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Is There a Correlation Between Platelet Count, Mesenteric Lymph Node Involvement, and Hematogenous Metastases in Advanced Stage Ovarian Cancer?

NICOLAE BACALBASA[1,2#], SORIN PETREA[2,3#], BOGDAN GASPAR[2,4#], LUCIAN POP[5,6], VALENTIN VARLAS[5,7], ADRIAN HASEGAN[8], GABRIEL GORECKI[9,10], CRISTINA MARTAC[11], MARILENA STOIAN[12,13#], ANCA ZGURA[14,15], ALEXANDRU CIULCU[16#] and IRINA BALESCU[17]

[1]*Department of Visceral Surgery, Center of Excellence in Translational Medicine "Fundeni" Clinical Institute, Bucharest, Romania;*
[2]*Department of Surgery, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania;*
[3]*Department of Surgery, "Ion Cantacuzino" Clinical Hospital, Bucharest, Romania;*
[4]*Department of Visceral Surgery, "Floreasca" Clinical Emergency Hospital, Bucharest, Romania;*
[5]*Department of Obstetrics and Gynecology, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania;*
[6]*Department of Obstetrics and Gynecology, National Institute of Mother and Child Care Alessandrescu-Rusescu, Bucharest, Romania;*
[7]*Department of Obstetrics and Gynecology "Filantropia" Clinical Hospital, Bucharest, Romania;*
[8]*Department of Urology, Sibiu Emergency Hospital, Faculty of Medicine, University of Sibiu, Sibiu, Romania;*
[9]*Department of Anesthesia and Intensive Care, CF 2 Clinical Hospital, Bucharest, Romania;*
[10]*Faculty of Medicine, Titu Maiorescu University, Bucharest, Romania;*
[11]*Department of Anesthesiology, Fundeni Clinical Hospital, Bucharest, Romania;*
[12]*Department of Internal Medicine, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania;*
[13]*Department of Internal Medicine and Nephrology, "Ion Cantacuzino" Hospital, Bucharest, Romania;*
[14]*Department of Medical Oncology, Oncological Institute Prof. Dr. Al. Trestioreanu, Bucharest, Romania;*
[15]*Department of Medical Oncology, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania;*
[16]*Department of Obstetrics and Gynecology, "Ion Cantacuzino" Clinical Hospital, Bucharest, Romania;*
[17]*Ph.D. Student at "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania*

Abstract. *Background/Aim: Ovarian cancer remains a major cause of death in women worldwide, mainly due to late diagnosis and the lack of a reliable screening test for early detection of the disease. In this context, attention has been focused on the identification of other prognostic factors that might allow a better identification of cases with worse long-term outcome. Patients and Methods: Data of patients who underwent cytoreductive surgery between 2014-2019 were retrospectively reviewed and 57 patients were considered eligible for this study. These cases were further classified according to preoperative platelet count, with a cut-off value of 335,000/μl as a positive predictive value for long-term survival. Results: According to this value, there were 27 cases with a preoperative platelet count lower than 335,000/μl and 30 cases with a preoperative platelet count higher than 335,000/μl. Cases in the second group had a significantly higher peritoneal carcinomatosis index (p=0.002), a higher proportion of digestive serosa involvement (p<0.001), and a higher proportion of mesenteric lymph node involvement and hematogenous metastases (p=0.005 and p=0.001, respectively).*

[#]These Authors contributed equally to this study.

Correspondence to: Alexandru Ciulcu, Department of Obstetrics and Gynecology, "Ion Cantacuzino" Clinical Hospital, Bucharest, Romania. E-mail: aciulcu2000@yahoo.com

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When analyzing long-term outcomes, all these factors had a significant impact on overall survival. Conclusion: Preoperative thrombocytosis appears to be positively associated with gastrointestinal serosa involvement, mesenteric lymph node invasion, and the presence of hematogenous metastases, thus significantly influencing the long-term outcome of patients with advanced ovarian cancer.

Despite advances in cytoreductive surgery and systemic oncological therapies, ovarian cancer remains a significant cause of death in women worldwide, even in cases where complete debulking to no residual disease is feasible (1-4). For this reason, surgeons worldwide have questioned whether completeness of cytoreduction is the only significant prognostic factor or whether other factors, such as tumor biology, should be considered (5-9). In this context, particular interest has been shown in investigating the impact of preoperative platelet count, as well as inflammatory and nutritional status, on the long-term outcome of these patients (5, 10, 11). Previous studies have shown a strong correlation between procoagulant status and stage at diagnosis (8-14).

When it comes to the patterns of spread of ovarian cancer, it seems that malignant cells have the capacity to spread *via* multiple routes, such as the peritoneal route, direct invasion, lymphatic or hematogenous contamination, leading to the apparition of metastatic disease (12-14). One of the most commonly invaded areas is the rectosigmoid loop, due to the close proximity of the bowel loop to the ovaries at the level of the pelvic cavity. In such cases, a rectosigmoid resection is usually performed to maximize the debulking effect (15-17). Interestingly, in such cases, anatomopathological studies have shown that not only the intestinal serosa but also the mesenteric lymph nodes show malignant contamination, and therefore it can be considered that ovarian cancer begins to behave similarly to colorectal cancer. In this respect, based on the pattern of dissemination of rectal cancer, the next question is whether hematogenous metastasis *via* the portal circulation is to be expected in such cases (18-20).

While the prognostic value of mesenteric lymph node involvement in ovarian cancer patients has been established in the literature, information regarding the risk of developing hematogenous metastases *via* the portal vein is rather scarce (21-25). Furthermore, no information has been reported on the possible correlation between preoperative factors such as platelet count and the risk of developing this pattern of spread. Therefore, the aim of the present work was to analyze the behavior of a group of patients undergoing per primam debulking surgery with regard to digestive serosa involvement, mesenteric lymph node involvement, and the risk of developing hematogenous liver metastases *via* the portal flow, as well as the possible correlation between this pattern of spread and the preoperative platelet count.

Patients and Methods

Study design. Between 2014 and 2019, 57 patients diagnosed with advanced stage ovarian cancer underwent surgery at the "Ion Cantacuzino" Clinical Hospital. After obtaining ethics committee approval number 21/2024, the data of these patients were retrospectively reviewed.

Study participants. Inclusion criteria were age over 18 years, absence of neo-adjuvant chemotherapy and histopathological confirmation of advanced stage ovarian cancer (FIGO stages IIIC-IV according to FIGO 2018 classification) (26). Exclusion criteria were age under 18 years, the use of neoadjuvant therapies as first-line treatment, personal history of splenectomy or other conditions that could affect platelet count (long history of corticoid administration), and personal history of hematological diseases.

Variables. Data collected related to demographics, functional status, extent of disease, peritoneal carcinomatosis index, histopathological findings, completeness of cytoreduction, and intraoperative and postoperative outcomes.

In all cases, complete debulking was defined as the absence of any macroscopically visible disease, whereas incomplete debulking was defined as the presence of macroscopically visible tumors at the end of the cytoreductive process. Postoperative complications were classified according to the Clavien-Dindo scale (27), while histopathological classification was performed according to the WHO system (28).

Survival was defined as the period between the first debulking surgery and the time of death, while cases not reported as dead at the last follow-up were considered alive.

Statistical methods. Statistical analysis was performed using SPSS version 24 (IBM, Armonk, NY, USA).

To determine the predictive value of preoperative platelet count for long-term survival, a receiver operating curve (ROC) was constructed using a cut-off value of 335,000/μl; for this value, the area under the curve was 0.756, with a sensitivity of 0.8 and a specificity of 0.344. The ROC curve is shown in Figure 1.

Categorical variables were analyzed using the chi-squared test, continuous variables were assessed with Student's *t*-test, and long-term outcomes were compared using Kaplan-Meier survival curves with the log-rank test. The Cox proportional hazard model was used for univariate analysis and the multivariate Cox proportional hazard model for multivariate analysis, with a *p*-value of less than 0.05 considered statistically significant.

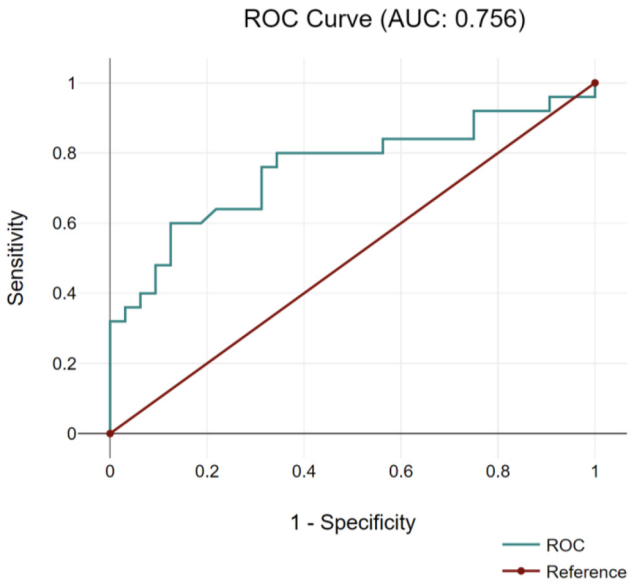

Figure 1. *ROC curve for predicting long-term survival. A cut-off value of 335,000/μl for circulating platelets was identified to predict the achievement of long-term survival.*

Results

Using a cut-off value of 335,000/μl, the initial study group of 57 patients was further divided into two groups: the first with preoperative platelet (PLT) count <335,000/μl, which included 27 patients, and the second with preoperative PLT >335,000/μl, which included 30 patients. The mean value of PLT was 272,830/μl in the first group and 452,939/μl in the second group. The mean age was 53.8 years in the first group and 57.8 years in the second group (the difference was marginally statistically significant, p=0.05). Meanwhile, the presence of associated comorbidities, *BRCA* mutation, and FIGO classification were similar between the two groups. However, when examining the extent of peritoneal carcinomatosis lesions between the two groups, cases with higher preoperative levels of circulating platelets tended to have more extensive peritoneal lesions [defined by a higher value of the peritoneal carcinomatosis index (PCI)-determined intraoperatively]. Meanwhile, the preoperative level of CA 125 was significantly higher in cases with higher levels of circulating platelets, as was the intraoperative volume of ascites. When investigating the correlation between the preoperative platelet count and the pathological findings, no significant relationship was observed between the circulating platelet count and the histopathological subtype or degree of differentiation. However, when short-term outcomes were analyzed, patients with a higher preoperative platelet count tended to have more postoperative complications and a significantly longer hospital stay than those with a lower platelet count (Table I).

As can be observed, a statistically significant difference was obtained between cases with a lower preoperative platelet count and the presence of digestive serosal invasion (p<0.001), the presence of mesenteric lymph node involvement (p=0.005), the presence of hematogenous metastases (p=0.001), and the radicality of the surgical procedure (p=0.006) when compared to cases with a higher preoperative platelet count.

In multivariate analysis, the presence of digestive serosa involvement (beta=59,344.51, [1,994.87; 116,694.16], p=0.042) and the presence of hematogenous metastases (beta=72,096.64, [2,311.81; 141,881.47], p=0.043) and mesenteric lymph node involvement (beta=112,600.65, [35,449.64; 189,751.67], p=0.005) were associated with higher preoperative platelet counts. However, upper abdominal extension (beta=–36,063.78, [–95,088.04; 22,960.48], p=0.225) and completeness of debulking surgery (beta=24,678.25, [–62,231.23; 111,587.73], p=0.571) were not associated with preoperative platelet count. The forest plot of the results is shown in Figure 2.

An interesting aspect to be discussed is the distribution of patients presenting with serosal invasion, mesenteric lymph node involvement, and hematogenous metastases. Among the cases with low preoperative platelet levels, there were nine cases with digestive serosal invasion, two of these nine cases also presented mesenteric lymph node metastases and one of these two presented disseminated hematogenous liver metastases (this finding is responsible for the impossibility of achieving complete debulking). It should also be emphasized that there were individual cases in which mesenteric lymph node involvement and liver metastases were present. In the second group, including cases with PLT>335,000/μl, there were 30 cases, 25 of which presented digestive serosa involvement. Among the 30 cases, there were 12 cases with mesenteric lymph node involvement, a single case of these 12 patients reporting positive mesenteric adenopathy in the absence of digestive serosa involvement. In this study group, there were nine cases of liver metastases. Seven of these cases had digestive serosa involvement and positive mesenteric lymph nodes. One patient was diagnosed with liver metastases with mesenteric lymph node metastases but without digestive serosa involvement. The remaining patient had hematogenous liver metastases and digestive serosa involvement but no positive mesenteric lymph nodes. Regarding the influence of the presence of mesenteric lymph node involvement or liver metastases on the completeness of cytoreduction, we demonstrated that among the 11 cases in which incomplete debulking was performed, four cases were caused by the presence of disseminated liver metastases. Of these four, one case had a PLT of less than 335,000/μl, and three had a PLT greater than 335,000/μl. Another four cases were caused by mesenteric lymphatic obstruction, all with a preoperative PLT greater than 335,000/μl. The remaining three cases involved extensive mesenteric nodules of peritoneal carcinomatosis.

Table I. *The correlation between the preoperative platelet level and both preoperative and intraoperative findings.*

	PLT <335,000/μl (n=27 cases)	PLT >335,000/μl (n=30 cases)	*p*-Value
Age (mean, years)	53.8 (years)	57.8 (years)	0.051
Associated comorbidities			
Yes	8	14	0.221
No	19	16	
FIGO stage			
IIIC	22	22	0.513
IV	5	8	
PCI:			
<10	8	5	0.002
<20	13	8	
>20	6	17	
BRCA mutation			
Yes	5	7	0.752
No	22	23	
CA125 (U/dl)	923.8	5,080	<0.001
Ascites (ml)	1,566	2,895	<0.001
Mean number of PLT	272,830	452,939	0.022
Digestive serosa invasion			
Yes	9	25	<0.001
No	18	5	
Types of bowel resection			
Rectosigmoid resection	4	8	NA
Right colectomy	2	6	
Small bowel resection	2	9	
Subtotal colectomy	1	2	
Histological subtype:			
Serous	20	19	0.422
Nonserous	7	11	
Differentiation degree			
G1	5	5	1
G2, G3	22	25	
Mesenteric lymph node involvement			
Yes	2	12	0.005
No	25	18	
Upper abdominal extension			
Yes	7	10	0.512
No	20	20	
Hematogenous metastases			
Yes	1	9	0.001
No	26	21	
Type of cytoreduction			
Complete	26	20	0.006
Incomplete	1	10	
Postoperative outcome			
No postoperative complication	24	17	0.008
Clavien-Dindo I, II complications	1	7	
Clavien-Dindo III-V complications	2	6	
Postoperative hospital in stay (days, mean)	8,8	11.7	0.042

Having demonstrated the correlation between preoperative platelet count and extent of disease, we aimed to determine the impact of extent of disease on the long-term outcomes of the study group. We therefore analyzed the impact of upper abdominal extension, hematogenous metastases, mesenteric lymph node involvement, and digestive serosa involvement on disease-free and overall survival. The results are shown in Table II and Table III. As shown in Table II, statistically significant differences in disease-free survival were observed for completeness of cytoreduction, digestive serosa involvement, mesenteric lymph node involvement, and the presence of hematogenous metastases.

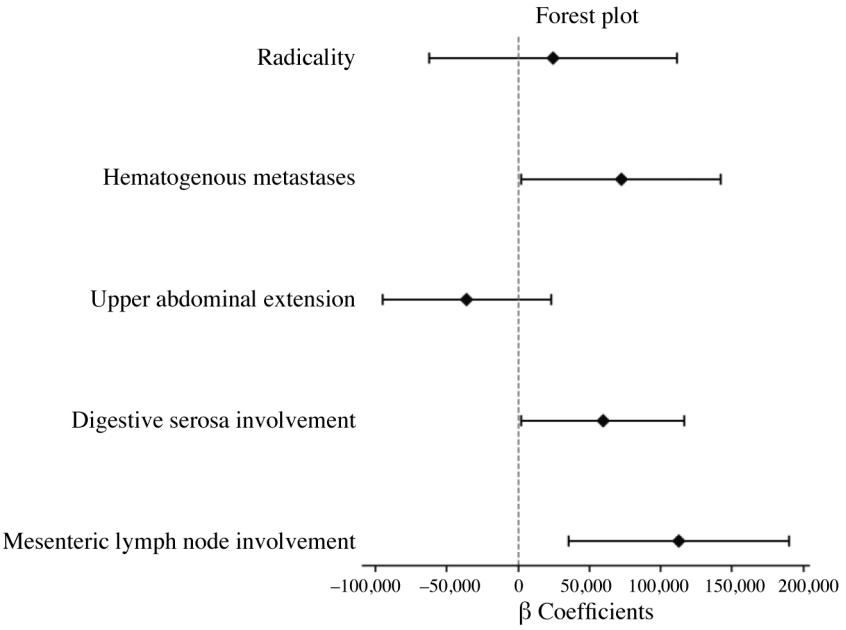

Figure 2. *Forest plot representation of parameters introduced in multivariate analysis.*

In multivariate analysis, digestive serosa involvement (beta=–9.68, [–14.81; -4.55], $p<0.001$) and the presence of hematogenous metastases (beta=–7.26, [–13.5; -1.02], $p=0.023$) were associated with lower disease-free survival, while radicality (beta=–7. 22, [–14.99; 0.56], $p=0.068$), the presence of mesenteric lymph node involvement (β=–6.66, [–13.56; 0.23], $p=0.058$) and upper abdominal extension (β=2.25, [–3.02; 7.53], $p=0.395$) were not associated with this parameter. The forest plot illustrating these results is shown in Figure 3. The correlation between extent of disease and overall survival is shown in Table III.

In multivariate analysis, mesenteric lymph node involvement (beta=–13.68, [–23.27; -4.08], $p=0.0061$), digestive serosa involvement (beta=–12.35, [–19.48; -5.22], $p=0.001$) and the presence of hematogenous metastases (beta=–10.82, [–19.5; -2.14], $p=0.015$) were associated with poorer overall survival. However, completeness of cytoreduction (beta=–10.18, [–20.99; 0.63], $p=0.064$) and upper abdominal extension (beta=3.12, [–4.22; 10.46], $p=0.396$) were not associated with overall survival. The forest plot of these results is shown in Figure 4.

The data obtained to date highlight the fact that the presence of digestive serosa involvement, mesenteric lymph node involvement, and the presence of hematogenous metastases are associated with poorer disease-free and overall survival.

Discussion

The issue of mesenteric lymph node involvement as a prognostic factor in advanced-stage ovarian cancer has become an interesting topic of debate in recent decades, after it was widely demonstrated that this issue strongly influences long-term outcomes in advanced-stage colorectal cancer. Therefore, studies conducted to date in colorectal cancer patients have shown that the presence of mesenteric lymph node involvement is associated with an increased risk of locoregional recurrence, liver metastases, and poorer long-term outcomes, leading clinicians to consider that this should be a criterion for the administration of adjuvant therapy (29-32).

In this regard, studies have shown that from this point of view, ovarian cancer invading the rectosigmoid loop behaves like colorectal cancer and leads to the appearance of mesenteric lymph node involvement. In colorectal cancer, once tumor cells reach this level, they are translocated to the level of the distal capillaries, which continue to form the portal vein; by this mechanism, tumor cells invading the mesenteric lymph nodes are discharged in the portal flow and lead to the appearance of hematogenous liver metastases (22-25). Regarding ovarian cancer, an interesting finding was presented in the study by Scarabelli *et al*. in 2000; at that time, the authors considered a study group of 66 patients diagnosed with ovarian cancer and macroscopic rectosigmoid involvement who underwent surgery between 1990 and 1997. In multivariate analysis, not only residual disease but also tumor infiltration of the bowel wall were independent risk factors for recurrence or death. Regarding the sites of development of recurrent disease, the liver was involved in 29.8% of cases (32). Therefore, it is expected that patients who present with digestive serosa involvement at the time of

Table II. *The correlation between the extent of the disease and disease-free survival (DFS).*

	DFS – mean (±SD), months	DFS – median, months	*p*-Value
Hematogenous metastases			
Yes	11.3±5.5	13	0.051
No	19.8±12.7	17	
Upper abdominal extension			
Yes	16.2±13.8	14	0.307
No	19.2±11.5	16	
Mesenteric lymph node involvement			
Yes	6.79±5.35	6	0.001
No	22.09±11.43	21	
Digestive serosa involvement			
Yes	12.5±9.12	11.5	
No	27.4±10.3	28	0.001
Completeness of cytoreduction			
R0	21.7±11	17.5	0.001
R1	4.18±3.8	2	

Table III. *The correlation between the extent of the disease and overall survival (OS). Statistically significant differences were obtained for the type of cytoreduction, digestive serosa involvement, and mesenteric lymph node involvement.*

	OS – mean (±SD), months	OS – median, months	*p*-Value
Hematogenous metastases			
Yes	20±8.24	22.5	0.147
No	32.1±18.6	28	
Upper abdominal extension			
Yes	26.7±19.9	21	0.205
No	31.4±16.9	26	
Mesenteric lymph node involvement			
Yes	11±2.1	10	0.001
No	31.6±5	27	
Digestive serosa involvement			
Yes	21.2±14.5	21	
No	43.09±14	46	0.001
Completeness of cytoreduction			
R0	35.2±15	28.5	0.001
R1	8.1±5.6	9	

initial surgery will also have positive mesenteric lymph nodes and even micrometastatic disease at the level of the liver. Based on these findings, we can consider that even if no visible residual disease is obtained at the end of the surgical procedure, such cases will leave the operating room with micrometastatic liver disease and will be at risk of developing macroscopic lesions after a short period of time. In this regard, such cases should be excluded from per primam debulking surgery and are more likely to be candidates for neoadjuvant systemic therapy to reduce malignant cluster cells at the time of initial debulking.

In order to avoid such situations, attention has been focused on identifying potential prognostic markers that could offer a better selection of cases proposed for per primam surgery *versus* neoadjuvant chemotherapy followed by interval debulking surgery. In this regard, over the last decade, attention has been focused on identifying preoperative prognostic factors that might allow for a better identification of such cases. The strong correlation between the number of circulating platelets and the biological aggressiveness of different types of malignancies has been widely studied (33-35). It appears that malignant cells induce the secretion of interleukin-6, which further leads to the appearance of thrombocytosis, while thrombocytosis induces the secretion of interleukin-10 and tumor necrosis factor, which further induce tumor growth and dissemination (36, 37). In ovarian cancer, the impact of preoperative thrombocytosis on long-term outcomes can be explained by multiple mechanisms, such as inducing and promoting epithelial-to-mesenchymal transition, protecting tumor cells from natural killer cells, stimulating

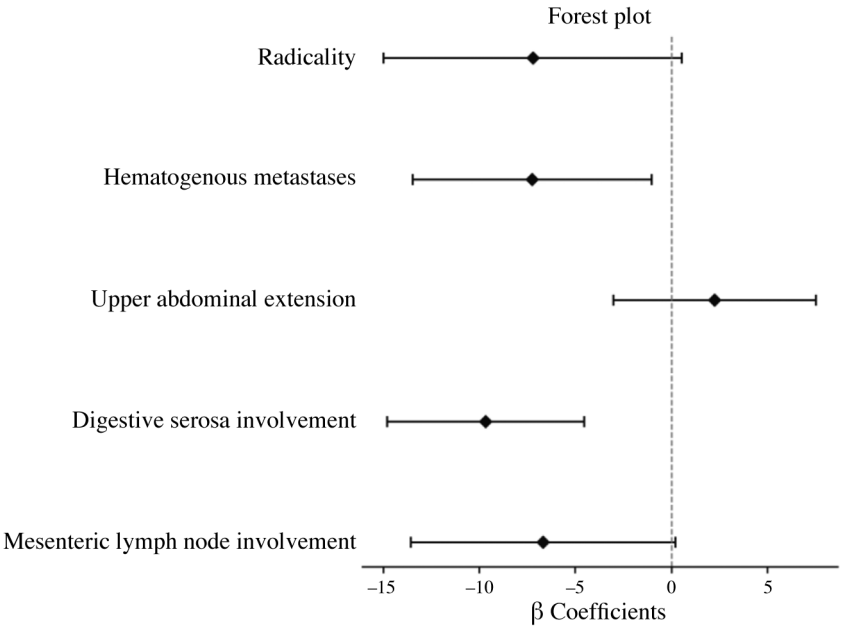

Figure 3. *Forest plot representation used to illustrate the parameters influencing the progression-free survival interval, which were investigated in multivariate analysis.*

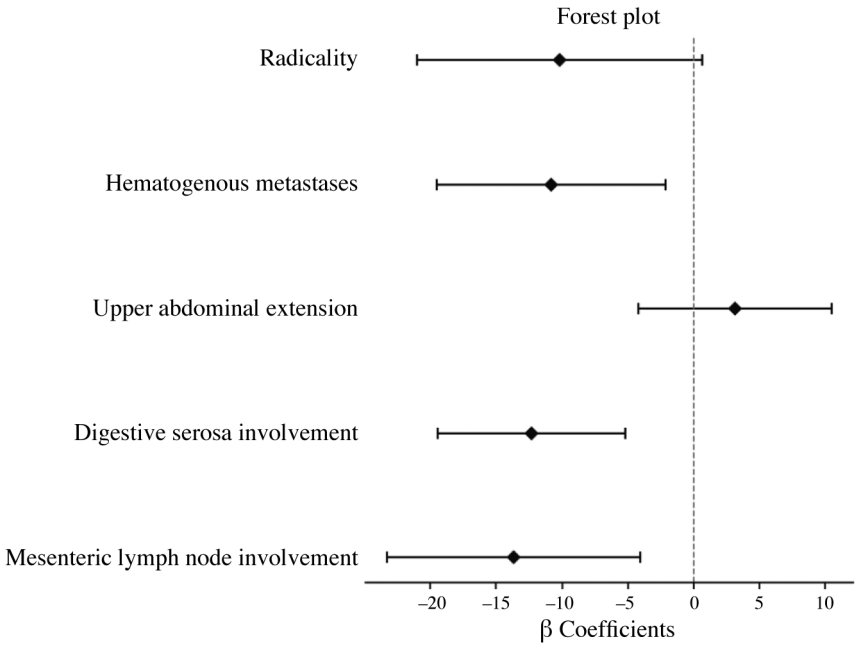

Figure 4. *Forest plot representation used to illustrate the parameters influencing the overall survival interval, which were investigated in multivariate analysis.*

angiogenesis, or releasing growth factors that further stimulate tumor proliferation (38-41). Epithelial-to-mesenchymal transition is the cornerstone of tumor dissemination; according to this mechanism, polarized, fixed epithelial cells lose their apical-basal polarity, disrupt intercellular junctions and develop a highly invasive behavior; all these mechanisms appear to be strongly influenced by the presence of higher levels of transforming growth factor beta (TGFβ), a molecule

traditionally synthesized by circulating platelets. Therefore, once thrombocytosis develops, higher levels of circulating TGFβ can be expected, further stimulating epithelial-to-mesenchymal transition (42). In ovarian cancer patients, it is estimated that up to 37% of cases are associated with thrombocytosis at the time of initial diagnosis, cases that are more likely to progress to advanced stages with massive peritoneal contamination (37, 43). Therefore, according to Guo's studies, patients with thrombocytosis are more likely to have tumor spread to the omentum, peritoneum, and mesentery (44).

Based on this observation, the aim of our study was to investigate whether the preoperative platelet count could be considered as a prognostic marker for identifying cases at risk of digestive serosa invasion, positive mesenteric lymph nodes, and hematogenous metastases. According to our results, a higher number of platelets is expected to be associated with an increased risk of peritoneal contamination, which translates into a higher risk of digestive serosa involvement. In addition, we have shown that a significant proportion of cases with digestive serosa invasion also have a higher risk of mesenteric lymph node metastasis from the outset, which may per se be a factor in incomplete debulking surgery.

Conflicting results have been reported regarding the impact of positive mesenteric lymph nodes on the long-term outcome of ovarian cancer patients. While it was initially stated that no significant difference in survival was to be expected between cases with positive mesenteric lymph nodes and those with negative nodes, more recent studies have underlined the fact that this finding is an important prognostic factor influencing long-term outcomes (23, 24).

Meanwhile, cases with liver metastases identified in our group were more likely to be found among cases with increased platelet count, digestive serosa involvement and mesenteric lymph node metastases. Moreover, the presence of liver metastases was another frequently incriminated reason for the inability to achieve complete debulking. Based on these findings, we believe that in cases in which high levels of circulating platelets are found preoperatively, special attention should be paid to analyzing the imaging aspects of the mesenteric lymph nodes and the liver in order to exclude cases in which tumor dissemination has already occurred at this level. Once identified, these cases should rather be subjected to neoadjuvant systemic therapy followed by debulking surgery. Furthermore, we believe that the analysis of these parameters in an artificial intelligence software could create a predictive model to allow a more appropriate selection of patients for debulking surgery as first intent therapy. However, the main limitations of this study are related to the small number of cases included in the study group and the retrospective nature of the work (45, 46). Therefore, larger prospective studies are needed to validate our findings.

Conclusion

Preoperative thrombocytosis appears to be particularly common in cases with digestive serosa involvement in the setting of advanced stage ovarian cancer. Furthermore, thrombocytosis appears to be positively associated with the presence of mesenteric lymph node involvement and liver metastases, two of the most commonly reported causes of incomplete debulking surgery. Moreover, according to our results, all these findings seem to be statistically significantly associated with long-term outcomes. Therefore, such cases should be considered as candidates for systemic neoadjuvant therapy rather than per primam debulking surgery.

Conflicts of Interest

There are no conflicts of interest to declare regarding this study.

Authors' Contributions

I.B. - Conceptualization; I.B., N. B. - methodology; I.B., S.P. - software; S.P. - validation; B.G. and G.P.G - formal analysis; A.Z., L. P. - investigation; C.M. resources; V.V. - data curation, I.B. - writing—original draft preparation; N.B. - writing—review and editing; A.H. - visualization; S.P., A.C.- supervision; M.S. - project administration. All Authors have read and agreed to the published version of the manuscript.

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