Research Square

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Study on long non-coding RNA CCAT1 as a potential serum biomarker for epithelial ovarian cancer

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Research Article

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Abstract

Background

Long non-coding RNA colon cancer-associated transcript 1 (CCAT1) has been implicated in multiple malignancies, yet its potential as a serum biomarker for epithelial ovarian cancer (EOC) remains unexplored.

Objective

To evaluate whether serum CCAT1 can serve as a clinically useful tool for the early diagnosis and prognostic assessment of EOC.

Methods

Serum specimens were collected from 165 individuals, including patients with newly diagnosed EOC (n = 22), postoperative EOC (n = 12), post-chemotherapy EOC (n = 68), benign ovarian neoplasm (n = 12), ovarian cyst (n = 27), and healthy controls (n = 23). CCAT1 expression was quantified by RT-qPCR. Diagnostic performance was assessed by ROC curve analysis. while the Pearson correlation coefficient (PCC) was adopted to analyze the correlation among the expression levels of the three indicators (CCAT1, CEA and CA125). Finally, the diagnostic value of CCAT1 combined with CEA and CA125 for EOC was comprehensively evaluated.

Results

Serum CCAT1 was significantly elevated in EOC, ovarian neoplasm (BON), and patients with ovarian cyst (OC) patients versus Normal Control ($P < 0.001$). CCAT1 levels were higher in stage III + IV than in stage I + II EOC ($P = 0.008$), and higher in postoperative than in post-chemotherapy patients ($P = 0.004$). Elevated CCAT1 was positively associated with FIGO stage, lymph node metastasis, distant metastasis, and pelvic-abdominal effusion (all $P < 0.05$). For distinguishing Normal control from early (I + II) EOC, CCAT1 achieved an AUC of 0.8152; For distinguishing stage I + II from stage III + IV EOC, CCAT1 achieved an AUC of 0.8393. The CCAT1 + CA125 combination yielded 86.36% sensitivity and 100.00% specificity.

Conclusion

Serum CCAT1 represents a potential independent biomarker for EOC, and its combination with CA125 may enhance overall diagnostic performance.

Introduction

Ovarian cancer ranks as the seventh most common cause of cancer-related death among women and is the deadliest gynecologic malignancy worldwide, accounting for approximately 314,000 new cases and 207,000 deaths each year [1]. Epithelial ovarian cancer (EOC), which makes up 80–90% of all ovarian malignancies, poses a particularly serious threat to women's health [1]. Across the past three decades, both incidence and mortality have trended upward in China: the age-standardized incidence rate climbed from 2.21 per 100,000 in 1990 to 6.52 per 100,000 in 2019 (an average annual increase of 3.85%), while mortality rose from 1.40 to 4.17 per 100,000 over the same period [2]. Despite steady advances in surgery, chemotherapy, and targeted agents, overall survival for ovarian cancer patients has remained disappointing [3]. A major contributing factor is the deep pelvic location of the ovaries, which keeps early symptoms subtle. By the time most patients present for care, they are already at advanced stages, often reporting abdominal distension, pelvic discomfort, fatigue, weight loss, and reduced appetite [4]. Identifying reliable biomarkers for early detection is therefore critical to improving survival and long-term outcomes.

Clinical screening and diagnosis of ovarian cancer at present relies heavily on serologic markers such as CA125 and HE4, together with imaging modalities like transvaginal ultrasonography [5]. Even so, a considerable proportion of early-stage cases escape detection, and the 5-year survival rate for ovarian cancer remains below 40% [6]. Although CA125 and HE4 are well-established markers, both carry a risk of false-positive results [7]. The Risk of Ovarian Malignancy Algorithm (ROMA) index has shown utility in distinguishing ovarian cancer from benign ovarian tumors [8], yet its diagnostic performance varies across geographic regions and socioeconomic contexts, which limits its broader applicability [9].

Ever since circulating tumor cells were first observed in human body fluids in 1869, advances in liquid biopsy have steadily opened doors to non-invasive or minimally invasive strategies for disease diagnosis [10]. Biological fluids and metabolic products participate in tumor biology through multiple routes, and a growing array of specimen types—urine [11], pleural effusion [12], ascites [13], serum [14], plasma [15], and extracellular vesicles [16]—have drawn interest for their diagnostic potential. In the work described here, we selected serum as the matrix for exploring early EOC biomarkers, given how readily it can be collected and how well it fits our existing clinical laboratory platform.

Long non-coding RNAs (lncRNAs) are a class of RNA transcripts longer than 200 nucleotides that do not encode proteins but exert regulatory effects on gene expression at the transcriptional, post-transcriptional, and epigenetic levels [17]. Their dysregulation has been documented across many cancer types. Colon cancer-associated transcript 1 (CCAT1), a lncRNA encoded at the 8q24.21 locus, was originally identified in colorectal cancer but has since been linked to multiple malignancies [18]. A handful of studies have explored CCAT1 as a serum biomarker. Wang et al [19] reported that the combined detection of serum CCAT1 and SOX2OT could effectively screen for non-small cell lung cancer. Yang [20] found that serum CCAT1 holds diagnostic value for colorectal cancer, and Galamb et al [21] confirmed its diagnostic and prognostic utility in colorectal tumors using both tissue and circulating specimens. However, whether serum CCAT1 might serve as a biomarker for EOC—and whether its measurement could improve upon existing clinical tools—are questions that remain open.

To address these gaps, we measured serum CCAT1 expression by RT-qPCR across EOC patients (covering newly diagnosed, postoperative, and post-chemotherapy cases), patients with benign ovarian neoplasm (BON), patients with ovarian cyst (OC), and healthy female controls. Our aim was to evaluate the clinical value of serum CCAT1 for the early diagnosis and prognostic assessment of EOC.

Materials and Methods

Study Population

A total of 165 serum specimens were collected from patients with histologically confirmed EOC (newly diagnosed, postoperative, and post-chemotherapy), BON, and OC at the Department of Clinical Laboratory, Zunyi First People's Hospital (The Third Affiliated Hospital of Zunyi Medical University) between June 2020 and December 2021. Healthy women who underwent routine physical examinations at the same hospital during the same period were enrolled as normal controls (Table 1). Clinical information—age, tumor size, FIGO stage, lymph node metastasis, and distant metastasis—along with CEA and CA125 results, was extracted from electronic medical records and the laboratory information system.

Table 1
Distribution of research subjects

Group	Sample number
EOC	22
Postoperative EOC (pre-chemotherapy)	12
Postoperative chemotherapy EOC	68
Benign ovarian neoplasm (BON)	12
Ovarian cyst (OC)	27
Normal Control	23
Total	165

Footnote: Blood sampling for postoperative EOC was completed prior to initiation of adjuvant chemotherapy.

Inclusion and Exclusion Criteria

EOC, BON, and OC patients were all newly diagnosed and treatment-naïve, with no history of prior therapy. They also had no concurrent malignancies, polyps, inflammatory conditions, genetic disorders, or immunodeficiency at other sites. Patients whose postoperative pathology ruled out EOC, BON, or OC were excluded, as were women who were pregnant or lactating and those who declined to participate.

Diagnostic criteria followed the Guidelines for the Diagnosis and Treatment of Ovarian Malignancies (2021 Edition) issued by the Gynecologic Oncology Committee of the Chinese Anti-Cancer Association [4]. The study protocol was approved by the Ethics Committee of Zunyi First People's Hospital (Approval No. 2025-1-1000).

Specimen Collection and Storage

Fasting venous blood (2 mL) was drawn from each participant into RNase-free Eppendorf tubes. Samples were transported on ice and stored immediately at − 80°C (AUCMA, China) until analysis.

RT-qPCR

Total RNA was extracted from serum using the TRIzol method. RNA concentration and purity were assessed by measuring absorbance at 260 nm and 280 nm on a UV spectrophotometer (Ph. Biotech, USA). cDNA was synthesized from total RNA with the Prime Script RT Reagent Kit (Takara Bio, Japan) on a C1000 Thermal Cycler (Bio-Rad, USA) and kept at − 20°C. Target fragment amplification was carried out on a CFX96 Real-Time PCR System (Bio-Rad, USA) using 2× SYBR Green PCR Master Mix (Solar bio, Beijing, China), with GAPDH serving as the endogenous reference. All reactions were run in triplicate. Primer sequences were as follows: CCAT1: forward 5'-TATCACCTACGCATACCTCT-3', reverse 5'-GAATTTCGTGTTCGTTTACT-3'; GAPDH: forward 5'-GGAGCGAGATCCCTCCAAAAT-3', reverse 5'-GGCTGTTGTCATACTTCTCATGG-3'. Relative gene expression levels of serum CCAT1 were quantified using the $2^{-\Delta\Delta C_T}$ method, the formula was defined as follows:

$$\Delta\Delta C_T=(C_{T(\mathrm{CCAT1})}-C_{T(\mathrm{GAPDH})})_{\text{experimental group}}-(C_{T(\mathrm{CCAT1})}-C_{T(\mathrm{GAPDH})})_{\text{control group}}$$

where C_T represents the threshold cycle value, CCAT1 is the target gene, and GAPDH serves as the endogenous reference gene.

Statistical Analysis

Data were analyzed with SPSS 25.0 and GraphPad Prism 8.0. Normally distributed continuous variables are reported as mean ± SD and were compared between groups with the independent-samples t-test. Non-normally distributed continuous variables are given as median (P25–P75) and were compared using the Mann–Whitney U test. Categorical variables are presented as frequencies or percentages and were compared by Fisher's exact test. Receiver operating characteristic (ROC) curves were plotted to evaluate the diagnostic performance of CCAT1, CEA, and CA125. Pearson correlation analysis was used to examine associations among the three markers. A two-sided $P < 0.05$ was taken as statistically significant.

Results

Serum CCAT1 Expression Across EOC, BON, OC, and Normal Controls

Relative CCAT1 expression was calculated by the 2 − ΔΔCt method (Fig. 1, Table 2). Serum CCAT1 levels were significantly higher in the EOC, BON, and OC groups than in normal controls (P < 0.001). Across the three disease groups—EOC, BON, and OC—no meaningful differences were observed (P > 0.05).

Table 2
Serum CCAT1 relative expression across cohorts

Group	n	Normality P	Mean ± SD	Median(P_{25}–P_{75})
EOC	22	0.0034		2.620(2.015–5.315)
Post-op EOC	12	0.2186	4.771 ± 2.748	
Post-chemo EOC	68	> 0.1000	2.975 ± 1.758	
BON	12	0.7413	3.232 ± 1.604	
OC	27	0.3647	2.532 ± 1.613	
Normal Control	23	0.2208	1.138 ± 0.531	

Serum CCAT1 Is Higher in Stage III + IV EOC than in Stage I + II

Serum CCAT1 expression in stage III + IV EOC patients measured 4.177 (2.460–6.742), substantially above the 2.068 (1.404–2.459) recorded in stage I + II patients (P = 0.008) (Fig. 2).

Serum CCAT1 Is Higher in Postoperative EOC Patients than in Post-Chemotherapy Patients

Serum CCAT1 expression in postoperative EOC patients was 4.771 ± 2.748, significantly higher than the 2.975 ± 1.758 observed in post-chemotherapy patients (P = 0.004) (Fig. 3).

Association of Serum CCAT1 Expression with Clinicopathological Parameters in EOC Patients

To determine whether serum CCAT1 reflects EOC progression and holds diagnostic value, we examined its association with clinicopathological features. Using the median CCAT1 expression (2.620) as a cutoff, EOC patients were split into high- and low-expression groups (Table 3). CCAT1 expression

showed no link to age (P > 0.05) or tumor size (P > 0.05), but was significantly associated with FIGO stage (P = 0.024), lymph node metastasis (P = 0.008), distant metastasis (P = 0.008), and pelvic-abdominal effusion (P = 0.024).

Table 3
Correlation between CCAT1 expression and EOC clinical features (n = 22)

Clinical index	Case number	Low CCAT1	High CCAT1	P-value
Age (years)				
≤ 55	12	6	6	1.000
> 55	10	5	5	
Tumor Size (cm)				
≤ 10	11	4	7	0.395
> 10	11	7	4	
FIGO Staging				
I + II	8	7	1	0.024
□+□	14	4	10	
Lymph Node Metastasis				
Yes	13	3	10	0.008
No	9	8	1	
Distant Metastasis				
Yes	13	3	10	0.008
No	9	8	1	
Pelvic and abdominal effusion				
Yes	14	4	10	0.024
No	8	7	1	

ROC-based diagnostic performance of CEA, CA125 and CCAT1

Healthy control vs early (I + II) EOC: AUC (CEA = 0.6821, CA125 = 0.8750, CCAT1 = 0.8152); Healthy control vs advanced (III + IV) EOC: AUC (CEA = 0.5978, CA125 = 1.0000, CCAT1 = 0.9658); Early vs advanced EOC differentiation: AUC (CEA = 0.5402, CA125 = 0.6786, CCAT1 = 0.8393) (Figs. 4). By comparison of the three indicators, both CCAT1 and CA125 exhibit favorable diagnostic performance for

EOC. Moreover, CCAT1 shows superior capacity in differentiating early-stage from advanced-stage epithelial ovarian cancer.

Figure 4. (A) Diagnostic performance of CEA to differentiate healthy controls, stage I + II and stage III + IV EOC; (B) Diagnostic performance of CA125 to differentiate healthy controls, stage I + II and stage III + IV EOC; (C) Diagnostic performance of CCAT1 to differentiate healthy controls, stage I + II and stage III + IV EOC.

Correlation of Serum CCAT1 with CEA and CA125 in EOC Patients

Pearson correlation analysis showed that serum CCAT1 expression had no significant correlation with CEA (r = − 0.182, P = 0.417) or CA125 (r = 0.055, P = 0.809) in patients with EOC (Table 4).

Table 4
Pearson correlation coefficients among three serum markers

CCAT1	**CCAT1**	**CEA**	**CA125**
	1	**-0.182 (P = 0.417)**	**0.055(P = 0.809)**
CEA	-0.182(P = 0.417)	1	0.022(P = 0.921)
CA125	0.055(P = 0.809)	0.022(P = 0.921)	1

Combined Diagnostic Value of CCAT1, CEA, and CA125 for EOC

Using the serum CCAT1, CEA, and CA125 levels measured in EOC patients, we calculated the sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) for CCAT1 alone and in combination with CEA and/or CA125 (Table 5). The combination of CCAT1 with CA125 delivered a sensitivity of 86.36%, specificity of 100.00%, and accuracy of 93.33%, clearly outperforming CCAT1 alone or its pairing with CEA.

Table 5
Combined diagnostic parameters of different marker panels (%)

Marker combination	**Sensitivity**	**Specificity**	**Accuracy**	**PPV**	**NPV**
Single CCAT1	95.45	52.17	60.00	65.63	92.31
CCAT1 + CEA	9.09	100.00	55.56	100.00	53.49
CCAT1 + CA125	86.36	100.00	93.33	100.00	88.46
Triple combined	9.09	100.00	55.56	100.00	53.49

Discussion

Research on CCAT1 in ovarian cancer has, to date, focused primarily on tumor tissue and cell line models. Cao et al [22] were the first to report marked upregulation of CCAT1 in EOC tissues, demonstrating that it drives epithelial-mesenchymal transition (EMT), migration, and invasion through the CCAT1/miR-152/miR-130b/ADAM17/WNT1/STAT3/ZEB1 regulatory network. Multivariate Cox regression in that study identified CCAT1 as an independent prognostic indicator for EOC. In a complementary line of work, Brovkina et al [23] mined The Cancer Genome Atlas (TCGA) and confirmed CCAT1 overexpression in 54 ovarian cancer tissue samples by qPCR, further proposing that CCAT1 may activate EMT-related genes—including MAPK1, c-MET, TGFB2, SNAIL1, and WNT4—through a ceRNA mechanism mediated by miR-203 and miR-124. Both of those studies, however, relied on tumor tissue or cell-based approaches. No prior work has systematically examined the diagnostic value of serum CCAT1 in EOC. What distinguishes the present study is the use of serum as the detection matrix and the direct assessment of CCAT1's diagnostic performance in EOC, addressing a gap left by tissue-only analyses and providing a candidate biomarker for EOC liquid biopsy.

CCAT1 carried in serum extracellular vesicles has been reported to distinguish gastric cancer from atypical hyperplasia, chronic gastritis, and healthy controls ($P < 0.001$) [24]. In our analysis, serum CCAT1 did separate EOC from normal controls ($P < 0.0001$), but it could not differentiate EOC from BON or OC patients ($P > 0.05$), nor could it distinguish BON from OC patients ($P > 0.05$). Several factors may account for this discrepancy. We measured free circulating CCAT1 rather than the vesicle-associated form, and inherent biological differences across tumor types likely play a role. Even so, both BON ($P < 0.0001$) and OC ($P < 0.001$) patients showed significantly higher serum CCAT1 than normal controls, hinting that elevated serum CCAT1 might also be useful in early screening for benign ovarian tumors and ovarian cysts. Stage III + IV EOC patients had higher serum CCAT1 [4.177 (2.460–6.742)] than stage I + II patients ($P = 0.008$), pointing to a relationship between CCAT1 levels and disease progression. In addition, serum CCAT1 levels differed between postoperative (pre-chemotherapy) and post-chemotherapy EOC patients ($P = 0.004$), raising the possibility that CCAT1 may have utility in EOC prognostic assessment.

Numerous studies have documented close links between upregulated lncRNAs and histological grade, FIGO stage, and lymph node metastasis in ovarian cancer [25]. Consistent with this pattern, serum CCAT1 expression in our EOC patients was independent of age and tumor size ($P > 0.05$) but positively associated with FIGO stage ($P < 0.05$), lymph node metastasis ($P < 0.05$), and distant metastasis ($P < 0.05$). These findings echo Cao et al [22] who reported that CCAT1 overexpression in EOC tissue tracks with advanced FIGO stage and lymph node involvement. Additionally, EOC patients with high serum CCAT1 were more likely to present with pelvic-abdominal effusion ($P < 0.05$). In the absence of long-term follow-up data, how CCAT1 relates to survival in EOC patients warrants further investigation.

Serum CEA, CA125, HE4, and the ROMA index are routinely used for ovarian cancer screening and auxiliary diagnosis [26, 27], and abnormal elevations of these markers raise suspicion for malignancy. To understand where CCAT1 fits alongside CEA and CA125 in early screening and diagnosis of EOC, we turned to ROC analysis. CA125 outperformed CEA and CCAT1 when the task was separating normal

controls from early-stage (I + II) or advanced-stage (III + IV) EOC. CCAT1, on the other hand, did a better job of distinguishing early-stage from advanced-stage disease, suggesting that while CCAT1 falls somewhat short of CA125 for early warning of EOC, it captures disease progression more effectively. Owing to platform constraints, we were not able to evaluate how CCAT1 performs when combined with HE4 or the ROMA index for early EOC diagnosis.

We next asked whether serum CCAT1 expression was influenced by CEA or CA125 levels. Correlation analysis turned up no significant associations ($P > 0.05$), in agreement with Cao et al [28], pointing to serum CCAT1 acting independently of CEA and CA125 and possibly exerting its oncogenic effects through separate molecular routes.

On the front of sensitivity, specificity, and related diagnostic indices, we evaluated the performance of CCAT1 both alone and in combination with CEA and CA125. Because CEA and CA125 are well-established tumor markers with extensive use in ovarian malignancy screening, we did not re-assess their stand-alone performance here [29–31]. Drawing on the serum CCAT1, CEA, and CA125 levels from our EOC cohort, we computed the sensitivity, specificity, accuracy, PPV, and NPV for each marker alone and in combination. The CCAT1 + CA125 pairing reached a sensitivity of 86.36%, specificity of 100.00%, and accuracy of 93.33%—the strongest overall diagnostic performance observed in this study, surpassing CCAT1 alone or its combination with CEA. These results suggest that joint detection of CCAT1 and CA125 carries greater promise for clinical application. That said, the oncogenic mechanisms of lncRNAs remain incompletely mapped, and the present study is constrained by its sample size. Longer follow-up and larger multicenter studies will be necessary to establish the clinical utility of serum CCAT1 for early screening and diagnosis of EOC.

Conclusion

Measuring serum CCAT1 expression makes it feasible to separate EOC patients from healthy women and to distinguish early-stage (I + II) from advanced-stage (III + IV) EOC, supporting its candidacy as an independent tumor biomarker for early diagnosis and disease monitoring in EOC. Pairing CCAT1 with CA125 raises the overall diagnostic power for EOC still further, they offer potential for early screening and diagnosis of ovarian cancer.

Abbreviations

BON	Benign ovarian neoplasm
CA125	Cancer antigen 125
CCAT1	Colon cancer-associated transcript 1
CEA	Carcinoembryonic antigen
EMT	Epithelial–mesenchymal transition
EOC	Epithelial ovarian cancer
FIGO	International Federation of Gynecology and Obstetrics
HE4	Human epididymis protein 4
lncRNA	Long non-coding RNA
NPV	Negative predictive value
OC	Ovarian cyst
PPV	Positive predictive value
ROMA	Risk of Ovarian Malignancy Algorithm
ROC	Receiver operating characteristic
RT-qPCR	Reverse transcription quantitative polymerase chain reaction
AUC	Area under the curve
SD	Standard deviation

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Zunyi First People's Hospital (The Third Affiliated Hospital of Zunyi Medical University) (Approval No. 2025-1-1000). Written informed consent was obtained from all participants prior to blood sample collection and data acquisition.

Consent for publication

Not applicable. No individual person's data in any form (including individual details, images, or videos) are included in this manuscript.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Zhengfei Gan: Conceptualization, Investigation, Methodology, Data curation, Formal analysis, Writing – original draft.

Xiaoxue Huang: Sample collection, Data analysis, Software, Visualization.

Huasu Chen: Sample collection, Data curation, Validation.

He Zha: Conceptualization, Project administration, Funding acquisition, Resources, Supervision, Writing – review & editing, Read and approved final version.

All authors have read and approved the final version of the manuscript.

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Figures

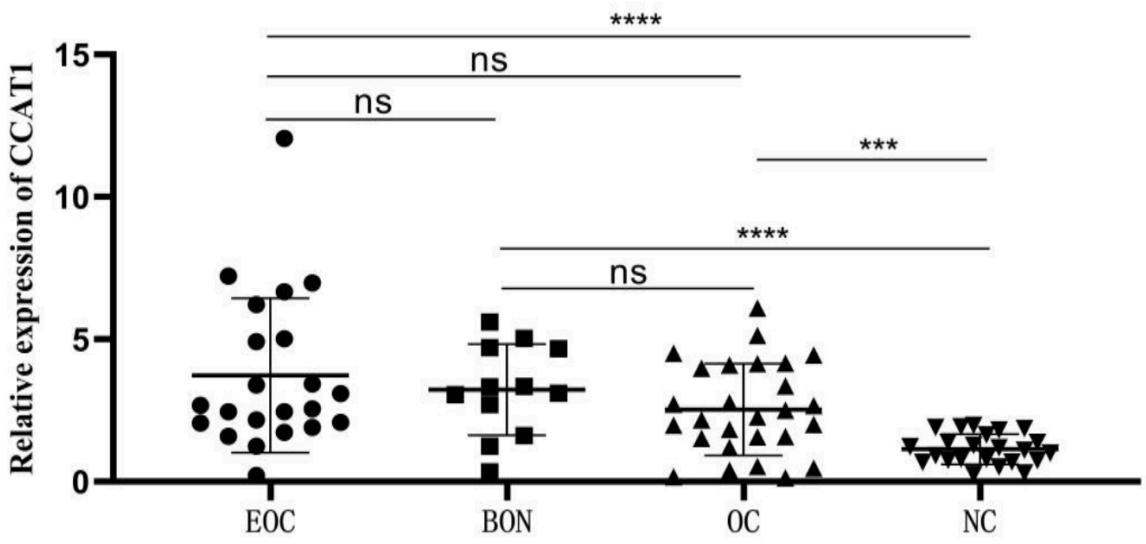


Figure 1

Comparative analysis of serum CCAT1 expression among all groups; ****P<0.0001, ***P<0.001, ns = not statistically significant.

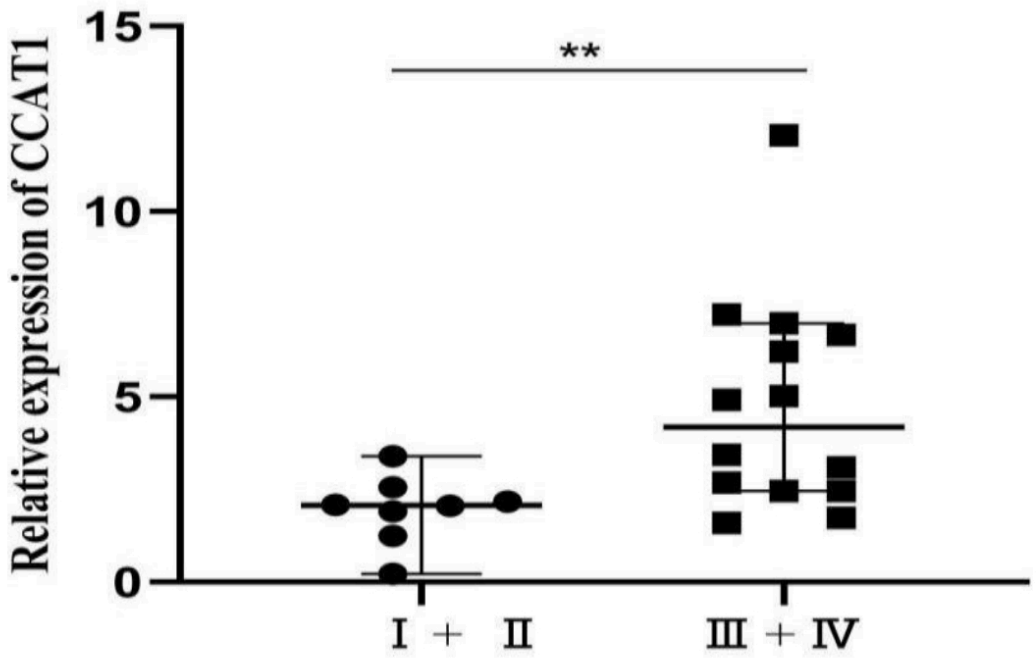


Figure 2

The serum expression level of CCAT1 in patients with stage Ⅰ+Ⅱ EOC is higher than that in patients with stage Ⅲ+Ⅳ; **P<0.01.

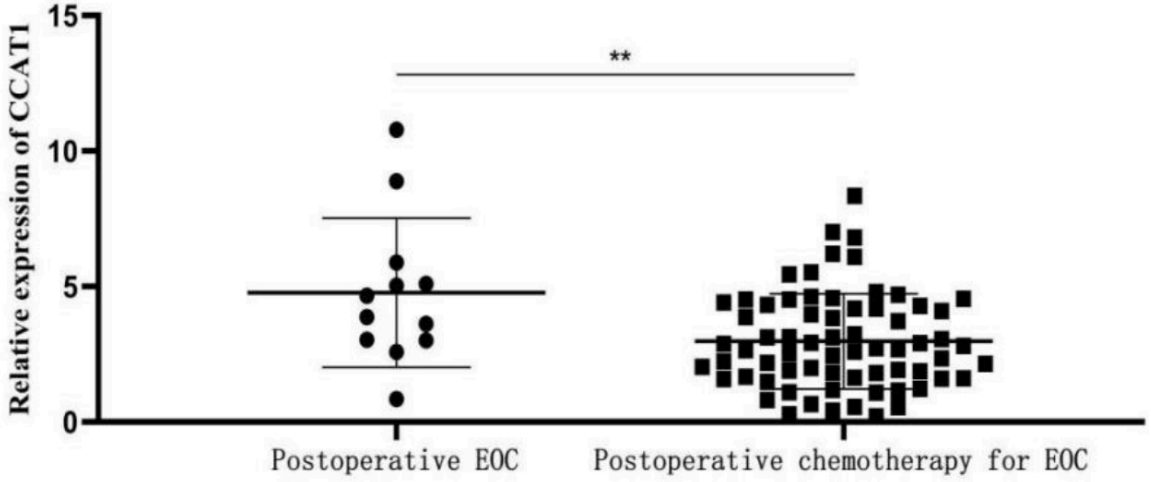


Figure 3

Serum CCAT1 is higher in pre-chemotherapy postoperative EOC; **P<0.01.

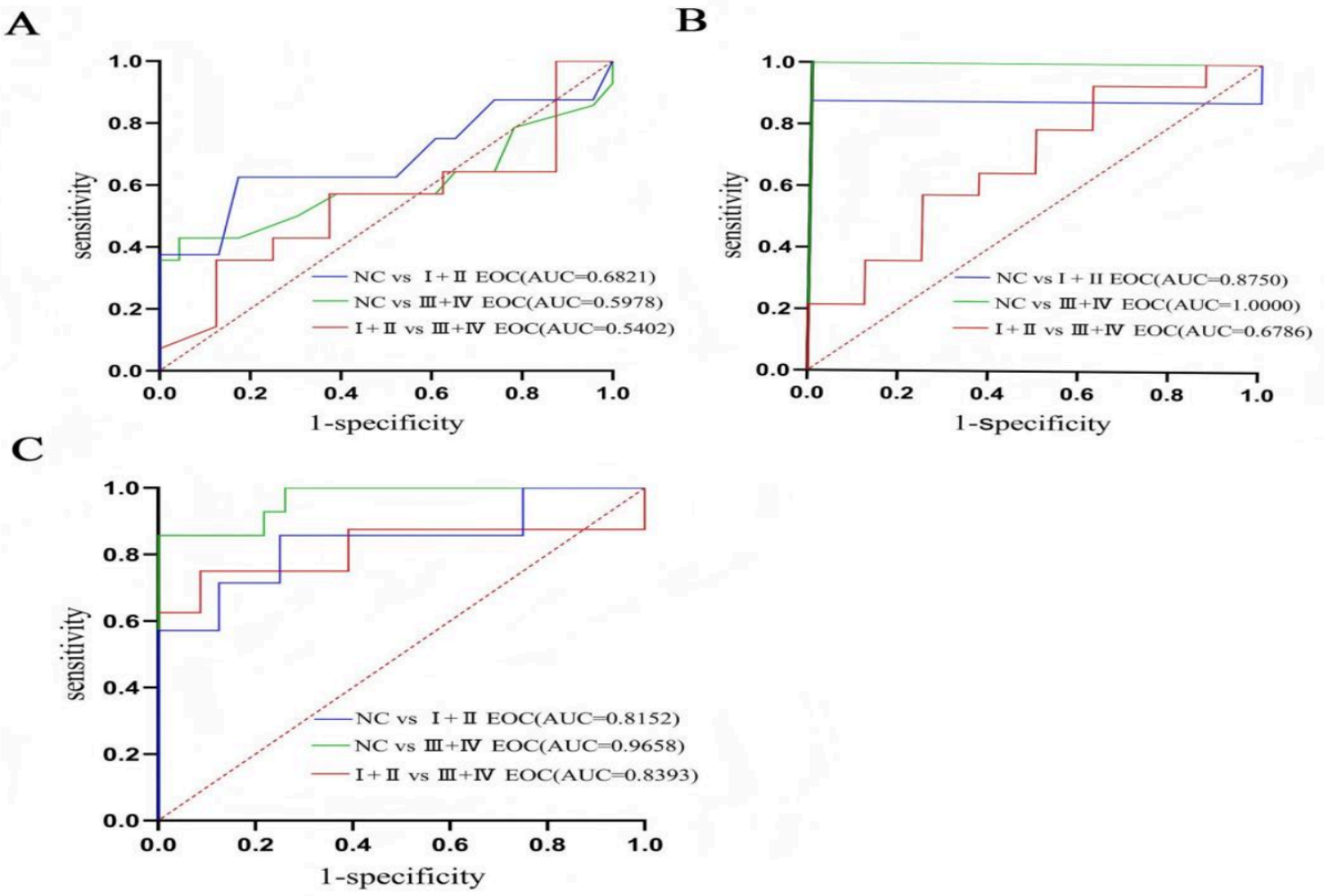


Figure 4

(A) Diagnostic performance of CEA to differentiate healthy controls, stage I+II and stage III+IV EOC; (B) Diagnostic performance of CA125 to differentiate healthy controls, stage I+II and stage III+IV EOC; (C) Diagnostic performance of CCAT1 to differentiate healthy controls, stage I+II and stage III+IV EOC.