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ORIGINAL RESEARCH

Low Serum Cholinesterase Levels Predict Poor Prognosis in Patients with Ovarian Cancer

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Objective: Previous studies reported that low cholinesterase (ChE) levels were associated with poor prognosis in various cancers, including bladder, pancreatic, lung, and colorectal cancers. This study aimed to evaluate the clinical significance of serum ChE levels as a prognostic biomarker in ovarian cancer.

Materials and Methods: A retrospective cohort analysis was conducted on 168 patients diagnosed with epithelial ovarian cancer at the Suzhou Ninth People's Hospital from 2019 to 2020. Serum ChE levels were measured before initiating treatment and stratified into low and high groups based on the median level (7600 U/L). Clinical and pathological data, such as FIGO stage, age, tumor histological type, and survival outcomes, were collected. Kaplan-Meier analysis and Cox proportional hazards regression were used to assess the relationship between ChE levels and overall survival and disease-free survival.

Results: ChE levels were significantly correlated with clinicopathological features of epithelial ovarian cancer, including FIGO stage ($p < 0.001$), surgery completeness ($p = 0.001$), and platinum-resistant ($p = 0.001$). Kaplan-Meier analysis demonstrated that patients in the low ChE group had significantly worse overall survival ($p = 0.003$) and disease-free survival ($p = 0.005$) than those in the high ChE group. Multivariate Cox regression analysis identified low serum ChE levels as an independent predictor of poor overall survival and disease-free survival.

Conclusion: Low serum ChE levels are independently associated with poor prognosis in ovarian cancer patients, reflecting systemic inflammation, malnutrition, and potential hepatic dysfunction. These findings suggest that ChE could serve as a cost-effective and non-invasive biomarker for risk stratification and prognosis in clinical practice.

Keywords: cholinesterase, ovarian cancer, disease-free survival, overall survival

Introduction

Ovarian cancer is among the most deadly gynecologic cancers worldwide. According to international cancer statistics, more than 324,398 new cases were diagnosed, and 206,839 deaths were reported in 2022.[1] This high mortality rate is largely attributable to the subtle and nonspecific nature of symptoms in the early stages, which often leads to delayed diagnosis and treatment.[2,3] Consequently, over 70% of patients are diagnosed at an advanced stage (FIGO stage III or IV) at the time of initial presentation.[4] Despite significant advancements in surgical techniques and systemic therapies, high rates of recurrence and resistance to chemotherapy remain major challenges, limiting improvements in survival outcomes.[5,6] Therefore, the identification of reliable biomarkers for early detection, prognostic assessment, and disease monitoring is crucial for enhancing clinical outcomes in ovarian cancer.

Serum biomarkers are increasingly recognized as valuable tools for cancer prognosis due to their accessibility, affordability, and non-invasive nature.[7] Among serum enzymes, those such as lactate dehydrogenase, alkaline

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phosphatase, gamma-glutamyltransferase, and alanine aminotransferase have garnered substantial research interest.[8–10] Serum cholinesterase (ChE) is an alpha-glycoprotein synthesized in the liver, primarily known for its role in hydrolyzing acetylcholine.[11] However, emerging evidence suggests that ChE levels may reflect systemic inflammation, malnutrition, and hepatic dysfunction, all of which have been implicated in cancer progression and prognosis.[12]

Previous studies have identified low ChE levels as a poor prognostic marker in various malignancies, including lung, pancreatic, bladder, and colorectal cancers.[11–14] Despite these findings, the potential prognostic value of ChE in ovarian cancer remains largely unexplored. Existing research has not comprehensively assessed the association between ChE levels and key clinicopathological factors, disease progression, or survival outcomes in ovarian cancer patients. This gap in knowledge highlights the need for further investigation into ChE as a potential prognostic biomarker in ovarian cancer. By addressing this gap, our study aims to determine whether ChE levels can serve as an independent predictor of ovarian cancer prognosis, thereby contributing to improved patient management and risk assessment strategies.

Materials and Methods

Study Design

This study was designed as a retrospective cohort analysis. Medical records of patients newly diagnosed with epithelial ovarian cancer between January 1, 2019, and December 31, 2020, were retrieved from the Suzhou Ninth People's Hospital, China. The hospital utilizes a comprehensive hospital information system (HIS) that integrates a patient information system and a follow-up system. The patient information system maintains and updates all inpatient and outpatient clinical data on a daily basis. For this research, the extracted data included demographic and pathological characteristics, serum parameters, details of surgical procedures, chemotherapy regimens and courses, survival time, and survival status at the final follow-up.

Patient selection was guided by the following inclusion and exclusion criteria. The inclusion criteria were as follows: (1) the primary tumor site was the ovary; (2) histological confirmation of epithelial ovarian cancer by a pathologist; and (3) availability of complete clinical, pathological, surgical, and follow-up data. The exclusion criteria were: (1) tumors originating outside the ovary; (2) patients who did not receive standard treatment; and (3) incomplete clinical or follow-up data. Based on these criteria, 168 patients with epithelial ovarian cancer were ultimately included in the study. The detailed patient screening process is depicted in Figure 1. Informed consent was obtained from the study participants before the commencement of the study, and the study complies with the Declaration of Helsinki. Ethical approval for the study was granted by the Medical Research Ethics Committee of the Suzhou Ninth People's Hospital (Approval No. 31342422).

ChE Measurement

ChE levels were measured before the initiation of ovarian cancer treatment. Serum samples were analyzed in the clinical laboratory center of our hospital using the Ortho VITROS 5.1 FS and 5600 Integrated System (Ortho Clinical Diagnostics, Raritan, NJ, USA). Analytical procedures were conducted in strict accordance with the manufacturer's guidelines, which included preventive maintenance, functional checks, calibration, and quality control measures, all verified to meet specifications prior to sample testing. The rate of color loss was determined using reflectance spectrophotometry at a wavelength of 400 nm. The rate of change in reflection density was directly proportional to the ChE activity in the sample, providing a quantitative measure of ChE levels. The median ChE level was measured to be 7600 U/L, which was used as the cut-off value to categorize the study patients into the low ChE group and high ChE group.

Patient Treatment and Follow-Up

Patients underwent comprehensive staging surgery or interval debulking surgery, followed by paclitaxel and platinum-based chemotherapy, following the National Comprehensive Cancer Network (NCCN) guidelines. Follow-up evaluations included clinical examinations and tumor marker assessments at each visit. When indicated, additional imaging studies such as ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI) were performed. Recurrence was defined as histological confirmation through tumor biopsy and/or the identification of new lesions on imaging. Overall survival (OS) was defined as the time from the initial diagnosis to death from any cause or the date of the last follow-up in June 2024. Disease-free survival (DFS)

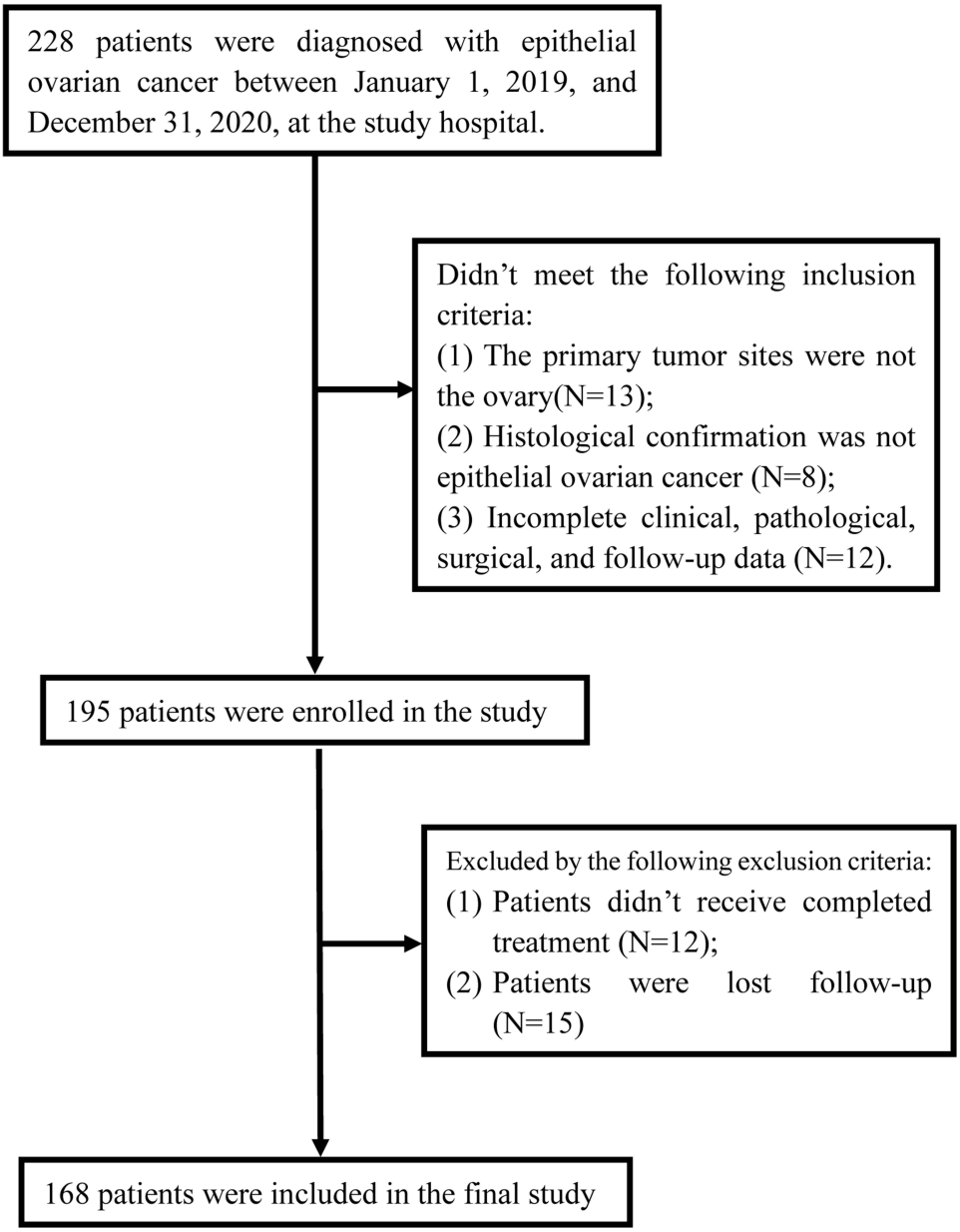

Figure 1 The flow chart of the study population recruitment.

was defined as the duration of time a patient survived following curative resection without evidence of disease on radiological imaging or death from any cause.[15]

Statistical Analysis

Statistical analyses were performed using IBM SPSS software and GraphPad Prism software. Kaplan-Meier survival curves were generated to visualize survival outcomes, and Log rank tests were used to assess differences between groups. Associations between categorical variables were analyzed using the chi-square test. Univariate and multivariate Cox proportional hazards models were applied to identify prognostic factors in patients with ovarian cancer. A p-value of less than 0.05 was considered statistically significant.

Results

Characteristics of Study Patients

The characteristics of the study patients are summarized in Table 1. The median age at diagnosis was 55 years old, with 75 (44.64%) patients younger than 55 years and 93 (55.36%) patients aged 55 years or older. Among the 168 patients included, 13 (7.74%) were diagnosed with FIGO stage I, 44 (26.19%) with FIGO stage II, 65 (38.69%) with FIGO stage III, and 46 (27.38%) with FIGO stage IV. The histological types identified included 91 (54.17%) patients with serous carcinoma, 42 (25.00%) with mucinous carcinoma, 21 (12.5%) with endometrioid carcinoma, and 14 (8.33%) with clear cell carcinoma.

Surgical treatment consisted of complete surgery for 63 (37.5%) patients, optimal surgery for 66 (39.29%) patients, and suboptimal surgery for 39 (23.21%) patients. Adjuvant chemotherapies with paclitaxel and cisplatin or carboplatin were administered to 160 (95.24%) patients, while 8 (4.76%) patients did not receive adjuvant chemotherapy due to the early stage of their disease. Regarding treatment outcomes, 117 (73.13%) had a platinum-sensitive and 43 (26.87%) showed platinum-resistant.

Associations Between ChE Levels and Clinicopathological Characteristics of Ovarian Cancer Patients

The associations between ChE levels and the clinicopathological characteristics of ovarian cancer patients are shown in Table 2. ChE levels were significantly correlated with clinicopathological features of epithelial ovarian cancer, including

Table 1 Characteristics of Study Patients

Characteristics	n	%
Total	168	100
Age		
< 55	75	44.64
≥ 55	93	55.36
FIGO stage		
I	13	7.74
II	44	26.19
III	65	38.69
IV	46	27.38
Histological type		
Serous carcinoma	91	54.17
Mucinous carcinoma	42	25.00
Endometrioid carcinoma	21	12.5
Clear cell carcinoma	14	8.33
Surgery completeness		
Complete	63	37.5
Optimal	66	39.29
Suboptimal	39	23.21
Adjuvant chemotherapies		
No	8	4.76
Yes	160	95.24
Neoadjuvant chemotherapy		
No	33	19.64
Yes	135	80.36
Platinum-resistant		
No	117	73.13
Yes	43	26.87

Notes: The statistical significance was analyzed by a chi-square test. A p <0.05 was considered statistically significant and was marked in bold text.

Table 2 Associations Between ChE Levels and Clinicopathological Characteristics of Ovarian Cancer Patients

Characteristics		ChE Levels		*p-value*
		Low ChE (90)	High ChE (78)	
Age (year)				0.107
< 55	75	35	40	
≥55	93	55	38	
FIGO stage				**< 0.001**
I	13	5	8	
II	44	5	39	
III	65	50	15	
IV	46	30	16	
Histological type				0.973
Serous carcinoma	91	48	43	
Mucinous carcinoma	42	22	20	
Endometrioid carcinoma	21	12	9	
Clear cell carcinoma	14	8	6	
Surgery completeness				**0.001**
Complete	63	25	38	
Optimal	66	35	31	
Suboptimal	39	30	9	
Adjuvant chemotherapies				0.097
No	8	2	6	
Yes	160	88	72	
Neoadjuvant chemotherapy				0.900
No	33	18	15	
Yes	135	72	63	
Platinum-resistant				**0.001**
No	117	50	67	
Yes	43	32	11	

Notes: A chi-square test analyzed the statistical significance. A p <0.05 was considered statistically significant and was marked in bold text.

the FIGO stage ($p < 0.001$), surgery completeness ($p = 0.001$), and platinum-resistant ($p = 0.001$). However, no significant associations were found between ChE levels and other factors such as age, tumor histological type, adjuvant chemotherapy, or neoadjuvant chemotherapy.

Low Serum ChE Levels Correlate with Reduced Overall Survival in Ovarian Cancer Patients

Kaplan-Meier analysis revealed that ovarian cancer patients with low serum ChE levels had shorter overall survival compared to those with high serum ChE levels (Figure 2). To identify factors influencing overall survival, both univariate and multivariate Cox proportional hazards regression analyses were conducted.

The univariate analysis identified FIGO stage, surgery completeness, adjuvant chemotherapy, platinum-resistant, and serum ChE levels as factors significantly associated with overall survival (Table 3). After adjusting for confounding variables, including age, FIGO stage, surgery completeness, histological type, adjuvant chemotherapy, and platinum-resistant, the multivariate analysis confirmed that serum ChE levels, FIGO stage, and surgery completeness were independent risk factors for overall survival (Table 3).

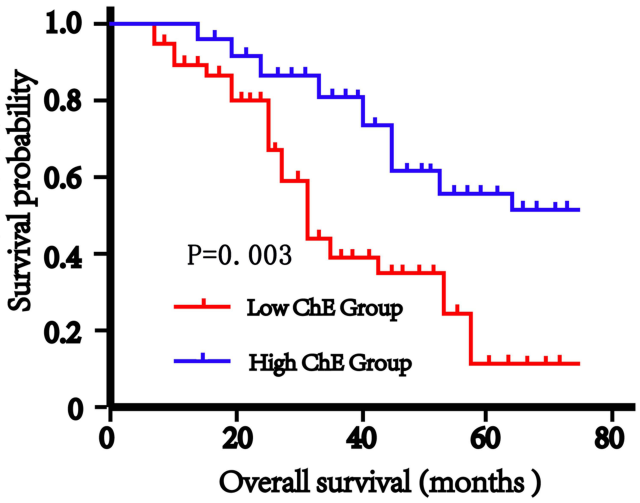

Figure 2 Kaplan-Meier curves for ovarian cancer patients with low serum ChE levels showed worse overall survival rates than patients with high serum ChE levels (p = 0.003). Log rank tests assessed the survival differences and p-values of less than 0.05 were considered statistically significant.

Low Serum ChE Levels Correlate with Reduced Disease-Free Survival in Ovarian Cancer Patients

Kaplan-Meier analysis was performed to assess disease-free survival, revealing that patients with low serum ChE levels had significantly shorter disease-free survival compared to those with high serum ChE levels (Figure 3). To identify

Table 3 Identification of Risk Factors for Overall Survival Using Univariate and Multivariate Cox Proportional Hazards Regression Model

Variables	Univariate Analysis HR (95% CI)	*p-value*	Multivariate Analysis HR (95% CI)	Adjusted *p-value*
Age (year)				
< 55	1.00 (Reference)		1.00 (Reference)	
≥55	1.02 (0.83–1.23)	0.104	1.14 (0.87–1.61)	0.212
FIGO stage				
I	1.00 (Reference)		1.00 (Reference)	
II	2.46 (1.37–4.28)	**0.001**	2.78 (1.21–4.15)	**0.004**
III	3.38 (2.52–5.34)	**0.011**	3.73 (1.94–5.09)	**0.013**
IV	4.64 (3.71–6.25)	**0.003**	4.03 (3.12–5.94)	**0.006**
Histological type				
Serous	1.00 (Reference)		1.00 (Reference)	
Mucinous	0.93 (0.79–1.04)	0.268	1.12 (0.91–1.41)	0.171
Endometrioid	1.07 (0.94–1.22)	0.371	0.87 (0.74–1.12)	0.262
Clear cell	0.91 (0.82–1.27)	0.412	0.93 (0.85–1.08)	0.304
Surgery completeness				
Complete	1.00 (Reference)		1.00 (Reference)	
Optimal	3.34 (2.41–5.62)	**0.004**	3.58 (2.35–5.82)	**0.003**
Suboptimal	5.07 (3.28–7.21)	**0.002**	4.79 (3.28–6.37)	**0.006**
Adjuvant chemotherapies				
No	1.00 (Reference)		1.00 (Reference)	
Yes	2.54 (1.41–3.15)	**0.001**	1.22 (0.82–2.48)	0.081

(*Continued*)

Table 3 (Continued).

Variables	Univariate Analysis HR (95% CI)	*p-value*	Multivariate Analysis HR (95% CI)	Adjusted *p-value*
Platinum-resistant				
No	1.00 (Reference)		1.00 (Reference)	
Yes	2.42 (1.13–3.02)	**0.001**	1.14 (0.85–1.32)	0.193
ChE levels				
High	1.00 (Reference)		1.00 (Reference)	
Low	3.45 (1.27–5.14)	**0.002**	2.51 (1.14–3.87)	**0.008**

Notes: CI, Confidence interval; HR, hazard ratio. Adjusted for potential confounding factors, including age, histological type, FIGO stage, platinum-resistant, and adjuvant chemotherapies. A $p < 0.05$ was considered statistical significance and marked in bold text.

factors influencing disease-free survival in ovarian cancer patients, univariate and multivariate Cox proportional hazards regression analyses were conducted.

The univariate analysis indicated that FIGO stage, surgery completeness, platinum-resistant, and serum ChE levels were all associated with disease-free survival (Table 4). After adjusting for confounding variables, including age, FIGO stage, surgery completeness, histological type, adjuvant chemotherapy, and platinum-resistant, the multivariate analysis identified serum ChE levels, FIGO stage, and platinum-resistant as independent risk factors for disease-free survival (Table 4).

Subgroup Analysis According to the Tumor FIGO Stage

The above findings demonstrated that the FIGO stage of the tumor is an independent predictor of both overall survival and disease-free survival in ovarian cancer patients. To further explore the prognostic value of serum ChE levels, Kaplan-Meier analyses were conducted within subgroups stratified by the FIGO stage. Among patients with FIGO stage I and II tumors, those in the low-ChE group had significantly poorer overall survival and disease-free survival compared to those in the high-ChE group (Figure 4). Similar trends were observed in patients with FIGO stage III and IV tumors (Figure 4).

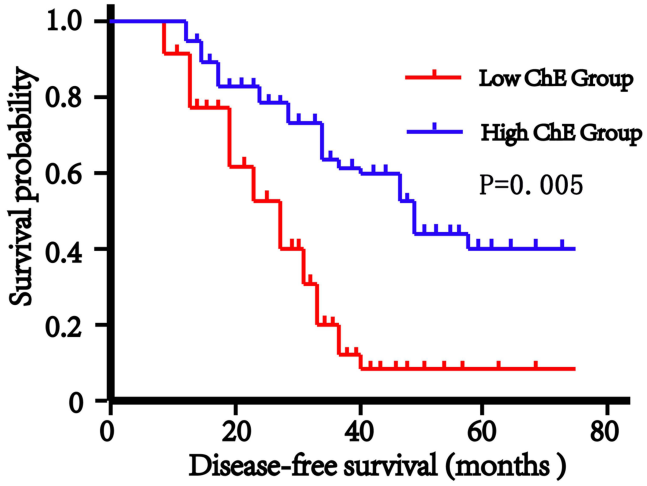

Figure 3 Kaplan-Meier curves for ovarian cancer patients with low serum ChE levels showed worse disease-free survival rates than patients with high serum ChE levels ($p = 0.005$). Log rank tests assessed the survival differences and p-values of less than 0.05 were considered statistically significant.

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Table 4 Identification of Risk Factors for Disease-Free Survival Using Univariate and Multivariate Cox Proportional Hazards Regression Model

Variables	Univariate Analysis HR (95% CI)	*p-value*	Multivariate Analysis HR (95% CI)	Adjusted *p-value*
Age (year)				
< 55	1.00 (Reference)		1.00 (Reference)	
≥55	0.94 (0.72–1.31)	0.276	1.049(0.85–1.27)	0.093
FIGO stage				
I	1.00 (Reference)		1.00 (Reference)	
II	2.14 (1.62–3.68)	**0.002**	2.57 (2.12–4.33)	**0.004**
III	3.37 (2.41–4.93)	**0.001**	3.02 (2.09–4.18)	**0.006**
IV	4.85 (3.07–5.87)	**0.005**	4.53 (3.28–6.25)	**0.001**
Histological type				
Serous	1.00 (Reference)		1.00 (Reference)	
Mucinous	1.14 (0.92–1.47)	0.342	0.92 (0.81–1.29)	0.215
Endometrioid	0.98 (0.81–1.32)	0.157	1.13 (0.95–1.34)	0.327
Clear cell	1.02 (0.87–1.23)	0.285	0.96 (0.84–1.26)	0.634
Surgery completeness				
Complete	1.00 (Reference)		1.00 (Reference)	
Optimal	2.47 (1.13–4.25)	**0.001**	1.35 (1.12–2.42)	0.151
Suboptimal	3.21 (2.21–4.57)	**0.003**	1.23 (0.94–2.13)	0.434
Adjuvant chemotherapies				
No	1.00 (Reference)		1.00 (Reference)	
Yes	1.24 (0.82–1.89)	0.181	1.07 (0.73–1.52)	0.327
Platinum-resistant				
No	1.00 (Reference)		1.00 (Reference)	
Yes	5.03 (2.41–7.24)	**0.013**	4.27 (2.32–6.18)	**0.006**
ChE levels				
High	1.00 (Reference)		1.00 (Reference)	
Low	4.31 (2.18–6.25)	**0.004**	3.26 (1.57–5.21)	**0.003**

Notes: CI, Confidence interval; HR, hazard ratio. Adjusted for potential confounding factors, including age, histological type, FIGO stage, platinum-resistant, and adjuvant chemotherapies. A $p < 0.05$ was considered statistical significance and marked in bold text.

Discussion

This study demonstrated that serum ChE levels were significantly correlated with clinicopathological features of epithelial ovarian cancer, including the FIGO stage ($p < 0.001$), surgery completeness ($p = 0.001$), and platinum-resistant. Furthermore, low serum ChE levels correlated with reduced overall survival and disease-free survival, establishing them as an independent prognostic factor for poorer outcomes. These findings suggest that ChE may serve as a valuable biomarker for prognosis in ovarian cancer, facilitating early identification of high-risk individuals and enabling timely therapeutic interventions.

ChE is an alpha-glycoprotein synthesized in the liver, rapidly released into the bloodstream, and has been extensively studied in various medical contexts.[16] Elevated ChE levels are linked to conditions such as fatty liver disease, obesity, and metabolic syndrome.[17,18] Conversely, reduced ChE levels are commonly associated with acute and chronic liver damage, cirrhosis, tumor liver metastasis, malnutrition, and inflammatory response.[19,20] Notably, ChE levels inversely correlate with pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α).[20] Decreased ChE levels have been observed in advanced and metastatic cancers, where anorexia, malnutrition, and hepatic dysfunction often dominate the clinical picture. Consistent with findings in colorectal, lung, bladder, and prostate cancers, our results demonstrate that low serum ChE levels are linked to worse overall survival and disease-free survival

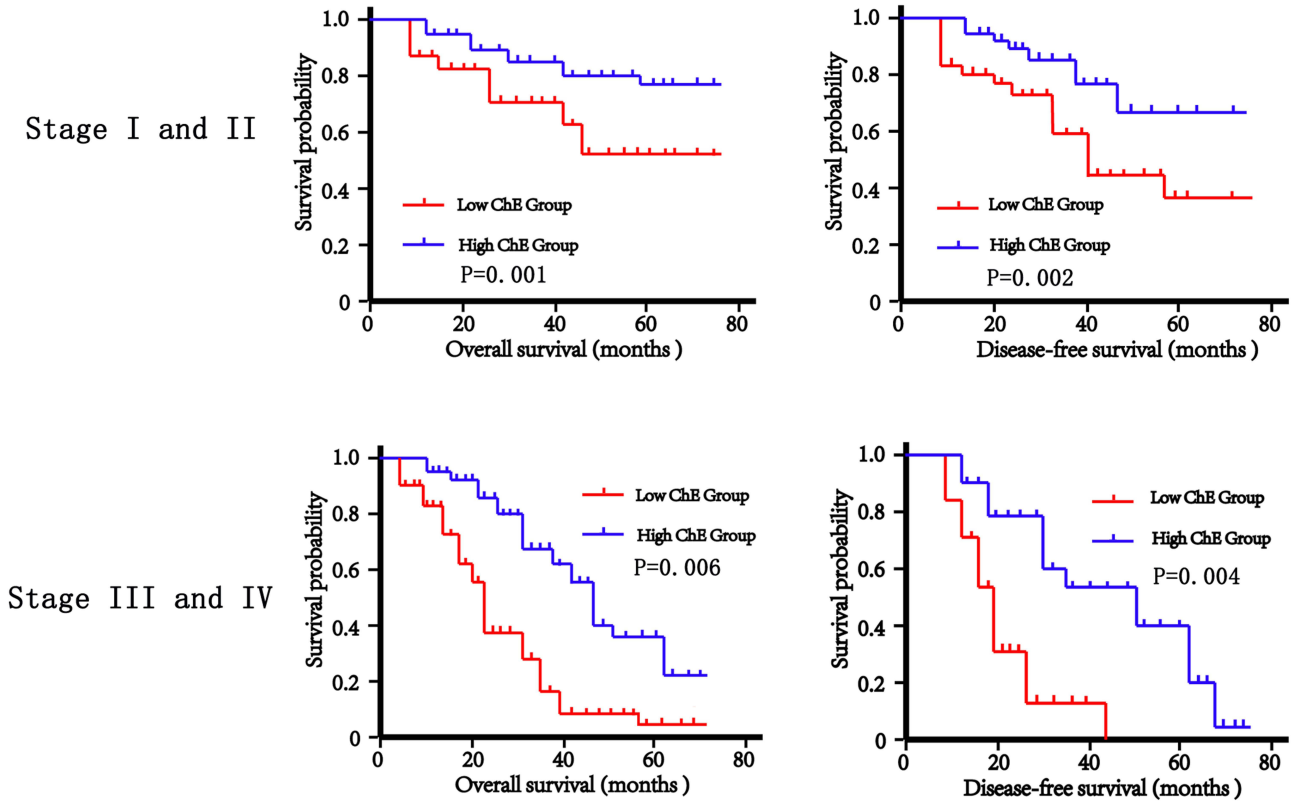

Figure 4 Kaplan–Meier curves for overall survival and disease-free survival comparing patients with low serum ChE levels and patients with high serum ChE levels for FIGO stages I and II and FIGO stages III and IV.

outcomes in ovarian cancer.[11–14] However, the exact mechanisms underlying this association in ovarian cancer remain unclear, highlighting the need for further investigation.

Several mechanisms could explain the observed association. First, low ChE levels may reflect an underlying state of systemic inflammation, a hallmark of cancer progression.[21] Pro-inflammatory cytokines such as IL-6 and TNF-α are known to suppress hepatic ChE synthesis.[22] This inflammatory environment not only promotes tumor growth and metastasis but also reduces the body's capacity to produce ChE, creating a vicious cycle that exacerbates disease progression.[23] Second, malnutrition which is frequently seen in advanced-stage ovarian cancer patients, may contribute to reduced ChE levels.[24,25] Malnutrition leads to hepatic dysfunction, impairing the synthesis of proteins like ChE.[26,27] The frequent occurrence of cachexia in ovarian cancer underscores the importance of addressing nutritional status as a part of comprehensive cancer care.

Another plausible explanation involves hepatic dysfunction. Advanced ovarian cancer often metastasizes to the liver, compromising its synthetic capacity, including ChE production.[27,28] Consequently, low ChE levels may serve as a surrogate marker for hepatic metastases, a condition associated with particularly poor survival outcomes. Future studies that integrate imaging modalities and detailed liver function assessments could help clarify this potential relationship.

Clinically, the prognostic utility of ChE could complement established markers such as CA-125. Although CA-125 is widely used to monitor disease progression and treatment response in ovarian cancer patients, it often lacks specificity and may be influenced by benign conditions.[29,30] In contrast, ChE levels might offer additional, independent prognostic insights, especially for patients with advanced disease. Incorporating ChE measurements into routine clinical practice could enhance risk stratification, enabling more personalized therapeutic strategies. For example, patients with low ChE levels may benefit from more aggressive treatment regimens, closer surveillance, or enrollment in clinical trials exploring novel interventions.

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Subgroup analyses in this study revealed that the prognostic significance of ChE levels persisted across all FIGO stages. Notably, even patients with early-stage disease and low ChE levels exhibited worse outcomes compared to those with higher levels, underscoring the potential of ChE as a prognostic marker regardless of disease stage. These findings are particularly meaningful as they suggest that ChE levels could help guide adjuvant chemotherapy decisions, even in patients with early-stage ovarian cancer.

Despite these promising findings, the study has several limitations. First, its retrospective design may introduce selection bias and limit the generalizability of the results. Prospective, multicenter studies with larger cohorts are necessary to validate these findings. Second, it is possible that the clinicians had an awareness of the study design and ChE levels before treatment initiation. This awareness could have led to differences in patient management, thereby affecting prognosis and confounding the observed associations between ChE levels and survival outcomes. Third, as the study was conducted at a single institution, it may not fully capture the heterogeneity of ovarian cancer populations across different geographic and healthcare settings. Finally, while ChE levels were measured before treatment initiation, dynamic changes during and after treatment were not evaluated. Longitudinal monitoring of ChE levels could provide valuable insights into its role as a marker for treatment response or disease recurrence.

Conclusion

This study provides compelling evidence that low serum ChE levels are independently associated with adverse survival outcomes in ovarian cancer patients. ChE levels could serve as a simple, cost-effective biomarker for risk stratification and prognosis in clinical practice. Future studies should validate these findings across diverse populations, investigate the biological mechanisms underlying this association, and explore integrating ChE into multimodal prognostic models for ovarian cancer. Such efforts could improve patient management and lead to better clinical outcomes in this challenging disease.

Ethics Approval

Informed consent was obtained from the study participants before the commencement of the study, and the study complies with the Declaration of Helsinki. This study was approved by the Ethics Committee of the Suzhou Ninth People's Hospital (No. 31342422).

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Disclosure

The auhtors declared no conflicts of interest in this work.

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