Submitted: 28 June, 2024 Accepted: 29 July, 2024 Published: 15 March, 2025 DOI:10.22514/ejgo.2025.033

ORIGINAL RESEARCH

European Journal of Gynaecological Oncology

Association of ultrasound findings with hematological parameters, cytokines and survival in ovarian cancer

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Abstract

Background: The objectives of the study were to evaluate the association of ultrasound findings with hematologic parameters, tumor markers and serum cytokines in malignant adnexal neoplasms and borderline tumors; and to evaluate the association of these findings with overall survival (OS) and disease-free survival (DFS). **Methods**: The study included 33 patients with a confirmed pathological diagnosis of borderline ovarian tumor (n = 10) and malignant ovarian/tube neoplasm (n = 23). The anatomopathological, tumor markers, hematologic parameters, serum cytokine levels (interleukin (IL)-2, IL-5, IL-6, IL-8, IL-10 and tumor necrosis factor (TNF)-alpha) and ultrasound findings (adnexal mass volume and largest diameter, vegetation, solid areas, septa, thickness of the capsule, vascularization on Doppler) were evaluated. Comparison of values between groups was performed using the Mann-Whitney test. Survival was assessed using Kaplan-Meier curves and log-rank test. The significance level was 0.05. **Results**: Shorter OS and DFS were demonstrated in patients with a tumor volume greater than 245 mL and ovarian cancer (p = 0.031 and p = 0.024, respectively). Moreover, there was an association between higher red cell distribution width (RDW) value and the presence of thick septa (p = 0.0355), and tumor volume >245 mL with lower levels of hemoglobin (p = 0.0102) and hematocrit (p = 0.0095), levels more elevation of serum IL-8 (p = 0.0453) and higher levels of neutrophil-lymphocyte ratio (NLR) (p = 0.0227). The presence of vascularization on Doppler was associated with higher platelet values (p = 0.0339). Regarding borderline tumors, no association between ultrasound, laboratory parameters and survival was demonstrated. **Conclusions**: Ultrasonographic findings in adnexal masses may reflect parameters of systemic inflammatory and immunological response in ovarian cancer. In particular, greater tumor volume is associated with lower OS and DFS.

Keywords

Ultrasonographic findings; Ovarian tumor; Hematologic parameters; Citokynes; Survival

1. Introduction

Global Cancer Observatory estimated that 324,603 women were diagnosed with ovarian cancer worldwide in 2022 and that there were 206,956 deaths from the disease in the same year [1]. The high lethality, the highest among gynecological cancers, arises from the fact that this disease presents non-specific symptoms in its initial stages, making diagnosis difficult [2]. Furthermore, screening asymptomatic women has not been shown to be effective in reducing ovarian cancer mortality in large studies [3, 4]. This results in a late diagnosis of the disease, predominantly in stages III and IV. The survival rate varies even between patients with the same pathological stage and using the same treatment. These differences may be caused by the patient's biological variables and their diverse inflammatory responses [5].

The inflammatory response is involved in almost all stages of tumor development [6]. Gynecological cancer appears to be associated with inflammation and its growth, differentiation and signaling can be regulated by cytokines, acting in the epithelial-mesenchymal transition [7]. The expression of these cytokines may vary according to the subtype of ovarian carcinoma, contributing to prognostic factors [8]. Therefore, cytokines may have a prognostic value in ovarian cancer [9, 10].

In addition to cytokines, and tumor staging and grade, which are already recognized, there are other prognostic factors being studied in ovarian cancer and include neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR) [11–13], other blood count parameters [13–15] and tumor markers [11, 16].

Imaging exams can also be prognostic factors, since there are models that can predict the behavior of the tumor and its classification [17], in some cases they can even predict the histological type of the tumor and assess the tumor extension. This pre-operative information changes surgical planning and may even preserve the patient's fertility [18]. And the suspicion of metastatic ovarian cancer requires a more extensive evaluation to identify the origin and type of the tumor [19].

Therefore, the discovery of prognostic factors in ovarian malignancy can improve patient management, using more aggressive adjuvant treatments in those with worse prognostic factors [20]. This may influence disease-free survival and overall survival of patients.

The present study aims to evaluate the association of ultrasound findings with hematologic parameters, tumor markers and serum cytokines in malignant adnexal neoplasms and borderline tumors; and to evaluate the association of these findings with overall survival and disease-free survival.

2. Materials and methods

It is a study carried out at the Laboratory of Applied Sciences for Women (LaCam)/Department of Gynecology and Obstetrics, Federal University of Triângulo Mineiro. The study included 33 patients who underwent surgical treatment for adnexal lesions according to pre-established criteria [21], whose anatomopathological diagnosis confirmed borderline ovarian tumor (n = 10) or malignant ovarian/tube neoplasm (n = 23).

The serum tumor markers cancer antigen (CA)-125, CA-15.3 and CA-19.9 and the blood count are already routine tests performed before surgery, and are recorded in the study's specific database. The hematological parameters evaluated were hemoglobin, red blood cells, hematocrit, neutrophils, eosinophils, basophils, monocytes, lymphocytes, platelets, neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR) and red cell distribution width (RDW).

The staging system for ovarian cancer was described according to the International Federation of Gynecology and Obstetrics (FIGO), being surgical and based on the results obtained at the time of surgery [22].

Disease-free survival (DFS) and overall survival (OS) were evaluated. DFS was considered from the date of diagnosis to the date of first recurrence. OS was considered from the date of diagnosis to the date of death from any cause.

The technique for performing ultrasound and measuring serum cytokines are described below.

2.1 Ultrasonography

All ultrasounds were performed by trained radiologists with experience in this examination. Ultrasound devices were used, with transvaginal probe frequencies ranging between 5 and 12 MHz. Radiologists also used transabdominal ultrasound to evaluate large masses that could not be seen in their entirety with the use of a transvaginal probe. Morphological and blood flow variables were obtained using color and grayscale Doppler ultrasound images to characterize each adnexal mass.

On ultrasonography, the following morphological aspects of adnexal masses have been described: dominant echogenicity (anechoic, hypoechoic, isoechoic, heterogeneous or hyperechoic), presence of papillary projections or vegetations (projections of solid tissue from an internal surface that projects towards the light of the image), presence of septa (solid fibrillar projections that cross the interior of the lesion from an internal wall to the contralateral wall; a thick septum was considered when greater than 3 mm); internal and external walls (the internal walls of a cystic image were carefully evaluated in an attempt to observe any irregularity; in solid images, the external walls were evaluated for the regularity of their outline); posterior acoustic shadow; ascites; and Doppler (evaluation of the presence of blood flow in the adnexal mass and papillae). For statistical analyses, the following parameters were used: tumor volume, largest diameter of the adnexal mass, presence of vegetation, solid areas, thin septa and thick septa, presence or absence of vascularization on Doppler.

2.2 Determination of serum cytokine levels by ELISA

Serum levels of the cytokines IL-2, IL-5, IL-6, IL-8, IL-10 and TNF-alpha were determined by immunoenzymatic method (ELISA). In summary, 100 μL of standards were added to the wells of the ELISA plate, coated with capture monoclonal antibodies for IL-2, IL-5, IL-6, IL-8, IL-10 and TNF-alpha. The ELISA plate was covered with adhesive sealant and incubated for 2 h at room temperature on a micro plate shaker. Then, the wells were aspirated and washed 5 times with 300 μL of Wash Buffer using automatic multichannel micropipettes. After the last wash, the plate was inverted onto absorbent paper to remove any residual buffer, then adding 100 μL of working solution (Detection Antibodies to IL-2, IL-5, IL-6, IL-8, IL-10 and TNF-alpha + Streptavidin Peroxidase Conjugate) and incubated for 1 h at room temperature. Aspiration and washing were repeated as described above, then 100 μL of Substrate Solution (Tetramethylbenzidine + Hydrogen Peroxide) was added and a third incubation was carried out for 30 minutes at room temperature (RT) in a plate micro shaker completely protected from light. After incubation, 50 μL of Stop Solution (1M H_3PO_4) was added to each well. Finally, the optical density of each well was determined using a microplate reader set at 450 nm. The test has a detection limit of 1 pg/mL, inter-assay precision of 8–10% and intra-assay precision of 4–6%. Concentrations were calculated by comparing them with their standard curves. The results were expressed in pg/mL.

2.3 Statistical analysis

GraphPad Prism (version 6, GraphPad Software, Boston, MA, USA), IBM SPSS Statistics (version 22.0., IBM Corp, Armonk, NY, USA) and MedCalc (version 19.0.4, MedCalc Software Ltd, Ostend, Belgium) Software were used. Initially, receiver operating characteristic (ROC) curves were constructed to verify whether there is a cut-off value between the quantitative ultrasound variables (volume and largest diameter of the adnexal tumor) that may be associated with death and recurrence. DFS and OS were assessed using Kaplan-Meier curves and log-rank test. Mann-Whitney test was used to demonstrate the comparison between values above and below the cut-off

values found of quantitative ultrasound variables, in the case of significant *p*. In evaluating the presence of vegetation, solid areas, thin septa, thick septa and vascularization on Doppler, the Mann-Whitney test was used to compare the values of tumor markers and blood count parameters between groups with the presence or absence of these ultrasound findings. The significance level was 0.05.

The study was approved by CEP/UFTM, CAAE: 32185020.0.0000.5154.

3. Results

The study included 33 patients with a confirmed pathological diagnosis of borderline ovarian/tube tumor (n = 10) and malignant ovarian/tube neoplastic disease (n = 23).

The average ages of the borderline tumor and ovarian cancer group were 50 ± 17.5 years and 50.17 ± 17.65 years, respectively. In the malignant group, the majority of patients (56.5%) were over 50 years of age. Regarding malignant tumors, there were 10 (43.48%) serous cystadenocarcinomas, 1 (4.35%) mucinous cystadenocarcinoma, 1 (4.35%) endometrioid adenocarcinoma, 2 (8.69%) clear cell carcinomas, 4 (17.39%) granulosa cell tumors, 2 (8.69%) dysgerminomas, 1 (4.35%) immature teratoma, 1 (4.35%) endodermal sinus tumor and 1 (4.35%) mixed germ cell tumor. Regarding borderline tumors, there were 6 (60%) mucinous tumors and 4 (40%) serous tumors.

ROC curves were constructed to verify whether there is a cut-off value between the quantitative ultrasound variables (volume and largest diameter of the adnexal tumor) that may be associated with death and recurrence, and Kaplan-Meier curves were drawn to evaluate OS and DFS. In relation to tumor volume and death, a cut-off value >245 mL had a sensitivity of 100% and a specificity of 61.5% (Area Under the Curve (AUC) = 0.769 and $p = 0.013$) in malignant tumors. Kaplan-Meier curve demonstrated shorter OS in patients with a tumor volume greater than 245 mL ($p = 0.031$) (Fig. 1). Regarding tumor volume and DFS, a cut-off value >245 mL had a sensitivity of 100% and specificity of 57.1% (AUC = 0.726 and $p = 0.059$, at the threshold of significance) in malignant tumors. With this cut-off value, a Kaplan-Meier curve was created, showing shorter DFS in patients with a tumor volume greater than 245 mL ($p = 0.024$) (Fig. 2). There was no statistical significance in relation to the largest diameter of the adnexal tumor.

To evaluate the association of ultrasound findings with hematological parameters, the values of these parameters were compared between the group in which the qualitative findings (presence of vegetation, solid areas, thin septa and thick septa, vascularization on Doppler) were present and the group in which they were absent. For comparison with the quantitative parameter (tumor volume), the cut-off value found in the previous ROC curve (245 mL) was used (the values of hematologic parameters were compared between the group in which the tumor volume was ≤245 mL and the group in which tumor volume was >245 mL). Regarding malignant neoplasms, there was an association between higher RDW value and the presence of thick septa ($p = 0.0355$), and tumor volume >245 mL with lower levels of hemoglobin ($p = 0.0102$) and hematocrit ($p = 0.0095$), levels more elevation of serum IL-8 ($p = 0.0453$) and higher levels of NLR ($p = 0.0227$). The presence of vascularization on Doppler was associated with higher platelet values ($p = 0.0339$) (Fig. 3). Tumor volume >245 mL was also related to a lower lymphocyte count ($p = 0.0528$) and higher PLR values ($p = 0.0585$), at the significance threshold. No association was found with the other hematological parameters and the values of the tumor markers evaluated.

Regarding borderline tumors, no association between ultrasound, laboratory parameters and survival was demonstrated.

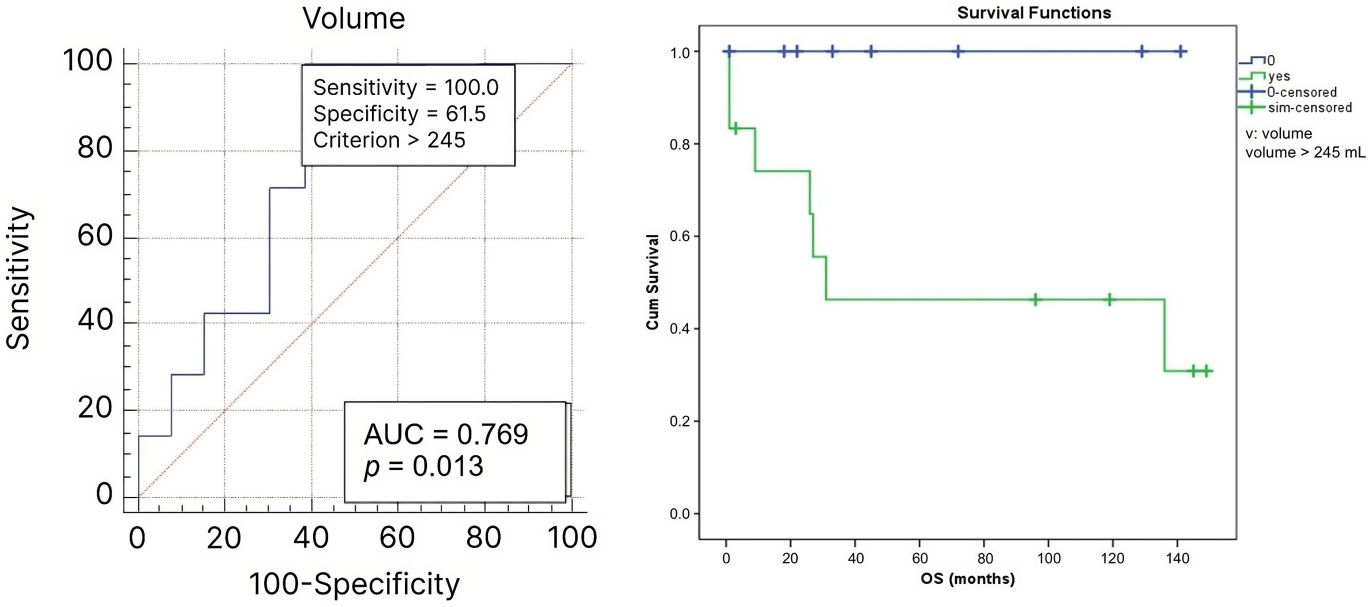

FIGURE 1. ROC curve relating tumor volume and death, and survival curve demonstrating shorter overall survival in patients with ovarian cancer and tumor volume >245 mL (Kaplan-Meier curves and log-rank test). AUC: Area Under the Curve; OS: overall survival.

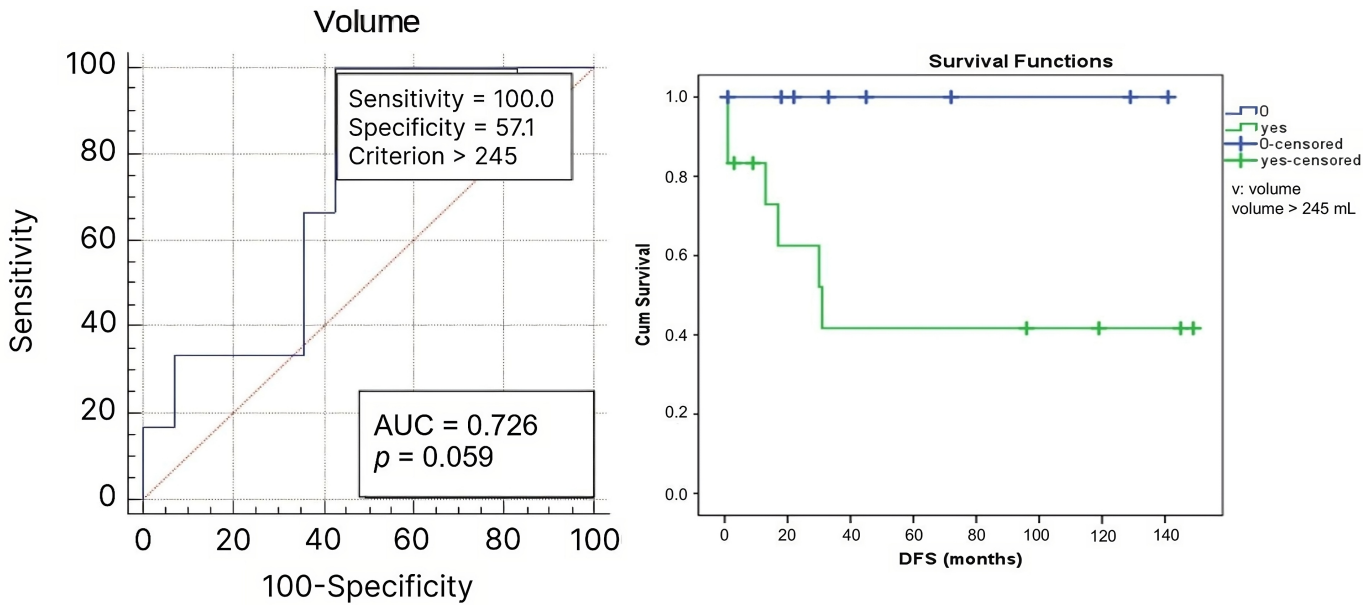

FIGURE 2. ROC curve relating tumor volume and recurrence, and survival curve demonstrating shorter disease free survival in patients with ovarian cancer and tumor volume >245 mL (Kaplan-Meier curves and log-rank test). AUC: Area Under the Curve; DFS: disease-free survival.

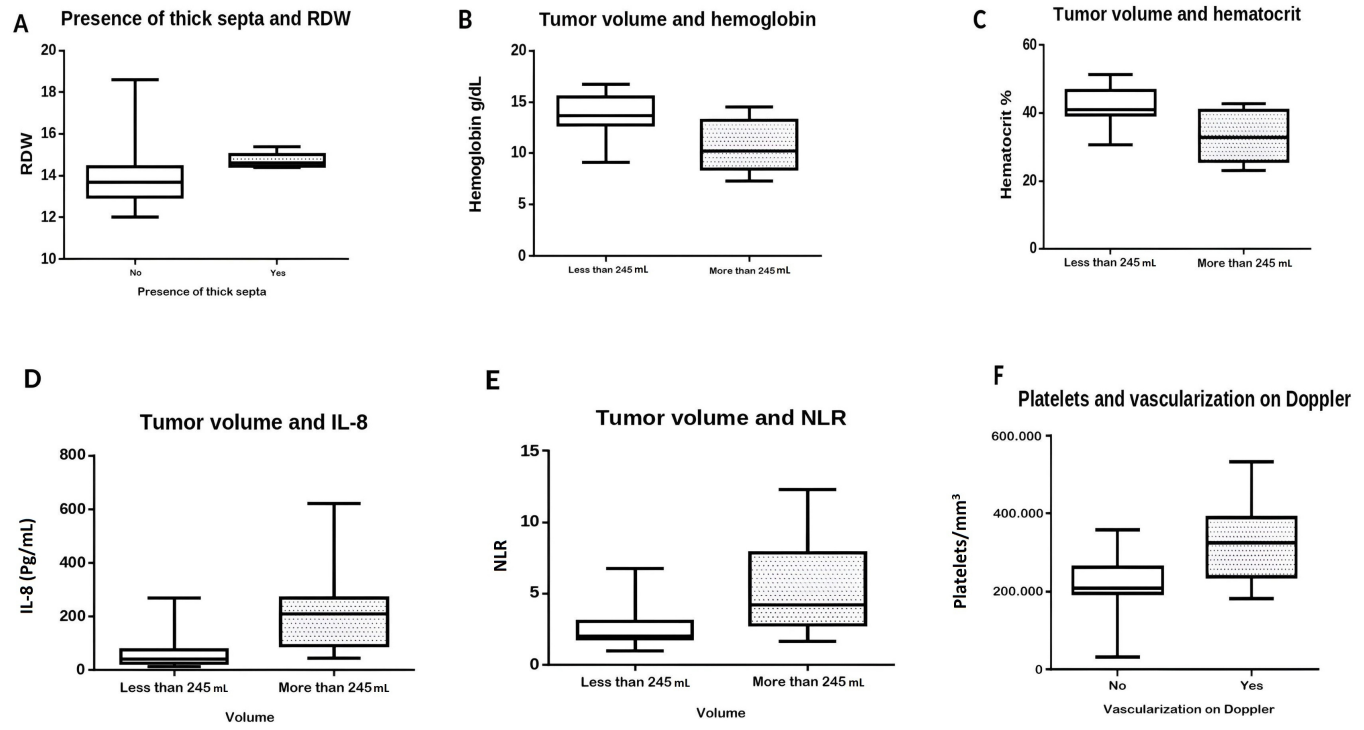

FIGURE 3. Association of hematological parameters and ultrasound findings in ovarian cancer (Mann-Whitney test). (A) Presence of thick septa and RDW. (B) Tumor volume and hemoglobin. (C) Tumor volume and hematocrit. (D) Tumor volume and IL-8. (E) Tumor volume and NLR. (F) Platelets and vascularization on Doppler. There was an association between higher RDW value and the presence of thick septa ($p = 0.0355$), and tumor volume >245 mL with lower levels of hemoglobin ($p = 0.0102$) and hematocrit ($p = 0.0095$), levels more elevation of serum IL-8 ($p = 0.0453$) and higher levels of NLR ($p = 0.0227$). RDW: red cell distribution width; IL: Interleukin; NLR: neutrophil-lymphocyte ratio.

4. Discussion

The literature points out some factors that can affect the overall survival of patients with ovarian tumors: age, comorbidities, cancer stage, histological type, gene expression, patient management. For example, taxane-based chemotherapy as first-line therapy increases survival [23]. Although some prognostic factors are already consolidated, such as tumor stage, chemotherapy treatment with taxanes and residual tumor volume after primary cytoreductive surgery, prognostic factors are necessary that precede the surgical procedure, to define a better initial approach for the patient. In this sense, blood count and ultrasound parameters may be promising prognostic factors in ovarian cancer [20].

Chronic inflammation is defined as a risk factor for ovarian cancer and other malignant tumors [24]. Some studies have evaluated the prognostic function of inflammatory markers in the blood count. One study showed for the first time that platelet-lymphocyte ratio is a new independent prognostic marker in patients with ovarian cancer [13]. Other study evaluated two hundred and forty-four patients diagnosed with invasive epithelial ovarian cancer and concluded that elevated PLR, neutrophil-lymphocyte ratio (NLR) and higher platelet count were significantly related to poor prognosis, advanced stage disease, poor differentiation and high risk of recurrence in the survival analysis [25]. Our study demonstrated an association between higher levels of NLR in patients with ovarian cancer and tumor volume greater than 245 mL. Moreover, tumor volume >245 mL was related to a lower lymphocyte count and higher PLR values, at the significance threshold.

RDW, combined with other tumor markers such as CA-125, may help differentiate between benign and malignant ovarian neoplasms [26]. RDW may also be related to overall survival in ovarian cancer [27]. We did not find any study in the literature relating hematological parameters to ultrasound findings. Our study demonstrated that higher RDW was associated with the presence of thick septa on ultrasound.

Low preoperative hematocrit may be related to poor prognostic factors in epithelial ovarian cancer [28] and borderline ovarian tumors [14]. Our study showed lower hemoglobin and hematocrit levels in patients with ovarian cancer and tumor volume greater than 245 mL.

A recent study evaluated, in addition to PLR and NLR, the monocyte-to-lymphocyte ratio (MLR) and red blood cell distribution width (RDW) in patients with epithelial ovarian cancer undergoing exploratory laparotomy and observed a worse prognosis in patients with a significantly higher value these parameters [28]. In another retrospective study, Jamal MP *et al*. [29] showed that CA-125 levels can predict greater overall and disease-free survival and a PLR <200 can suggest greater disease-free survival [29]. Our study found an association of tumor volume with NLR, PLR and RDW, but did not find an association with tumor marker levels (CA-125, CA-15.3 and CA-19.9).

Serum levels of the cytokine IL-8 can help distinguish between benign and malignant ovarian neoplasms [30]. Furthermore, IL-6 and IL-8 in serum [9, 31] and IL-6 in ascites [32] may be associated with a worse prognosis in ovarian cancer. Higher levels of IL-6, IL-8 and nitric oxide (NO) have been shown in the intracystic fluid of ovarian cancer compared to benign neoplasms [33]. Thus, as IL-8 is produced in the tumor microenvironment, larger volume tumors are expected to produce greater amounts of IL-8, as demonstrated in our study.

Transvaginal ultrasound is still considered the first-line imaging technique for evaluating adnexal masses. There is constant improvement in this diagnostic imaging approach in an attempt to differentiate malignant from benign ovarian masses. The Ovarian-Adnexal Reporting & Data System (O-RADS) classification has shown a high sensitivity of 97% and specificity of 77% to differentiate pelvic masses between malignant and benign [34, 35]. Although there are many studies in the literature relating ultrasound imaging and diagnosis, the relationship between preoperative imaging data, overall survival and disease-free survival are scarce in ovarian tumors. In our study, we found an association between pre-surgical ultrasound tumor volume and overall survival and disease-free survival. The results showed a worse survival for a tumor volume greater than 245 mL, in addition to being associated with hematological parameters with a worse prognosis. The presence of vascularization on Doppler also was associated with higher platelet values. We did not find a similar association in the literature. Most studies relate postoperative residual tumor volume and survival.

A retrospective cohort study of women diagnosed with serous ovarian cancer or the presence of high-grade stage I fallopian cancer evaluated preoperative ultrasound examinations (size and volume; general appearance; thickness, vascularization of septations; morphology and vascularization of other solid components). Early-stage high-grade serous cancers rarely presented as masses smaller than 5 cm [36]. Studies have been attempted to validate image-based radiomics for prediction of prognosis and survival in ovarian cancer, with promising results [37–39]. These prognostic models based on radiomic features, ultrasound image statistics were highly predictive of risk of death and recurrence in not only epithelial but also non-epithelial ovarian cancer. These markers have the advantage of being non-invasive for individualized prognostic assessment and treatment decisions in ovarian cancer [39]. Large adnexal masses and the presence of peculiar morphological characteristics on ultrasound, such as the presence of solid areas, are related to malignant diseases. But there is still no definition in the literature whether these characteristics are associated with prognosis and survival.

Research has frequently been carried out to optimize the pre-surgical diagnosis and prognosis of patients with pelvic masses through biomarkers and imaging tests. The study has some limitations, such as the size, the retrospective design and single-center nature of the study. The heterogeneity of histological types may also be a limitation, as non-epithelial tumors have a better prognosis. But the results can help further research with a larger number of patients to elucidate the association of ultrasound findings with the systemic inflammatory and immunological response, as well as with survival. New larger multi-institution prospectives may provide more robust data to guide clinical decision-making. On the other hand, we did not find any study in the literature that relates ultrasound findings to a broad panel of hematological, inflammatory,

immunological parameters and survival in ovarian neoplasms. Both ultrasound and blood counts are low-cost, non-invasive and accessible exams. In this way, better exploring all the potential of these exams in prognosis and survival can help the clinician to better program the best treatment strategies for ovarian neoplasms.

5. Conclusions

The discovery of new prognostic factors is of great importance, as it helps to identify patients with a greater probability of an unfavorable outcome from diagnosis, enabling the institution of more aggressive treatments. In this study, tumor volume (>245 mL) was shown to be an important prognostic factor in ovarian malignancy, decreasing overall survival and disease-free survival.

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

RSN—Conceptualization, methodology, supervision, writing-original draft preparation, writing-reviewing and editing, funding acquisition, data curation, validation, project administration. MLST, PCAC—Data curation, writing-original draft. AMF, MPJ—Data curation, writing-original draft, methodology. DCM—Data curation, writing-original draft preparation, methodology. EFCM—Supervision, writing-reviewing and editing, validation, funding acquisition.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the UFTM Research Ethics protocol number 32185020.0.0000.5154 and the patients signed the Consent Form.

ACKNOWLEDGMENT

The authors wish to acknowledge the funding received from CNPq (National Council for Scientific and Technological Development—Brazil, process No.: 01115/2018-4 and research grant for Rosekeila Simões Nomelini process No.: 303086/2022-0), FAPEMIG (Minas Gerais Research Funding Foundation, process No.: APQ-00888-21 and RED-00011-14), FUNEPU (Uberaba's Teaching and Research Foundation, process No.: 02 2011), and CAPES (Brazilian Federal Agency for the Support and Evaluation of Graduate Education, process No.: 32012012001P5).

FUNDING

This article was funded from CNPq (National Council for Scientific and Technological Development—Brazil, process No.: 01115/2018-4 and research grant for Rosekeila Simões Nomelini process No.: 303086/2022-0), FAPEMIG (Minas Gerais Research Funding Foundation, process No.: APQ-00888-21 and RED-00011-14), FUNEPU (Uberaba's Teaching and Research Foundation, process No.: 02 2011), and CAPES (Brazilian Federal Agency for the Support and Evaluation of Graduate Education, process No.: 32012012001P5).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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How to cite this article: Rosekeila Simões Nomelini, Murilo Luiz Soares Tamburús, Paula Carolina Arvelos Crispim, Agrimaldo Martins Filho, Millena Prata Jammal, Douglas Cobo Micheli, *et al*. Association of ultrasound findings with hematological parameters, cytokines and survival in ovarian cancer. European Journal of Gynaecological Oncology. 2025; 46(3): 27-33. doi: 10.22514/ejgo.2025.033.