuvant chemotherapy. Due to the unremarkable value of CA125 in predicting the efficacy of neoadjuvant chemotherapy in patients with ovarian cancer, there are studies on seeking new biomarkers for predicting the efficacy of neoadjuvant chemotherapy in patients with ovarian cancer. Studies showed that the ratio of neutrophils to lymphocytes had a certain value in predicting the efficacy of neoadjuvant chemotherapy in patients with ovarian cancer. Patients with an increased ratio of neutrophils to lymphocytes tended to have a poorer response to neoadjuvant chemotherapy and poor prognosis (18-20). A high ratio of neutrophils to lymphocytes indicates that the level of systemic inflammation is increasing, and the number of lymphocytes killing tumor cells is decreasing. A high level of systemic inflammation can promote the proliferation and metastasis of tumor cells, leading to poor prognosis. Lymphocytes are powerful immune cells that kill tumor cells. A decreased level of lymphocytes indicates that the ability of the body to kill tumor cells is reduced. Recently, the concept of the SII has been proposed, which comprehensively takes the influence of platelets

Table 3 Predictive value of the SII and CA125 for postoperative death in stage III ovarian cancer patients after neoadjuvant chemotherapy

Test result variable(s)	Area	Std. Error	P value	95% confidence interval	
				Lower bound	Upper bound
SII	0.646	0.056	0.012	0.537	0.756
CA125	0.525	0.058	0.671	0.410	0.639

SII, systemic immune-inflammation index.

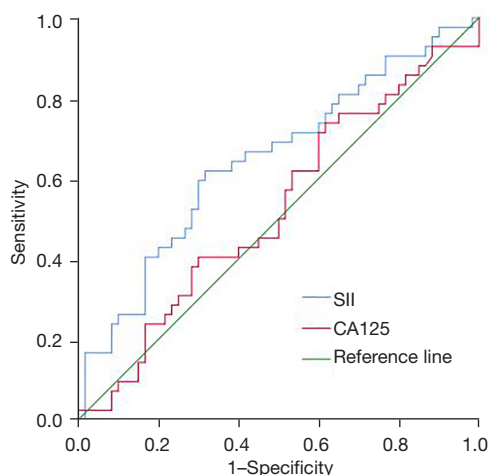


Figure 4 Predictive value of the SII and CA125 for postoperative death in stage III ovarian cancer patients after neoadjuvant chemotherapy. SII, systemic immune-inflammation index.

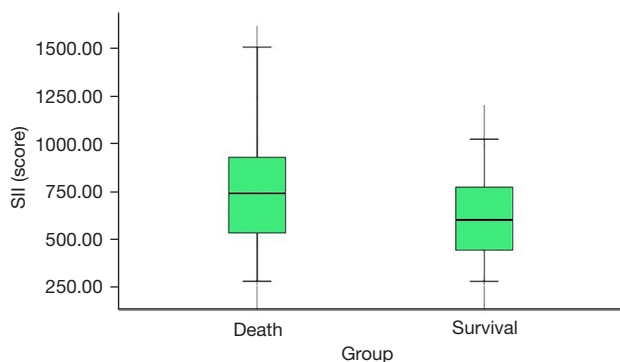


Figure 5 Preoperative SII level comparison between the death group and survival group. SII, systemic immune-inflammation index.

into consideration based on the ratio of neutrophils to lymphocytes. Platelets are small pieces of cytoplasm that detach from the cytoplasm of mature megakaryocytes in

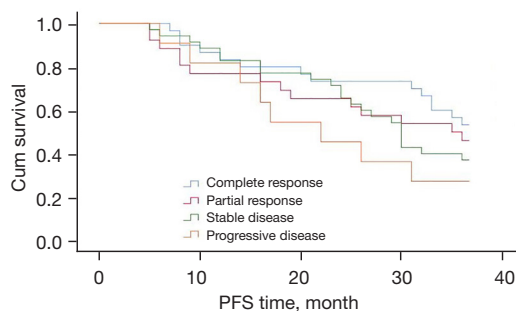


Figure 6 Correlation between neoadjuvant chemotherapy efficacy and progression-free survival. PFS, progression-free survival.

bone marrow, and participate in tumor growth, tumor cell extravasation, tumor metastasis, which can inhibit tumor cell apoptosis and maintain the integrity of tumor blood vessels (21-23). Previous studies showed that the progression-free survival and overall survival of ovarian cancer patients with a high SII (>612) were shortened, and a high level of SII was an independent factor resulting in poor prognosis (11). These results support our study. Our results showed that ovarian cancer patients with an increased SII had shorter progression-free survival and a lower 3-year overall survival rate. In addition, the SII level was related to the efficacy of neoadjuvant chemotherapy in patients with stage III ovarian cancer, which was of certain value in predicting the efficacy of neoadjuvant chemotherapy. This suggests that for patients with a high SII, neoadjuvant chemotherapy may need to be further adjusted to improve efficacy and ultimately achieve a better prognosis of ovarian cancer patients.

Limitations

This study was a retrospective clinical study. Only stage III ovarian cancer patients were included, so the sample size was relatively small. This was the deficiency of our study.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at <https://gs.amegroups.com/article/view/10.21037/gS-22-459/rc>

Data Sharing Statement: Available at <https://gs.amegroups.com/article/view/10.21037/gS-22-459/dss>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://gs.amegroups.com/article/view/10.21037/gS-22-459/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the ethics committee of Tongji Hospital of Tongji University (No. 2022-05-04-012). Individual consent for this retrospective analysis was waived.

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