Use of cancer antigen 125, cancer antigen 19-9, and the neutrophil-to-lymphocyte ratio to diagnose mature cystic teratoma with torsion

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Keywords: Cancer antigen 19-9; Cancer antigen 125; Mature cystic teratoma; Neutrophil-to-lymphocyte ratio; Torsion

Synopsis: Combined evaluation of cancer antigen 125, cancer antigen 19-9, and the neutrophil-to-lymphocyte ratio proved an efficient method to diagnose mature cystic teratoma with torsion.

ABSTRACT

Objective: To determine the efficacy of serum levels of cancer antigen 125 (CA125) and cancer antigen 19-9 (CA19-9), and the neutrophil-to-lymphocyte ratio (NLR) for diagnosis of mature cystic teratoma (MCT) with torsion.

Methods: A retrospective medical record review was conducted of data for women who had undergone surgery for ovarian MCT at the First Affiliated Hospital of Wenzhou Medical University, China, between January 1, 2008, and January 1, 2015.
Patients with torsion and a control group who underwent surgery on the same days were identified. Clinical characteristics and the serum levels of CA125, CA19-9, and the NLR were assessed.

**Results:** The serum levels of CA125, CA19-9, and the NLR were higher in the torsion group (n=68) than in the control group (n=120; $P \leq 0.001$ for all). Receiver operating characteristic analysis indicated that the area under the curve for the combined use of CA125, CA19-9, and NLR was 0.978 (95% confidence interval 0.954–1.000; $P < 0.001$). This combination had a diagnostic sensitivity of 93.9% and a specificity of 98.3%. Moreover, levels of these inflammatory markers were significantly increased among patients with large tumor diameters ($P < 0.01$ for all).

**Conclusion:** The combined measurement of CA125, CA19-9, and the NLR provided an efficient method for the diagnosis of MCT with torsion.

### 1 INTRODUCTION

Mature cystic teratoma (MCT)—also known as dermoid cyst or benign cystic teratoma of the ovary—is the most frequently diagnosed germ-cell ovarian tumor, particularly among reproductive-aged women [1]. Indeed, this condition accounts for 60% of all primary benign ovarian tumors worldwide [2]. Ovarian MCTs typically comprise well-differentiated tissues derived from the three germ-cell layers (endoderm, mesoderm, and ectoderm), and are usually made up of mature tissues (e.g. skin, hair, and fat) [3].
Most patients with MCT (64.5%) are asymptomatic [4]. Patients who are symptomatic often report pelvic pain (47.6%), swelling (15.4%), and vaginal bleeding (15.1%) [5]. Although most MCTs are benign, 20% of affected individuals experience complications, including torsion, rupture, infection, and malignant transformation [6].

Torsion is the most frequent complication of MCT, occurring among 15%–16% of all patients [2]. Owing to a moderate volume and contents of varying density, the center of gravity of an MCT is usually biased to one side [7]. Consequently, the tumor will twist when the patient undergoes physical activity, such as playing sport or changing posture during sexual intercourse. Laparoscopy is widely used in the clinical management of MCT [8,9]. Most patients undergo selective surgery; however, emergency procedures are suggested for patients with suspected adnexal torsions, who present with acute abdominal pain [10]. The surgical procedure used in such cases depends on the patient’s age, reproductive potential, and malignancy risk [9,10].

Delays in the recognition and treatment of torsion can result in loss of ovarian function and infertility; however, preoperative examinations have been reported to lead to diagnosis among only 46% of patients with MCT [11]. To date, no specific laboratory markers seem to have been found that aid preoperative diagnosis of MCT complicated by torsion.

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Inflammatory markers could offer a novel approach to the diagnosis of this condition. Elevated levels of cancer antigen 125 (CA125) are frequently found in epithelial ovarian cancer; however, increased concentrations of this marker can also be detected in endometrioma, uterine leiomyoma, several types of inflammatory disease, and MCT [12–14]. Another cancer antigen (CA19-9) has a glycolipid structure and was initially found to be elevated in gastrointestinal adenocarcinomas, particularly those of the pancreas [15]. Some studies have indicated that CA19-9 levels are also increased in MCT, especially among cases complicated by torsion [16]. The neutrophil-to-lymphocyte ratio (NLR) is an index of the systemic inflammatory response that can be used when identifying the degree of inflammation in various diseases, such as ovarian and lung cancers [17,18]. Of note, Ercan et al. [19] demonstrated that the NLR might also be a useful measurement in the diagnosis of adnexal torsion.

The aim of the present study was to investigate whether CA125, CA19-9, and the NLR might offer accurate preoperative diagnosis of MCT with torsion.

2 MATERIALS AND METHODS

A retrospective medical record review was conducted of women with ovarian MCT who underwent surgery in the Department of Gynecology, First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China, between January 1, 2008, and
January 1, 2015. Patients for whom torsion was suspected preoperatively and confirmed during surgery were considered the torsion group. A control group of patients without torsion who underwent surgery on the same days was identified. Patients with adenomyosis, ruptured tumor, preoperative inflammatory disease, other gastrointestinal tumors, or pregnancy were excluded from both groups. The present study was approved by the institutional ethics board of First Affiliated Hospital of Wenzhou Medical University. Informed consent was not necessary as a result of the retrospective nature of the study.

All patients underwent preoperative transabdominal or transvaginal ultrasonography. The mean size of MCT was determined by review of both the operative records and the ultrasonographic descriptions. Blood samples were collected from the patients within 3 days before surgery. Clinical and pathological data were extracted from the medical records.

The data were analyzed using SPSS version 20.0 (IBM, Armonk, NY, USA). Receiver operating characteristic (ROC) analysis was used to evaluate the diagnostic value of preoperative measurement of the inflammatory markers. The ROC area under the curve (AUC) was used to determine the sensitivity and specificity of each marker, either alone or in combination. The optimal cutoff values were calculated by ROC analysis and the Youden index. Continuous data were expressed as the mean ±
standard deviation. One-way analysis of variance (ANOVA) or the Student t test were used to evaluate between-group differences. P<0.05 was considered statistically significant.

3 RESULTS

A total of 68 patients formed the torsion group, and 120 patients were included in the control group (Figure 1). Of the patients in the torsion group, 52 (76.5%) presented with abdominal pain for a period of 1–7 days, 4 (5.9%) had symptoms of abdominal distention, and 12 (17.6%) were asymptomatic, with pelvic masses reported as the cause of hospital admission. Overall, 62 (91.2%) patients in the torsion group underwent laparoscopic procedures; 6 (8.8%) underwent laparotomy. During surgery, 56 (82.4%) patients had a cystectomy and 12 (17.6%) underwent salpingo-oophorectomy. In the control group, 89 (74.2%) patients were asymptomatic, 17 (14.2%) had pelvic pain, 8 (6.7%) presented with abdominal distention, and 6 (5.0%) were admitted with abnormal vaginal bleeding. Among the 120 patients, 111 (92.5%) underwent laparoscopic procedures and 9 (7.5%) underwent laparotomy. During surgery, 107 (89.2%) patients had a cystectomy and 13 (10.8%) underwent salpingo-oophorectomy.

The mean age of the cohort was 33.60 ± 11.53 years (range 11–77). The maximum diameter of the MCT ranged from 3 cm to 20 cm, with a mean value of 7.17 ± 3.48 cm. The mean carcinoembryonic antigen level was higher in the torsion
group than in the control group ($P=0.027$), as were the mean white blood cell, neutrophil, and lymphocyte counts ($P<0.001$ for all) (Table 1). Bilateral involvement was more frequent in the torsion group than in the control group ($P<0.001$) (Table 1). The mean serum levels of CA125 and CA19-9, and the NLR were all higher in the torsion group than in the control group ($P \leq 0.001$ for all), with the CA19-9 level found to be abnormally elevated in some patients with torsion (Table 1).

Table 2 outlines the relationship between MCT characteristics and CA125, CA19-9, and the NLR. The serum levels of CA125 and CA19-9, and the NLR were elevated among patients with large MCTs ($\geq 10$ cm maximum diameter; $P<0.01$ for all). A similar trend was observed for bilateral MCTs; however, the differences were not statistically significant.

The ROC analysis of the inflammatory markers among patients with torsion is shown in Figure 2, with the key diagnostic values outlined in Table 3. In all, 28 (41.2%) patients with torsion of MCT had a CA125 level of less than 20 U/mL, 36 (52.9%) had a CA19-9 level of less than 36.05 U/mL, and 35 (51.5%) had an NLR of greater than 3.56. The AUC for the combined measurement of CA125, CA19-9, and the NLR was 0.978 (95% confidence interval 0.954–1.000; $P<0.001$). This approach had a diagnostic sensitivity of 93.9%, a specificity of 98.3%, a positive likelihood ratio of 55.24, and a negative likelihood ratio of 0.06 (Table 3). This article is protected by copyright. All rights reserved.
The ROC analysis of the maximum diameter of MCT with torsion is shown in Figure 3. The AUC was 0.895 (95% confidence interval 0.85–0.94; \( P < 0.001 \)), with a cutoff value of 8.5 cm, a sensitivity of 81.6%, a specificity of 86.7%, a positive likelihood ratio 6.14, and a negative likelihood ratio of 1.38 (Table 3).

4 DISCUSSION

To the best of our knowledge, the present study was the first to demonstrate the efficacy of using CA125, CA19-9, and the NLR (either alone or in combination) as markers for the preoperative diagnosis of MCT with torsion. Of note, torsion was associated with abnormally high levels of CA19-9 and MCTs that were at least 8.5 cm in diameter. Likewise, the MCT diameter correlated with the serum levels of CA125, CA19-9, and the NLR, which suggested that patients with large tumors were at increased risk of torsion.

The present study found that the serum level of carcinoembryonic antigen was higher in the torsion group than in the control group. Furthermore, patients with torsion tended to have large tumors, a finding that might be indirectly related to the high levels of carcinoembryonic antigen observed in this group. Chen et al. [20] reported that 2.78% of MCTs expressed this marker. These investigators subsequently concluded that elevation of CA19-9 is probably the most reliable marker among many tumor markers for diagnosing MCT. This position is in agreement with the present study, which found a specificity of 99.2% for CA19-9 (although the sensitivity of this marker was only 63.6%).

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A previous study [6] found the levels of CA19-9 and CA125 to be elevated among 39.6% and 23.3%, respectively, of patients with MCT; the levels of CA19-9 were most likely to be raised, suggesting that this molecule is a potentially useful marker of MCT. Abnormal elevation of CA19-9, combined with mild elevation of CA125, has been reported among patients with torsions of MCT [2,21,22]. In the present study, the mean level of CA19-9 in the torsion group was 404.50 U/mL, whereas the mean level of CA125 was 68.54 U/mL. Abnormal elevations of CA19-9 and CA125 have been recorded for other types of ovarian lesion. Dai et al. [23] reported mean levels of CA19-9 and CA125 of 1058.07 U/mL and 797.89 U/mL, respectively, in a group of 43 patients with ruptured ovarian endometriomas. Biskup et al. [24] reported a mean CA125 level of 225.86 U/mL among patients with early-stage epithelial ovarian cancer. Another study [18] found that the mean CA125 level was 941.56 U/mL in a group of 143 patients with ovarian cancer. Chen et al. [25] evaluated the levels of various markers among 232 patients with pelvic masses (including 60 with ovarian cancer and 70 with benign ovarian masses). These researchers found that the AUC for CA125 was 0.926, whereas the AUC for CA19-9 was 0.488 [25]; however, they did not recommend combined detection of these two markers for ovarian malignancies.

The pretreatment NLR has been studied in localized papillary renal cell carcinoma [26] and non-small cell lung cancer [27]. Deng et al. [28] found that this inflammatory marker was an independent predictor of prognosis among patients with gastric cancer.
cancer. These researchers suggested that neutrophils and other leukocytes could be recruited by cancer cells through the activity of T cells, chemokines, and prostaglandins. Such recruitment would contribute to increased expression of inflammatory mediators and cytokines, with concomitant suppression of apoptosis, among patients with cancer. Gunay et al. [29] studied 269 patients with chronic obstructive pulmonary disease and found that NLR might be a novel marker for the assessment of inflammation in this population. These data are in line with those of the present study, which found preoperative NLR to be substantially higher among MCT patients with torsion than among those without this complication.

The mechanisms by which CA125, CA19-9, and the NLR become elevated among MCT patients with torsion have yet to be established. The MCT cavities are lined with simple mucinous epithelium. The presence of large amounts of CA19-9 within the apical cytoplasm of the epithelial lining suggested that this molecule is secreted into the cystic cavity, where it accumulates [30]. The cyst wall could become progressively weakened by the torsion process, which in turn might lead to leakage of CA19-9 into the bloodstream (detected as elevated serum levels). By contrast, the observed elevations of CA125 and the NLR might be caused by an inflammatory process. The presence of active pelvic inflammation among MCT patients with torsion is associated with an acute phase reaction [31]. Ovarian ischemia–reperfusion injury owing to twisting and subsequent release of the MCT is the main pathophysiological cause of torsion [32]. Previous studies have investigated various inflammatory mechanisms.
that could be involved in this process, such as mean platelet volume or cytokine expression [11,31,33,34]. In the present study, white blood cell, neutrophil, and lymphocyte counts were all markedly higher in the torsion group than in the control group. Elevated serum concentrations of interleukin-6 were previously shown to be associated with the occurrence of ovarian torsion [35]. Cytokines might also function in the elevation of CA125 and the NLR [28,36].

The present study was limited by the small size of the cohort investigated and the retrospective design. Additional studies are, therefore, required to confirm the roles of inflammatory markers in MCT with torsion.

In conclusion, the present study demonstrated that serum levels of CA125, CA19-9, and the NLR were raised among patients with MCT complicated by torsion. A diagnostic approach that combines the measurement of these three inflammatory markers could potentially aid preoperative identification of this condition.

**Author contributions**

All authors contributed to study conception, design, and coordination of the study. W-tX, FW, and X-xZ were responsible for data collection. W-tX, FW, X-xZ, and F-yZ reviewed the data. Y-qW, FW, and FL performed the statistical analysis. Y-qW, W-tX, F-yZ, and FL prepared the draft of the manuscript. All authors critically revised and approved the final manuscript.
Acknowledgments

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Conflict of interest

The authors have no conflicts of interest.

References


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Figure legends

**Figure 1** Flow of patients through the study. Abbreviation: MCT, mature cystic teratoma.

**Figure 2** Receiver operating characteristic analysis of inflammatory markers to diagnose mature cystic teratoma with torsion. Abbreviations: CA125, cancer antigen 125; CA19-9, cancer antigen 19-9; NLR, neutrophil-to-lymphocyte ratio.

**Figure 3** Receiver operating characteristic analysis of the maximum diameter of mature cystic teratoma with torsion.
Table 1 Baseline characteristics.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Torsion group (n=68)</th>
<th>Control group (n=120)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>31.64 ± 14.06</td>
<td>34.68 ± 9.77</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Carcinoembryonic antigen, U/mL</td>
<td>2.56 ± 4.87</td>
<td>1.54 ± 1.13</td>
<td>0.027</td>
</tr>
<tr>
<td>CA125, U/mL</td>
<td>68.54 ± 181.00</td>
<td>14.02 ± 5.58</td>
<td>0.001</td>
</tr>
<tr>
<td>CA19-9, U/mL</td>
<td>404.50 ± 1116.45</td>
<td>12.49 ± 9.28</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Neutrophil-to-lymphocyte ratio</td>
<td>5.28 ± 3.33</td>
<td>2.15 ± 0.77</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>White blood cell count, ×10(^9)/L</td>
<td>9.31 ± 3.48</td>
<td>6.14 ± 1.44</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Neutrophil count, ×10(^9)/L</td>
<td>7.04 ± 3.43</td>
<td>3.81 ± 1.18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lymphocyte count, ×10(^9)/L</td>
<td>1.54 ± 0.56</td>
<td>1.87 ± 0.50</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Maximum diameter of the ovarian mature cystic teratoma, cm</td>
<td>10.59 ± 2.84</td>
<td>5.79 ± 2.68</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ovarian involvement</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Unilateral</td>
<td>49 (74.2)</td>
<td>113 (94.2)</td>
<td></td>
</tr>
<tr>
<td>Bilateral</td>
<td>17 (25.8)</td>
<td>7 (5.8)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CA125, cancer antigen 125; CA19-9, cancer antigen 19-9.

\textsuperscript{a} Values are given as mean ± SD or number (percentage), unless indicated otherwise.
Table 2 The relationship between serum inflammatory markers and variables associated with mature cystic teratoma.\(^a\)

<table>
<thead>
<tr>
<th>Variable</th>
<th>CA125, U/mL</th>
<th>CA19-9, U/mL</th>
<th>Neutrophil-to-lymphocyte ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum diameter of the ovarian mature cystic teratoma, cm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10</td>
<td>16.84 ± 15.48</td>
<td>32.55 ± 107.83</td>
<td>2.56 ± 1.71</td>
</tr>
<tr>
<td>≥10</td>
<td>73.54 ± 211.60</td>
<td>418.84 ± 1296.93</td>
<td>4.06 ± 3.03</td>
</tr>
<tr>
<td>P value</td>
<td>0.004</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ovarian involvement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unilateral</td>
<td>32.89 ± 117.86</td>
<td>151.13 ± 730.64</td>
<td>3.14 ± 2.54</td>
</tr>
<tr>
<td>Bilateral</td>
<td>36.59 ± 31.66</td>
<td>154.69 ± 265.97</td>
<td>4.05 ± 2.61</td>
</tr>
<tr>
<td>P value</td>
<td>0.879</td>
<td>0.981</td>
<td>0.105</td>
</tr>
</tbody>
</table>

Abbreviations: CA125, cancer antigen 125; CA19-9, cancer antigen 19-9.

\( ^a \) Values are given as mean ± SD unless indicated otherwise.
Table 3 The diagnostic value of serum inflammatory markers for mature cystic teratoma with torsion.\textsuperscript{a,b}

<table>
<thead>
<tr>
<th>Marker</th>
<th>Cut off value</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>Area under the curve (95% confidence interval)</th>
<th>Positive likelihood ratio</th>
<th>Negative likelihood ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA125, U/mL</td>
<td>20.0</td>
<td>69.7</td>
<td>87.5</td>
<td>0.832 (0.764–0.899)</td>
<td>5.58</td>
<td>0.35</td>
</tr>
<tr>
<td>CA19-9, U/mL</td>
<td>36.05</td>
<td>63.6</td>
<td>99.2</td>
<td>0.820 (0.744–0.896)</td>
<td>97.50</td>
<td>0.37</td>
</tr>
<tr>
<td>Neutrophil-to-lymphocyte ratio</td>
<td>3.56</td>
<td>62.1</td>
<td>95.0</td>
<td>0.835 (0.769–0.902)</td>
<td>12.42</td>
<td>0.40</td>
</tr>
<tr>
<td>Combination \textsuperscript{c}</td>
<td>NA</td>
<td>93.9</td>
<td>98.3</td>
<td>0.978 (0.954–1.000)</td>
<td>55.24</td>
<td>0.06</td>
</tr>
<tr>
<td>Maximum diameter of the ovarian mature cystic teratoma, cm</td>
<td>8.5</td>
<td>81.6</td>
<td>86.7</td>
<td>0.895 (0.849–0.942)</td>
<td>6.14</td>
<td>1.38</td>
</tr>
</tbody>
</table>

Abbreviations: CA125, cancer antigen 125; CA19-9, cancer antigen 19-9; NA, not applicable.

\textsuperscript{a} Receiver operating characteristic analysis.

\textsuperscript{b} The $P$ value for the area under the curve was <0.001 for all markers assessed.

\textsuperscript{c} Comprising measurement of serum CA125 level, serum CA19-9 level, and serum neutrophil-to-lymphocyte ratio.