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ORIGINAL ARTICLE

Evaluation of Prognostic and Predictive Values of Hemogram Parameters in Patients with Advanced Stage Ovarian Carcinoma

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OBJECTIVE
The aim of the present study was to evaluate the impact of conventional hemogram parameters as a biomarker in epithelial ovarian cancer (EOC) patients; and the clinical importance of the difference after chemotherapy.

METHODS
We have evaluated the patients with advanced-stage EOC who diagnosed between January 2012 and December 2017.

RESULTS
Elevated levels of neutrophils, neutrophil/lymphocyte ratio (NLR), and platelet/lymphocyte ratio at the time of diagnosis were significantly associated with excess amount of ascites. Lower levels of neutrophils and hemoglobin (HGB); and higher levels of red cell distribution width (RDW), and RDW/HGB ratio were predictors of platinum-sensitivity. In univariate analysis, while decreased mean platelet volume (MPV) was associated with longer disease free survival (DFS); elevated RDW, decreased neutrophils, MPV, and NLR were effective for better overall survival (OS). In multivariate analysis, platinum sensitivity and MPV were significantly associated with DFS and OS. Importantly, patients with persistently low MPV group after chemotherapy had the best OS; while persistently high MPV group had the worst OS.

CONCLUSION
MPV is a marker that can be easily evaluated during complete blood counts, and might be a promising and practical prognostic biomarker in the field of EOC. Hemogram parameters are found useful to predict disease properties and survival in EOC.

Keywords: Complete blood count; ovarian cancer; predictive; prognostic; survival.

Introduction

Epithelial ovarian cancer (EOC) has the highest mortality rate among all gynecological cancers worldwide which has been historically called "the silent killer" because the symptoms of the disease cannot be seen until advanced stages.[1] The absence of symptoms in early stages leads to delayed diagnosis of most cases and

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5-year survival rate drops below 35% in the advanced stages.[2] At present, standard treatment of EOC involves primary debulking surgery (PDS), followed by adjuvant platinum-taxane combination chemotherapy. However, patients with unresectable tumors which confirmed by radiological assessment or laparoscopic evaluation and patients with low-performance scores due to comorbidities are not suitable for PDS. In such cases, neoadjuvant chemotherapy followed by interval surgery is an alternative strategy.[3]

However, to date, there is no reliable biomarker has been developed to predict the response to chemotherapy in ovarian cancer patients in adjuvant or neoadjuvant settings. Although attention has turned to genetic tests and molecular biomarkers in this regard, genetic tests are quite expensive and relatively time-consuming, and molecular biomarkers require special equipment and trained personnel, which has a high economic burden, also.[4] On the other hand, recent studies have shown that conventional biomarkers have promising results on the issue. It is now known that inflammation plays an important role in the development of carcinogenesis, and is involved in all stages of cancer development.[5-7] In this regard, many conventional biomarkers are in use to assess systemic inflammation including neutrophil and lymphocyte counts, mean platelet volume (MPV), and platelet to lymphocyte ratio (PLR). In addition to all these, platelets play an active role in systemic inflammation, both enzymatically and metabolically. In the chronic inflammatory process, there is an increase in the thrombotic functions of platelets. Accordingly, MPV increases as the stimulation of chronic inflammation process.[8] Several studies have evaluated conventional hemogram parameters such as neutrophil and lymphocyte counts, MPV, red cell distribution width (RDW), PLR, and neutrophil to lymphocyte (NLR) in terms of survival on different cancers including ovarian cancer.[9,10]

The aim of the present study was to evaluate the clinical importance of conventional biomarkers in newly diagnosed advanced-stage ovarian cancer patients before and after neoadjuvant chemotherapy compared to healthy controls and to investigate the clinical importance of conventional markers in terms of survival and platinum response on ovarian cancer patients.

Materials and Methods

Participants

Newly diagnosed patients with advanced stage ovarian carcinoma were evaluated for the study. The inclusion criteria were (a) patients with histologically confirmed serous ovarian carcinoma that recurring neoadjuvant treatment; (b) patients who completed planned chemotherapy; and (c) patients who operated in our center. The exclusion criteria were consisting the followings; (a) recurrent disease or history of secondary malignancy; (b) unavailability of laboratory and pathology results; (c) primary refractory disease; (d) the evidence of other comorbidities including hematologic, cardiopulmonary, and inflammatory disease; and (e) treatment with anti-aggregation/coagulant therapy, antilipidemic, and anti-inflammatory drugs as well as recent blood transfusions. Patients were given standard chemotherapy regimen with carboplatin AUC 5-6 and paclitaxel 175 mg/m^2 for every 21 days pre- and postoperatively for 3-4 cycles which was decided by clinician opinion. In addition, patients were followed up with physical examination and computed tomography every 3 months for 2 years and every 6 months after treatment.

Methods

Hematological parameters of patients at the time of the diagnosis and after three cycle of neoadjuvant chemotherapy were recorded. The following information was obtained from the patient charts: Age, menopause status, date of the operation, ascites, FIGO stage, postoperative residual tumor, and the final status of the patient. Optimal surgery is categorized as R1 in this study and defined as the presence of ≤1 cm residual tumor; while tumor free resection is categorized as R0. Complete blood counts (CBC) are measured routinely by Beckman Coulter DxH 800 Hematology Analyzer (Beckman Coulter UniCel DxH 800 Coulter Cellular Analysis System) in our center and blood samples are measured with tri-potassium ethylenediamine tetraacetic acid (K3-EDTA) and are analyzed 1 h after venepuncture. The PLR was calculated by dividing the platelet count by the lymphocyte count; and NLR was calculated by dividing the neutrophil count by lymphocyte count. Disease-free survival (DFS) is defined as the time between the date of the operation and radiologically confirmed disease recurrence. Overall survival (OS) is defined as the time between the date of the pathologically confirmed disease diagnosis and death or the date of the last control.

Statistical Analysis

Statistical analysis and data collection were performed with SPSS version 20.0 (SPSS Inc., Chicago, IL, USA). The results were summarized as descriptive statistics (median, minimum, and maximum). Patients were

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assigned to one of two study group which based on median values hemogram parameters for comparison. The relationship between the disease characteristics and categorized laboratory data was tested using Chi-square test. As the observed frequencies in the cells of in the test were not below 5, Pearson Chi-Square values are taken into consideration. Survival analyses were estimated using the Kaplan–Meier Curve and compared with log-rank test. Cox regression multivariate analyses were used to evaluate independence analysis and hazard ratio estimation. P value less than 0.05 was considered as statistically significant.

Results

Patient Population

Median age of the all patient population was 57 years (ranged between 38 and 78). Nineteen of patients (36.5%) were operated with optimal surgery; whereas tumor free resection is achieved in 63.5% (n=33). Median DFS was 23.3 months (ranged between 9.1 and 111 months). Median OS was 50.6 months (ranged between 15.3 and 111). Median and range values of hemogram parameters are shown in Table 1 and median values of hemogram parameters were accepted as cutoff values to organize categorical variables.

Table 1 Median and range values of hemogram parameters

Variable	Median	Minimum	Maximum
WBC count	7250	2800	15200
Neu count	4655	1210	12300
Lym count	1600	490	2900
Mono count	500	100	1450
HGB level	11.6	8.1	14.8
MCV	82.8	68.9	95.2
RDW	16.5	11	27.4
PLT count	337000	103000	889000
MPV	8.2	2.4	12.5
PDW	16.7	11.7	20.3
NLR	2.93	0.69	9.54
PLR	208.4	51.9	978.6

WBC: White blood cell; Neu: Neutrophil; Lym: Lymphocyte; Mono: Monocyte; HGB: Hemoglobin; MCV: Mean corpuscular volume; RDW: Red cell distribution width; PLT: Platelet; MPV: Mean platelet volume; PDW: Platelet distribution width; NLR: Neutrophil/lymphocyte ratio; PLR: Platelet/lymphocyte ratio

The Relationship of Hemogram Parameters with Disease Characteristics

The relationships between hemogram parameters at the time of diagnosis and disease characteristics/treatment response were tested. Elevated levels of neutrophils, NLR and PLR at the time of diagnosis were statistically significantly associated with excess amount of ascites (p=0.023, p=0.021, and p=0.012, respectively). Furthermore, the lower levels of neutrophils and hemoglobin (HGB); and higher levels of RDW, RDW/PLT, and RDW/HGB ratio than median were predictors of platinum-sensitivity (p<0.05 for all). Only MPV to lymphocyte ratio and HGB level at the time of diagnosis were associated with post-operative residual disease (p=0.044 and p=0.048, respectively) (Table 2).

Table 2 The relationship of hemogram parameters with disease characteristics

Factor	P-value for resection (R0 vs. R1)	P-value for platinum response (Sensitive vs. Refractory)	P-value for ascites (≤500 ml vs. >500 ml)
WBC count	0.773	0.180	0.087
Neutrophil count	0.773	**0.049**	**0.023**
Lymphocyte count	0.388	0.588	0.569
Monocyte count	0.253	0.510	0.756
HGB level	**0.015**	**0.024**	0.312
MCV	0.150	0.588	0.087
RDW	0.388	**0.009**	0.087
Platelet count	0.773	0.475	0.254
MPV	0.388	0.588	0.254
PDW	0.388	0.588	0.569
NLR	0.618	0.242	**0.012**
PLR	0.773	0.475	**0.023**

WBC: White blood cell; HGB: Hemoglobin; MCV: Mean corpuscular volume; RDW: Red cell distribution width; MPV: Mean platelet volume; PDW: Platelet distribution width; NLR: Neutrophil/lymphocyte ratio; PLR: Platelet/lymphocyte ratio. Significant p values are given in bold

The Relationship of Hemogram Parameters with Survival Results

In univariate analysis, while decreased MPV at the time of diagnosis (p=0.037), platinum sensitivity (p=0.047), and lower stage (p=0.049) were associated with longer DFS significantly; in multivariate analysis, platinum sensitivity, and MPV were statistically associated with DFS significantly (Table 3).

In addition, decreased neutrophils (p=0.042), elevated RDW (p=0.036), decreased MPV (p=0.046), decreased NLR (p=0.033), decreased CA 12-5 preoperatively (p=0.034), ascites amount of ≥500 cc preoperatively (p=0.049), presence of platinum sensitive disease (p=0.015), and lower stage (p=0.043) were significantly associated with longer OS in univariate analysis. Multivariate analysis is showed that platinum sensitivity and MPV were also significantly associated with OS statistically (Table 4).

Prediction of Chemotherapy Efficacy Based on the MPV

To investigate the effect of chemotherapy on variation of MPV and whether the difference is effective on survival, we also evaluated preoperative MPV levels of patients and analyzed as another factor. In univariate analysis, decreased level of preoperative MPV was effective for better OS results of the patients (p=0.036 for OS, p=0.270 for DFS). Furthermore, we divided all patients into four groups to investigate the relationship between prognosis of patients and MPV variation after chemotherapy: Low-low group, low-high group, high-low group, and high-high group. Patients with persistently low MPV group had the best OS; while persistently high MPV group had the worst OS in the groups (p=0.011, Fig. 1). Patients with high diagnostic MPV but low pre-operative MPV had an improved OS of 62.3 months, and patients with a persistently high MPV had a OS of 45.8 months.

Discussion

The current study has evaluated the prognostic and predictive importance of hemogram parameters in our patient population who received pre-operative chemotherapy for advanced ovarian carcinoma. Although, few studies are existing which assessed diagnostic potential of inflammatory markers in ovarian carcinoma; it is the first study that evaluating and demonstrating the MPV value is associated with survival results of patients with advanced ovarian carcinoma, to the best of our knowledge. In this study, multivariate analysis has showed that platinum sensitivity and MPV were statistically significantly associated with DFS and OS. Moreover, the patients with persistently low MPV group had the best OS; while persistently high MPV group had the worst OS in the groups. N MPV variation with chemotherapy was predictive of better survival which could be translated to predict the patients who will derive more benefit from treatment. Patients with high diagnostic MPV but low preoperative MPV had an improved OS of 62.3 months, and patients with a persistently high MPV had a OS of 45.8 months. Therefore, evaluation of pre- and post-treatment MPV levels may be considered as a potential predictor of better treatment response.

Hemogram parameters can contribute to the diagnosis of diseases and have a prognostic value in some pathology which is studying in the many latest researches. Changes in the serum levels of inflammatory parameters in the blood count (e.g., absolute leucocyte or neutrophil count, PLR, NLR, and recently, MPV) have prognostic impact on many cancer subtypes. Although the routine analysis of the complete blood tests is commonly used in carcinoma patients for many years; their clinical significance has not been elucidated, and their prognostic value has been limitedly studied in EOC. Recent studies have shown that thrombocytosis might be associated with advanced disease and probably has prognostic effect on EOC. [11,12] Cho et al.[13] have demonstrated that combination of preoperative NLR and CA125 could be useful as a discriminative marker for malign and benign ovarian pathologies. On the other hand, Yang et al.[14] conducted a meta-analysis with 12 studies and found that increased NLR was associated with worse survival results in patients with EOC significantly.

Kemal et al.[9] evaluated that MPV levels of patients with EOC and pre-operative higher MPV levels were measured in patients with EOC compared with their control group. In addition, they showed that MPV levels decreased significantly after surgical tumor resection. Inversely, the results of the study that held by Qin et al.[15] showed that RDW levels were higher; whereas lower MPV levels was observed in cancer group compared with patients with benign ovarian tumors. However, our study design was not appropriate for diagnostic evaluation of MPV due to lack of non-cancerous group, we have evaluated prognostic significance of MPV. After multivariate analysis MPV was found to be independent marker to predict better survival results in patients with lower levels. The association between survival of patients with EOC and

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Table 3 Univariate analysis of analyzed prognostics factors

	Disease free survival		Overall survival	
	Median±SE	**p***	**Median±SE**	**p***
WBC Count				
≤Median value	23.3±3.0	0.496	62.4±1.3	0.093
>Median value	34.3±4.0		45.8±4.2	
Neutrophil Count				
≤Median value	24.0±3.3	0.985	62.4±1.3	**0.042**
>Median value	23.3±3.2		45.8±4.0	
Lymphocyte Count				
≤Median value	20.3±2.5	0.393	59.1±7.6	0.513
>Median value	27.6±1.9		53.8±11.0	
Monocyte Count				
≤Median value	23.3±3.0	0.920	62.4±2.5	0.178
>Median value	24.4±4.1		46.3±3.0	
HGB level				
≤Median value	28.5±5.8	0.180	60.9±10.9	0.730
>Median value	21.3±1.9		59.1±11.1	
MCV				
≤Median value	19.9±5.2	0.272	53.8±11.8	0.972
>Median value	35.4±2.8		59.1±8	
RDW				
≤Median value	19.8±1	0.208	46.3±4.2	**0.036**
>Median value	28.4±5.7		63.2±2.8	
Platelet Count				
≤Median value	22.8±1.9	0.515	62.0±2.3	0.203
>Median value	15.4±5.4		46.3±6.6	
MPV				
≤Median value	27.6±13.3	**0.037**	62.6±1.6	**0.046**
>Median value	21.3±2.1		46.3±4.2	
PDW				
≤Median value	27.3±3.2	0.696	62.6±12.0	0.230
>Median value	23.3±2.9		54.4±8.1	
NLR				
≤Median value	22.8±5.4	0.810	62.6±0.9	**0.033**
>Median value	24.4±2.9		44.5±7.8	
PLR				
≤Median value	22.9±4.0	0.911	62.0±4.5	0.476
>Median value	24.0±3.9		46.3±10.8	
CA 125				
≤Median value	20.3±3.4	0.669	65.2±9.7	0.165
>Median value	25.4±2.6		48.6±7.7	
Ascites				
≤500 ml	19.9±7.3	0.790	62.0±6.4	**0.049**
>500 ml	24.3±1.7		45.8±12.1	
Resection				
R0	27.4±4.2	0.609	48.6±12.6	0.764
R1	22.8±5.1		59.1±5.6	
Stage				
3	26.4±2.7	**0.049**	62.4±1.3	**0.043**
4a	20.8±2.0		45.8±4.0	
Platinum response				
Sensitive	40.2±1	**0.047**	NA	**0.015**
Other	20.3±3.2		53.7±7.3	

SE: Standard error; WBC: White blood cell; HGB: Hemoglobin; MCV: Mean corpuscular volume; RDW: Red cell distribution width; MPV: Mean platelet volume; PDW: Platelet distribution width; NLR: Neutrophil/Lymphocyte ratio; PLR: Platelet/Lymphocyte ratio; *: p value. Significant p values are given in bold

Table 4 Cox regression analysis of overall survival results of the patients

	p	HR	95.0% CI
Stage (Ref: 3)	0.718	1.172	0.49-2.77
Operation type (Ref: R0)	0.101	0.507	0.23-1.14
Platin sensitivity (Ref: Sensitive)	0.006	4.447	1.52-12.98
MPV (Ref: Low group)	0.041	2.225	1.03-4.79
NLR (Ref: Low group)	0.055	2.131	0.98-4.61

HR: Hazard ratio; MPV: Mean platelet volume; NLR: Neutrophil/lymphocyte ratio

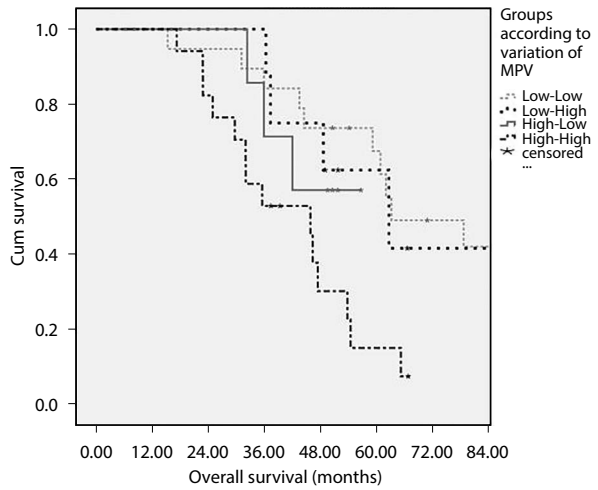

Fig. 1. The Kaplan-Meier plots of overall survival for patients according to variation of MPV.
MPV: Mean platelet volume.

the platelet parameters has been demonstrated in few studies. Allensworth et al.[16] suggested that thrombocytosis predicted poorer DFS and OS in patients with EOC. In contrast to our results, Yang et al. found that MPV was lower in patients with all subtype of gynecological cancer compared to controls, and patients with low MPV showed shorter OS. However, they have evaluated gynecological cancers comprehensively; their cohort was consisting of 34 ovarian cancer patients. Furthermore, they have not analyzed this specific subgroup separately.[17] Elevated MPV is associated with worse survival outcome in patients with various cancers; such as colorectal cancer,[18] gastric cancer,[19] breast cancer,[20] endometrial cancer,[21] and biliary tract cancer.[22] However, there are conflicting results in various other studies; which found that decreased MPV levels were predicting poor prognosis in lung cancer,[23] bladder cancer,[24] renal cell carcinoma,[25] and pancreas carcinoma.[26] Regarding the negatively or positively correlated outcomes that mentioned, MPV has been shown to have prognostic value in the previous studies of patients with malignancy. However, within the 906 studies that we retracted with the comprehensive PubMed search of "mean platelet volume, MPV, and survival" keywords, no studies have showed the survival effect of MPV on ovarian carcinoma. A recent large meta-analysis which attempted to evaluate prognostic and predictive value of MPV that held on with 9894 cancer patients showed that; high MPV had the strongest relationship with poor OS in gastric cancer, followed by pancreatic cancer. There were no patients with ovarian carcinoma in this meta-analysis.[27] Furthermore, another meta-analysis and review that held with 2053 patients and 1396 healthy subjects in 18 eligible studies, was not able to show survival effect of MPV on this specific population.[28]

Survival of Patients with Malignancy

We have also evaluated the relation of hemogram parameters and disease characteristics; and found that elevated levels of neutrophils, NLR and PLR at the time of diagnosis were statistically significantly associated with excess amount of ascites, HGB level and MPV to lymphocyte ratio at the time of diagnosis were associated with post-operative residual disease. In line with our study, Sahin et al.[10] evaluated inflammatory markers in patients with ovarian carcinoma who undergone primary resection; pre-operative PLR, NLR, and CRP elevation were correlated with disease characteristics such as ascites, stage, CA-125 levels and optimal resection rates in their study. In addition, we have evaluated predictors of platinum-sensitivity different from the previous study; and found lower levels of neutrophils and HGB; and higher levels of RDW, RDW/PLT, and RDW/HGB ratio than median were correlated with platinum sensitive disease ($p<0.05$ for all). The current study is one of the few studies that able to show correlation of hemogram parameters and treatment response. Jeerakornpassawat et al.[29] have shown that high NLR is a potential predictive factor for platinum resistance. However, we could not able to show any correlation in serous ovarian carcinoma cohort; Kim et al.[30] showed that elevated PLR was predicting incomplete response to chemotherapy in clear-cell cohort, which subgroup is not included in our study.

The present study has some limitations. First, this was a retrospective study with relatively small patient population who diagnosed with advanced EOC. Prospective studies with large patient populations are therefore needed to confirm our study results. Further-

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more, since targeted therapies such as bevacizumab or PARP inhibitors is not approved for first-line treatment for EOC in our country, our patient population was only used standard paclitaxel-carboplatin regimen for treatment and was not used any maintenance therapy. Hence, these results might be inconclusive for the patients who have used globally standardized other therapies. Nevertheless, to the best of our knowledge, our study provides one of the few evidences for the use of hemogram parameters for predicting survival and chemotherapy response in patients with EOC.

Conclusion

MPV is a marker that can be easily evaluated during CBC, with no additional cost to patients or health insurances. Regarding the findings of the current study, MPV might be a promising and a practical prognostic factor in the field of EOC. However, we found hemogram parameters are useful to predict disease properties and survival in EOC; current knowledge is extremely limited. Future studies should be designed with large patient populations and predefined cutoffs to reach firm conclusions.

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Ethics Committee Approval: The study was approved by the Istanbul University, Istanbul Faculty of Medicine Dean's Office Ethics Committee (No: 2021/156, Date: 05/02/2021).

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