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# Gamma-glutamyltransferase as a preoperative differential diagnostic marker in patients with adnexal mass

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ABSTRACT

*Objective:* Gamma-glutamyltransferase (GGT) is involved in tumor development, progression and chemotherapy resistance. The present study evaluated GGT serum levels as a preoperative predictive marker for ovarian cancer in patients with adnexal mass.
*Study design:* Preoperative GGT serum levels of 2235 patients with adnexal mass and subsequent surgery were ascertained (patients with benign ovarian tumors: n = 1811; borderline tumor of the ovary [BTO]: n = 85; epithelial ovarian cancer [EOC]: n = 339). Standardized expert transvaginal ultrasound was documented.
*Results:* Median (interquartile range) GGT serum levels in patients with benign ovarian tumors, BTO, and EOC were 15.0 U/l (11.0–23.0), 17.0 U/l (10.0–23.5), and 20.0 U/l (13.0–34.0), respectively (p = 0.002). Elevated GGT serum levels were associated with the presence of BTO/EOC in univariate analysis (p < 0.0001, hazard ratio 1.8, confidence interval 1.5–2.3). GGT did not outperform established tools for preoperative prediction of BTO/EOC in patients with adnexal mass, such as CA-125 measurement or transvaginal ultrasound.
*Conclusion:* Elevated GGT serum levels were not associated with the presence of BTO/EOC in women with suspicious adnexal mass in multivariate analysis. GGT serum levels did not outperform established risk factors and therefore might add only limited additional value to CA-125 serum levels in the differential diagnosis between benign and malignant adnexal masses.



## Introduction

Adnexal masses are common sonographic findings during transvaginal sonography (TVS). While approximately 75% of tumors are found to be benign, early detection and treatment of ovarian malignancy is crucial for the patients' prognosis [1–3]. However, preoperative differentiation between benign and malignant adnexal masses is challenging. Appropriate patient selection is crucial in order to avoid unnecessary surgical procedures and to provide optimal care to those who are likely to have ovarian cancer [1,2,4]. A variety of serum parameters, such as cancer antigen (CA)-125, C-reactive protein (CRP) and human epididymis protein 4 (HE4) have been investigated with the aim to successfully triage those patients [5–7].

In order to improve the differentiation of women with adnexal masses of unknown etiology, additional predictive markers, such as gamma-glutamyltransferase (GGT), are being tested. Secretory and absorptive cells show a high GGT activity. GGT is a membrane bound enzyme that is essential in the glutathione (GSH) metabolism modulation. GSH metabolism plays an important role in protecting cells against oxidants, which are produced during normal cell differentiation and proliferation [8,9]. In pathologic states of oxidative stress, such as carcinogenesis, increased GSH and GGT serum levels have been measured. Cell survival and apoptotic balance are influenced by the antioxidant GSH. Thereby, changes in GSH metabolism can have a strong effect on this balance [8,10–12].

It has been shown, that GSH and GGT play a role in tumor progression, invasion, and anticancer-drug resistance in various

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malignancies [10–16]. Elevated GGT serum levels are associated with an increased risk for cancer of female genital organs as shown in a large prospective epidemiological cohort study [17,18]. Moreover, elevated GGT serum levels are associated with advanced tumor stage and poor prognosis not only in ovarian, but also in cervical and endometrial cancer, and uterine leiomyosarcoma [19–23].

The objective of the present study was to investigate the value of GGT serum levels in combination with expert TVS as a biomarker for the prediction of ovarian malignancy in women with adnexal mass. We hypothesized that GGT might serve as an independent predictive marker for the presence of epithelial ovarian cancer (EOC) or borderline tumor of the ovary (BTO) subsequently adding additional preoperative predictive information to CA-125 serum levels.

## Material and methods

### *Patients & clinical management*

In total, 3234 consecutive patients who underwent surgery for adnexal masses from 2000 until 2012 at the Department of Obstetrics and Gynecology, Division of General Gynecology and Gynecologic Oncology, Vienna, Austria, Medical University of Vienna, were identified. Due to missing values and pathologies with non-ovarian origin (such as fibroids, sarcomas) in the final pathology result, 2235 patients with adequate documentation of preoperative TVS and GGT serum levels remained eligible for inclusion (Fig. 1).

Patients' assessment prior to surgery included blood tests, physical examination and a transvaginal ultrasound. Patients who presented with pre-existing co-morbidities, known to be possibly related to an elevation of GGT (i.e. hepato- biliary tract-, pancreatic-, and heart disease or alcohol abuse), were excluded. Ultrasound-based rules established by Timmerman et al. were used to describe the adnexal masses: B-Criteria included Acoustic shadows, unilocular cyst, smooth multilocular tumor less than 100 mm in largest diameter, presence of solid components where the largest solid component is < 7 mm in largest diameter, and no detectable blood flow on Doppler examination. M-Criteria included at least four papillary structures, ascites, irregular multilocular-solid tumor with a largest diameter of at least 100 mm, papillary irregular solid tumor, and very high color content on color Doppler examination. If at least one M-Criteria was present, the adnexal mass was considered as suspicious [24,18]. Further imaging, such as computer tomography (CT) or magnetic resonance imaging (MRI), was initiated, if a malignant process was suspected.

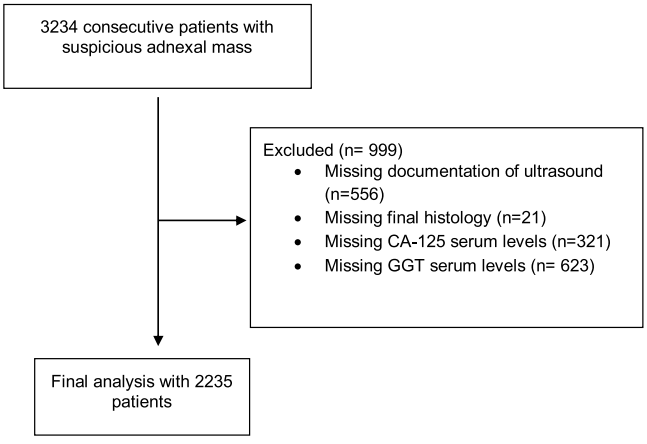


**Fig. 1.** CONSORT Diagram.

Patients were treated according to standards of our institution and tailored to the patient's risk for malignancy. Thus, either laparoscopy or laparotomy with cystectomy or unilateral/bilateral salpingo-oophorectomy (SO) was performed. In case of EOC or borderline tumor of the ovary (BOT), patients underwent comprehensive surgery to ensure adequate staging to ensure maximal cytoreduction. If primary cytoreductive surgery was not feasible, patients with EOC were treated with neoadjuvant chemotherapy and interval debulking surgery.

Preoperative GGT serum levels were compared with final pathology. Pathology was reviewed in all cases by one pathologist specialized in gynecologic oncology. Cases with an inexplicit result were discussed and presented to a second expert pathologist for final pathologic result.

### *GGT measurements*

GGT serum levels were measured by an enzyme kinetic assay (Modular Hitachi 747 and Hitachi 917, Roche Diagnostics), as described previously [25]. Patients were assigned to the previously described GGT risk groups as follows: GGT < 17.99 U/L: group A (normal low), 18.00–35.99 U/L: group B (normal high), 36.00–71.99 U/L: group C (elevated), and >72.00 U/L: group D (highly elevated) [10,15]

### *Statistical Analyses*

Descriptive statistics, such as mean, median, frequencies, and percentages, were used to describe the data and compared by chi-square or *t*-test as appropriate. Hazard ratios (HR) and 95% confidence intervals (CI) for etiology were calculated by applying logistic regression modeling adjusted for risk factors, such as menopausal status, sonographic features (presence of least one M-criteria), GGT serum levels (four risk groups) and CA-125 serum levels. These parameters were selected being already proven as possible risk factors for presence of malignant adnexal mass. A multivariate logistic regression model was conducted to analyze the association GGT serum levels with etiology adjusting for potential confounding variables. Therefore, risk group A was used as reference group. P-values <0.05 were considered statistically significant. For all the statistical analyses SPSS statistical software system version 25.0 was used.

### *Ethical approval*

The institutional review board Medical University of Vienna, Austria approved the present study (IRB-Number 1062/2015).

## Results

Initially 2235 patients who underwent surgery were included in the present study. Of these, 424 patients had a malignant adnexal mass (339 patients with EOC and 85 with BTO) and 1811 patients had a benign adnexal mass. Within the group of patients with EOC, the majority had advanced tumor stage FIGO 3–4 (72.0%) and showed high-grade serous histology (84.7%). Histologic subtypes were as follows: low-grade serous: n = 20 (6.0%), high-grade serous n = 205 (61.9%), low-grade endometrioid: n = 19 (5.7%), high-grade endometrioid: n = 37 (11.2%), mucinous: 16 (4.8%), clear cell: n = 9 (2.7%) and others: n = 25 (7.6%).

Pre-operative patients' characteristics, ultrasound findings, CA-125 serum levels and GGT serum levels broken down by histological features are shown in Table 1 [Table 1]. Median (IQR) GGT serum levels in patients with benign ovarian tumors, BTO, and EOC were 15.0 U/l (11.0–23.0), 17.0 U/l (10.0–23.5), and 20.0 U/l (13.0–34.0), respectively (p = 0.002). We observed an

**Table 1**
Patients' characteristics of women with benign adnexal masses, with borderline tumors of the ovary (BTO) and with epithelial ovarian cancers (EOC).

| | Benign N = 1811 (81%) | BTO N = 85 (4%) | EOC N = 339(15%) | P value |
|---|---|---|---|---|
| **Age in years, mean (SD)** | 43 (15) | 52 (16) | 60 (13) | <0.001[2] |
| **Menopausal status** | | | | <0.001[3] |
| Premenopausal (%) | 1245 (69) | 41 (48) | 73 (22) | |
| Postmenopausal (%) | 566 (31) | 44 (52) | 266 (78) | |
| **Ultrasound characteristics** | | | | |
| *Ascites* | | | | <0.001[3] |
| Yes (%) | 115(13) | 6 (18) | 122 (66) | |
| No (%) | 738 (87) | 28 (78) | 64 (34) | |
| *Unilateral Cyst* | | | | <0.001[3] |
| Yes (%) | 1316 (78) | 59 (72) | 170 (59) | |
| No (%) | 379 (22) | 23 (28) | 117 (41) | |
| *M- Criteria*[1] | | | | <0.001[3] |
| Yes (%) | 313 (23) | 29 (49) | 171 (73) | |
| No (%) | 1063 (77) | 30 (51) | 63 (27) | |
| **GGT (U/L) Median (IQR)** | 15.0 (11.0-23.0) | 17 (10.0-23.5) | 20 (13.0-34.0) | <0.002[2] |

BTO = borderline tumor of the ovary; EOC = epithelial ovarian cancer; GGT = Gamma-glutamyltransferase, IQR = Interquartile range.
[1] ≥ 1 M-criteria; [2]ANOVA-test; [3]Chi-square test.

association between higher pre-operative GGT serum levels and suspicious TVS, postmenopausal status, and elevated CA-125 serum levels [Table 2].

In addition, the predictive test characteristics of GGT serum levels to identify patients with EOC or BTO within our cohort were evaluated. Sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) for GGT and CA-125 were calculated. Sensitivity, specificity for GGT and CA-125 were 54.5%, 60.5% and 83.8, 73.9%, respectively. NPV and PPV for GGT and CA-125 were 85.0%, 24.4% and 92.9%, 52.8%, respectively. Moreover, the combination of the two markers to detect ovarian malignancy was tested. This led to an increase of both, sensitivity and specificity (85.2% and 81.1%). For the combination of the two markers, NPV and PPV were 62.2% and 93.6%, respectively. Particularly the increased PPV of combined CA-125 and GGT seemed to be clinically relevant. In addition, the number needed to treat (NNT) to detect one additionally patient with EOC or BTO after surgery for a suspicious adnexal mass was calculated. The combination of elevated CA-125 and GGT serum levels translated into a NNT of 5.95, 2.44, and 2.72 in premenopausal, postmenopausal women, and women overall, respectively. The additional benefit of GGT serum levels was not influenced by the menopausal status.

In univariate logistic regression analyses, elevated GGT serum levels, elevated CA-125 serum levels, postmenopausal status, and the presence of M-criteria on transvaginal ultrasound were independently associated with a higher risk for the presence of OC [Table 3]. In multivariate analysis, CA-125 serum levels, sonographic features, and menopausal status were identified as independent predictors for the presence of EOC and BTO. GGT was not an independent predictive factor in multivariate analysis despite showing a trend, that patients of the GGT high-risk group (group D) were more likely to present with EOC and BTO than patients of the GGT low-risk group (A) [Table 3].

**Table 2**
Median Gamma-glutamyltransferase values categorized by clinico-pathological parameters.

| Parameter | Median (IQR) GGT U/l | P |
|---|---|---|
| **Menopausal status** | | <0.0001[1] |
| premenopausal | 14.0 (11.0-21.0) | |
| postmenopausal | 19.0 (13.0-30.0) | |
| **Sonographic features** | | 0.006[1] |
| B-criteria | 15.0 (11.0-24.0) | |
| M-criteria | 16.0 (12.0-26.0) | |
| **CA-125**[2] | | 0.001[1] |
| <35.0 | 16.0 (11.0-24.0) | |
| >35.0 | 17.0 (12.0-31.0) | |

IQR = Interquartile range, CA 125 = Cancer Antigen 125.
[1] Mann-Whitney-U-test, [2] CA-125 in kU/l.

## Comment

In the present study, GGT serum levels could not be ascertained as an independent predictive marker for the presence of ovarian malignancy in women with an adnexal mass. Elevated GGT serum levels were associated with increased risk for EOC/BTO at the time of surgery only in univariate analysis. Moreover, GGT could not outperform established diagnostic tools in the preoperative differential diagnosis of adnexal masses such as CA-125 measurement or TVS. Nonetheless, GGT serum levels might add some additional value to CA-125 measurements as the combination of GGT and CA-125 resulted in a NNT (i.e., patients undergoing surgery for a suspicious adnexal mass and a postoperative histology of EOC or BTO) of 2.72.

In the present study, GGT could not outperform established diagnostic tools in the preoperative differential diagnosis of adnexal masses such as CA-125 measurement or TVS. In contrast, many recently published studies describe elevated GGT serum levels as an independent risk factor in various malignancies, such as cervical, esophageal, hepatocellular and prostate cancer [26–29]. This might have several reasons: First, the GGT cut-off types substantially vary between studies. Five studies used the stratification into the previously described four GGT serum level groups [21,22,19,20,30], two studies established new cut-off values by using the calculated quartiles of the study population [28,27], two studies used a cut-off level of 50U/L [29,16] and one study used a cut-off level of 36 U/L [23]. Of note, we used the well-established stratification into four GGT serum level groups. This decision has been made at the time of study design and has not been changed during statistical analysis. Second, some positive studies have limited population cohorts ranging between 44 and 520 patients. Third, positive study findings are more likely to be published than negative findings [31]. Thus, the association between GGT serum levels and malignancies might be presented more positive when reviewing the literature than it might be in real-life. Additionally, median GGT levels in the present study of OC patients were relatively low (GGT = 20U/l) compared to other studies. Mean GGT levels of 34 U/l and 36U/l in ULMS and cervical cancer patients were measured in the study by Schwameis and Zhu et al. [21,23]. This might also be explained by the small sample sizes in the reported other studies of 44 and 520 patients, respectively [23,21].

**Table 3**
Univariate and multivariate analysis of predictive markers to identify patients with epithelial ovarian cancer (EOC).

| Parameter | univariate | | multivariate | |
|---|---|---|---|---|
| | P | HR (95% CI) | P | HR (95% CI) |
| **Menopausal status**[1] | <0.0001[8] | 6.0 (4.7-7.6) | <0.0001 | 6.0 (4.0-8.9) |
| **Sonographic features**[2] | <0.0001[8] | 7.3 (5.5-9.6) | <0.0001 | 5.2 (3.6-7.5) |
| **GGT (U/L); Group A (ref)** 3 | <0.0001[8] | 1.8 (1.5-2.3) | 0.42 | – |
| **Group B**[4] | <0.0001[8] | 1.6 (1.3-2.0) | 0.29 | 1.6 (0.7-3.8) |
| **Group C**[5] | <0.0001[8] | 2.5 (1.8-3.4) | 0.43 | 1.4 (0.6-3.5) |
| **Group D**[6] | <0.0001[8] | 2.5 (1.5-4.2) | 0.13 | 2.1 (0.8-5.7) |
| **CA-125 (kU/L)**[7] | <0.0001[8] | 14.6 (10.8-19.9) | <0.0001 | 14.0 (9.3-21.0) |

[1] premenopausal/ postmenopausal; [2] ≥1 M-Criteria = suspicious; [3] Group A = Cut-off 17.99 U/L, [4] Group B = 18.00–35.99 U/L; [5] Group C = 36.00–71.99 U/L; [6] Group D= >72.00 U/L; [7] Cut off 35.0 kU/L, [8]Chi-squared test.

In addition, elevated GGT serum levels were described to correlate with GGT protein expression in the tumor tissue of patients with EOC. EOC patients with advanced tumor stage were observed to present with elevated GGT serum levels [22]. Moreover, elevated GGT serum levels were also associated with poorer prognosis in a variety of gynecological cancers such as ovarian, cervical, endometrial cancer and uterine leiomyosarcoma [19–23]. Therefore, GGT serum levels also seem to correlate with aggressive tumor biology. Thus, it seems clinically plausible, that GGT, a marker of oxidative stress, provides additional information both in the differentiation between benign and malignant adnexal masses and in the prognosis.

Elevated GGT most likely reflects the extent of malignant cell transformation and cell turnover caused by the extent of tumor load, the tumor's aggressiveness, and biological behavior by revealing the amount of pathologic oxidative stress in cancer patients. The biology of GGT and its impact on cancer development, progression, and drug resistance has already been investigated [10–12]. GGT and GSH play an important role in the cellular antioxidant defense mechanism by binding reactive oxygen species [8,32]. Interestingly, it was shown that GGT influences the cellular proliferative-apoptotic balance by exerting pro-oxidant effects at the membrane surface level and in the extracellular microenvironment [33]. Thus, it seems biologically plausible, that elevated GGT serum levels are associated with malignancy in patients with suspicious adnexal masses and therefore be useful in the preoperative differential diagnosis of these patients [22].

A precise preoperative risk estimation for malignancy is challenging but clinically highly relevant. Patients with a high likelihood of ovarian cancer should be transferred to a gynecologic oncology center before surgery. Test performance of GGT serum levels alone was not as good as test performance of CA-125 serum levels in predicting malignancy in patients with adnexal masses. However, the combination of GGT and CA-125 increased the PPV to 93.6% and reduced the NNT for the identification of EOC/BTO in premenopausal, postmenopausal women, and women overall, to 5.95, 2.44, and 2.72, respectively. In contrast, alternative serum markers such as HE4 have been described to detect EOC/BTO in 77.6% [34]. Thus, the combination of CA-125 and GGT might be of particular clinical value in triaging these patients in a high-risk or low-risk group for presence of malignancy. Moreover, GGT is a broadly available and cheap serum marker providing - in combination with CA-125 - at least comparable test characteristics to other more expensive markers. Nevertheless, even the combination of these two markers cannot be used to rule out EOC and BTO in women with an adnexal mass reliably, as the observed NPV was only 62%.

The present study is the first to evaluate GGT serum levels as a predictive biomarker for the presence of BTO/EOC. This is a clinically relevant endpoint, as the adequate triage of women with adnexal masses in specialized centers is crucial in the treatment for EOC. Moreover, the present study comprises a large cohort of patients, diagnosed and treated in a tertiary University hospital receiving a standardized and well documented TVS. The present cohort represents consecutive patients at our center providing a real-life clinical scenario. Nonetheless, the retrospective study design has to be considered as a limiting factor. Therefore, bias due to the study design cannot be ruled out, although patients were collected in a prospectively maintained database and all patients were seen by a general practitioner preoperatively to rule out severe comorbidities such as diseases potentially elevating GGT serum levels.

In summary, we were not able to ascertain GGT serum levels as a predictive marker of ovarian malignancy in women with suspicious adnexal masses as it was only elevated in univariate analysis but could not be confirmed in multivariate analysis. GGT serum levels were not able to outperform already established risk factor, but the combination of CA-125 and GGT serum levels resulted in a high PPV and low NNT for patients undergoing surgery for suspicious adnexal masses after standardized, expert TVS. Overall, GGT does not seem to add sufficient additional value in predicting presence of a malignant adnexal mass.

## Conflicts of interest

The authors declare no conflict of interest.

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