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ORIGINAL RESEARCH

# Identification and Clinical Validation of High HSP60 Expression Predicts Poor Prognosis in Patients with Ovarian Cancer

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**Objective:** This study aimed to investigate the clinical significance of heat shock protein 60 (HSP60) expression in ovarian cancer and evaluate its correlation with patient survival outcomes.

**Methods:** A total of 260 ovarian cancer patients diagnosed between 2017 and 2019 were enrolled. Immunohistochemistry was performed to assess HSP60 expression in tumor tissues. Patients were categorized into high- or low-HSP60 expression groups based on immunohistochemical staining intensity. The correlation between HSP60 expression status and the clinicopathological features of ovarian cancer patients was analyzed. Kaplan-Meier survival curves and Cox regression models were utilized to evaluate overall survival and disease-free survival.

**Results:** HSP60 expression was significantly higher in ovarian cancer tissues compared to normal ovarian tissues. High HSP60 expression was associated with larger tumor size, advanced FIGO stage, and increased lymph node metastasis. Patients with high HSP60 expression exhibited significantly shorter overall survival and disease-free survival than those with low expression. Multivariate Cox analysis identified HSP60 as an independent prognostic factor for both overall survival and disease-free survival.

**Conclusion:** High HSP60 expression is associated with poor prognosis and aggressive tumor characteristics in ovarian cancer. HSP60 may serve as a valuable biomarker for prognosis and a potential therapeutic target. Further randomized clinical trials are warranted to explore its role in ovarian cancer progression and treatment strategies.

**Keywords:** HSP60, ovarian cancer, disease-free survival, overall survival, Cox regression model

## Introduction

Ovarian cancer is one of the most lethal gynecologic malignancies globally, with an estimated 324,398 new cases and 206,839 deaths reported in 2022.[1] This high mortality rate is primarily attributed to the disease's asymptomatic nature in its early stages, resulting in over 70% of patients being diagnosed at advanced stages (FIGO stage III or IV).[2–4] Despite advancements in surgical techniques and systemic therapies, the prognosis remains poor due to high recurrence rates and resistance to chemotherapy.[5,6] Therefore, identifying reliable biomarkers that can improve early detection, prognostic evaluation, and therapeutic outcomes is critical.

Heat shock proteins (HSPs) are a family of highly conserved molecular chaperones that maintain cellular homeostasis under stressful conditions, such as exposure to toxins or heat shock.[7,8] Among these, Heat Shock Protein 60 (HSP60) plays a critical role in protein folding, mitochondrial function, and cellular survival. Recent studies suggest that HSP60 is overexpressed in multiple cancers, including breast, lung, and colorectal cancers, where it is associated with tumor progression, resistance to apoptosis, and metastasis.[9–11] Previous studies also found that the expression of HSP60 was

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upregulated in ovarian cancer.[12] However, its precise role as a prognostic biomarker remains underexplored. Moreover, the mechanisms by which HSP60 contributes to ovarian cancer's aggressive behavior and treatment resistance are poorly understood.

In this study, we investigated the clinical significance of HSP60 expression in ovarian cancer by analyzing its association with clinicopathological features, overall survival, and disease-free survival. Furthermore, the study aims to explore how these findings could translate into clinical practice, such as developing targeted therapies, enabling risk stratification, or tailoring patient management strategies based on HSP60 expression levels. By addressing these gaps, this research could pave the way for improved survival outcomes for ovarian cancer patients.

# Materials and Methods

## Patients

In this study, patients diagnosed with ovarian cancer between January 2017 and December 2019 at The First Affiliated Hospital of Chengdu Medical College were enrolled. The research was conducted following the ethical principles of the Declaration of Helsinki and received approval from the Ethics Committee of The First Affiliated Hospital of Chengdu Medical College (No. 23423727). All patients provided written informed consent before participation. The criteria for inclusion were: (1) the presence of an ovarian primary tumor; (2) histological diagnosis of epithelial ovarian cancer confirmed by a pathologist; and (3) availability of comprehensive clinical, pathological, surgical, and follow-up information. The exclusion criteria included: (1) tumors arising from sites other than the ovary; (2) patients with concurrent malignancies; (3) patients who did not undergo standard treatment protocols; and (4) missing clinical or follow-up data. Ultimately, a total of 260 patients were enrolled in this study. After enrollment, all patients received treatment based on NCCN guidelines and the follow-up period concluded in December 2023.[13] Another 260 patients who underwent total hysterectomy and bilateral adnexectomy because of uterine myomas were also enrolled as controls. All the control subjects had normal ovarian tissues. Disease-free survival (DFS) was defined as the time from cytoreductive surgery to recurrence, as detected by imaging, or death from any cause. Overall survival (OS) was measured from the date of cytoreductive surgery to the time of death or the last follow-up.

## Immunohistochemistry Assay

The tissue samples were fixed in 4% paraformaldehyde for 48 hours, subsequently embedded in paraffin, and sectioned at a thickness of 4 μm. These sections underwent dewaxing, dehydration, and antigen retrieval processes. After rinsing the sections three times with PBST, they were treated with 10% goat serum to prevent nonspecific binding. An anti-HSP60 antibody from Abcam was used for staining, with negative controls processed without the primary antibody. After three additional PBS washes, the sections were incubated with a secondary antibody. Following another set of PBS washes, diaminobenzidine was applied to develop the color. Pathologists evaluated PTX3 expression using a Zeiss LSM500 microscope.

## Evaluation of HSP60 Expressions by Immunohistochemistry Staining

HSP60 expression was evaluated using immunohistochemistry staining on full tumor slides, which were randomly reviewed by two independent pathologists. Both reviewers performed blinded assessments on two separate occasions. Staining intensity was graded on a four-point scale: 0 indicating no staining, 1 for weak, 2 for moderate, and 3 for strong intensity. The proportion of positively stained cells was scored as follows: 0 for no stained cells, 1 for 1–25%, 2 for 26–50%, 3 for 51–75%, and 4 for more than 75%. The final score was calculated by multiplying the intensity score by the percentage score, and the score of 8 was calculated as a cut-off point. Tumors with scores below 8 were classified as having low HSP60 expression, while those with scores of 8 or higher were considered to have high HSP60 expression.

## Statistical Analysis

SPSS statistical software was utilized to perform the data analysis. The independent sample *t*-test was applied to compare continuous variables that followed a normal distribution, while categorical variables were assessed by either the Chi-square

test or Fisher's exact test. Kaplan-Meier survival curves were used to compare survival differences, and prognostic factors were evaluated through multivariable analysis using the Cox proportional hazards regression model. Statistical significance was determined at a threshold of $p < 0.05$.

# Results

## HSP60 Expression in Ovarian Cancer Tissues and Normal Ovarian Tissues

An immunohistochemical analysis was performed to evaluate HSP60 staining in 260 ovarian cancer tissues and 260 normal ovarian tissues (Figure 1). The results demonstrated that 91.54% of the cancerous tissues showed positive HSP60 staining, compared to only 11.15% of the normal tissues. This difference in HSP60 expression between the cancerous and normal ovarian tissues was statistically significant (Table 1).

## Correlation of HSP60 Expression with Clinicopathological Features of Ovarian Cancer Patients

Patients were categorized into high- or low-HSP60 expression groups based on immunohistochemical staining intensity. High HSP60 expression was not significantly correlated with factors such as age, height, weight, BMI, histological type, or tumor differentiation. However, high HSP60 expression was significantly correlated with FIGO stage, tumor size, and lymph node metastasis (Table 2). Patients with high HSP60 expression exhibited larger tumors, increased lymph node involvement, and more advanced FIGO stages.

## High HSP60 Expression Correlates with Reduced Overall Survival in Ovarian Cancer Patients

Kaplan-Meier analysis showed that patients exhibiting high HSP60 expression experienced significantly poorer overall survival than those with low HSP60 expression (Figure 2). To determine the risk factors affecting overall survival in ovarian cancer patients, both univariate and multivariate Cox proportional hazards regression analyses were conducted. The univariate analysis identified age, tumor differentiation, lymph node metastasis, FIGO stage, and HSP60 expression status as factors influencing overall survival. After adjusting for confounders such as age, tumor differentiation, tumor size, lymph node metastasis, and FIGO stage, the multivariate analysis identified lymph node metastasis, FIGO stage, and HSP60 expression status as independent risk factors for overall survival (Table 3).

## High HSP60 Expression Correlates with Reduced Disease-Free Survival in Ovarian Cancer Patients

The disease-free survival was evaluated by Kaplan-Meier analysis. The result showed that patients with high HSP60 expression had notably shorter disease-free survival than those with low HSP60 expression (Figure 3). Univariate and multivariate Cox proportional hazards regression analyses were used to determine risk factors affecting disease-free

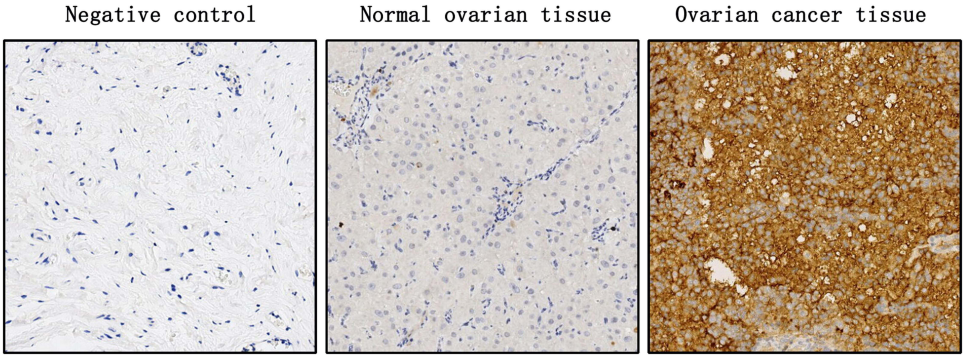


**Figure 1** Immunohistochemistry staining of HSP60 in ovarian cancer tissues and normal ovarian tissues (×200).


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**Table 1** HSP60 Expression in Ovarian Cancer Tissues and Normal Ovarian Tissues

| HSP60 Expression | Ovarian Cancer Tissues | Normal Ovarian Tissues | Total | p-value |
|---|---|---|---|---|
| Positive | 238 (91.54%) | 29 (11.15%) | 267 | <0.0001 |
| Negative | 22 (8.46%) | 231 (88.85%) | 253 | |
| Total | 260 | 260 | 520 | |

**Notes**: The statistical significance was analyzed by a chi-square test. A $p$ <0.05 was considered statistical significance.

**Table 2** Correlation of HSP60 Expression with Clinicopathological Features in Ovarian Cancer Patients

| Characteristics | Total (260) | HSP60 Expression | | p-value |
|---|---|---|---|---|
| | | Low (126) | High (134) | |
| **Age** (year) | | | | 0.874 |
| ≤60 | 121 | 58 | 63 | |
| >60 | 139 | 68 | 71 | |
| **Height** (cm) | | | | 0.359 |
| ≤160 | 106 | 55 | 51 | |
| >160 | 154 | 71 | 83 | |
| **Weight** (Kg) | | | | 0.306 |
| ≤60 | 163 | 75 | 88 | |
| >60 | 97 | 51 | 46 | |
| **BMI** ($kg/m^2$) | | | | 0.789 |
| ≤28 | 95 | 45 | 50 | |
| >28 | 165 | 81 | 84 | |
| **Tumor differentiation** | | | | 0.298 |
| Well and moderate | 95 | 42 | 53 | |
| Poor | 165 | 84 | 81 | |
| **Histological type** | | | | 0.395 |
| Mucinous carcinoma | 154 | 78 | 76 | |
| Serous carcinoma | 106 | 48 | 58 | |
| **FIGO stage** | | | | **0.0001** |
| I+ II | 135 | 81 | 54 | |
| III+ IV | 125 | 45 | 80 | |
| **Tumor size** | | | | **0.0001** |
| ≤5 | 144 | 85 | 59 | |
| >5 | 116 | 41 | 75 | |
| **Lymph node metastasis** | | | | **0.0005** |
| No | 151 | 87 | 64 | |
| Yes | 109 | 39 | 70 | |

**Notes**: The statistical significance was analyzed by a chi-square test. A $p$ <0.05 was considered statistical significance and was highlighted in bold text.

survival in ovarian cancer patients. The univariate analysis revealed that tumor size, lymph node metastasis, tumor differentiation, FIGO stage, and HSP60 expression were risk factors influencing disease-free survival. After adjusting for potential confounding variables, including age, tumor differentiation, tumor size, lymph node metastasis, tumor differentiation, and FIGO stage, the multivariate analysis determined that lymph node metastasis, FIGO stage, and HSP60 expression were independent risk factors for disease-free survival (Table 4).

## Discussion

The role of heat shock proteins (HSPs) in cancer biology has garnered increasing attention due to their involvement in critical cellular processes such as apoptosis, proliferation, and metastasis.[14–16] Among them, HSP60 is particularly

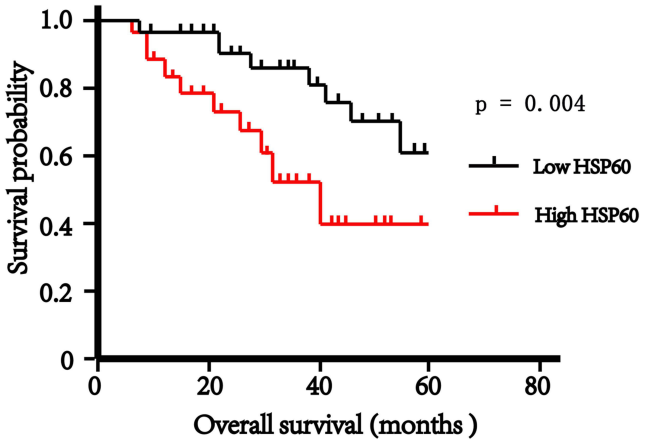


**Figure 2** Kaplan-Meier curves for ovarian cancer patients with high HSP60 expression showed worse overall survival rates compared to patients with low HSP60 expression ($p$ = 0.004).

**Table 3** Determination of Prognostic Factors for Overall Survival in Ovarian Cancer Patients Using a Cox Proportional Hazards Regression Model

| Characteristics | Univariate Analysis | *p-value* | Multivariate Analysis | Adjusted p-value |
|---|---|---|---|---|
| | HR (95% CI) | | HR (95% CI) | |
| **Age** (year) | | | | |
| ≤60 | 1.00 (Reference) | | 1.00 (Reference) | |
| > 60 | 2.52 (1.27–5.47) | **0.002** | 1.03 (0.62–2.45) | 0.132 |
| **Height** (cm) | | | | |
| ≤160 | 1.00 (Reference) | | 1.00 (Reference) | |
| >160 | 1.18 (1.01–2.52) | 0.313 | 0.92 (0.51–2.27) | 0.245 |
| **Weight** (Kg) | | | | |
| ≤60 | 1.00 (Reference) | | 1.00 (Reference) | |
| > 60 | 0.83 (0.53–2.71) | 0.122 | 1.04 (0.71–2.24) | 0.134 |
| **BMI** (kg/m$^2$) | | | | |
| ≤28 | 1.00 (Reference) | | 1.00 (Reference) | |
| >28 | 1.06 (0.74–3.22) | 0.241 | 0.84 (0.62–2.07) | 0.273 |
| **Tumor differentiation** | | | | |
| Well and moderate | 1.00 (Reference) | | 1.00 (Reference) | |
| Poor | 2.53 (1.62–3.52) | **0.003** | 1.13 (0.87–1.92) | 0.263 |
| **Histological type** | | | | |
| Mucinous carcinoma | 1.00 (Reference) | | 1.00 (Reference) | |
| Serous carcinoma | 0.92 (0.71–2.73) | 0.241 | 1.02 (0.73–1.65) | 0.123 |
| **FIGO stage** | | | | |
| I+ II | 1.00 (Reference) | | 1.00 (Reference) | |
| III+ IV | 3.34 (1.62–6.07) | **0.003** | 2.64 (1.07–3.92) | **0.002** |
| **Tumor size** (cm) | | | | |
| ≤5 | 1.00 (Reference) | | 1.00 (Reference) | |
| >5 | 2.85 (1.27–5.24) | 0.114 | 1.35 (0.83–2.67) | 0.213 |
| **Lymph node metastasis** | | | | |
| No | 1.00 (Reference) | | 1.00 (Reference) | |
| Yes | 3.74 (1.42–5.84) | **0.004** | 2.53 (1.04–4.13) | **0.002** |
| **HSP60 expression** | | | | |
| Low | 1.00 (Reference) | | 1.00 (Reference) | |
| High | 4.21 (2.67–5.73) | **0.001** | 3.14 (2.06–5.48) | **0.003** |

**Notes**: Adjusted for potential confounding factors, including age, tumor differentiation, FIGO stage, tumor size, and lymph node metastasis. A $p < 0.05$ was considered statistical significance and was highlighted in bold text.
**Abbreviations**: CI, Confidence interval; HR, hazard ratio.


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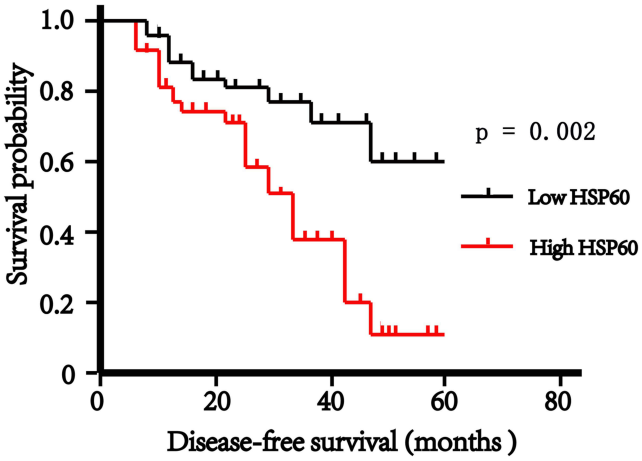


**Figure 3** Kaplan-Meier curves for ovarian cancer patients with high HSP60 expression showed worse disease-free survival rates compared to patients with low HSP60 expression ($p$ = 0.002).

**Table 4** Determination of Prognostic Factors for Disease-Free Survival in Ovarian Cancer Patients Using a Cox Proportional Hazards Regression Model

| Characteristics | Univariate Analysis | *p-value* | Multivariate Analysis | Adjusted p-value |
|---|---|---|---|---|
| | HR (95% CI) | | HR (95% CI) | |
| **Age** (year) | | | | |
| ≤60 | 1.00 (Reference) | | 1.00 (Reference) | |
| > 60 | 1.24 (1.06–2.72) | 0.091 | 1.01 (0.82–2.42) | 0.345 |
| **Height** (cm) | | | | |
| ≤160 | 1.00 (Reference) | | 1.00 (Reference) | |
| >160 | 0.94 (0.85–2.17) | 0.262 | 1.09 (0.65–2.68) | 0.403 |
| **Weight** (Kg) | | | | |
| ≤60 | 1.00 (Reference) | | 1.00 (Reference) | |
| > 60 | 1.13 (0.83–2.67) | 0.314 | 0.92 (0.62–2.97) | 0.352 |
| **BMI** ($kg/m^2$) | | | | |
| ≤28 | 1.00 (Reference) | | 1.00 (Reference) | |
| >28 | 0.87 (0.67–2.17) | 0.094 | 1.17 (0.75–2.25) | 0.443 |
| **Tumor differentiation** | | | | |
| Well and moderate | 1.00 (Reference) | | 1.00 (Reference) | |
| Poor | 3.07 (1.94–3.91) | **0.001** | 1.26 (0.96–1.81) | 0.324 |
| **Histological type** | | | | |
| Mucinous carcinoma | 1.00 (Reference) | | 1.00 (Reference) | |
| Serous carcinoma | 1.04 (0.83–2.51) | 0.327 | 0.87 (0.51–1.71) | 0.514 |
| **FIGO stage** | | | | |
| I+ II | 1.00 (Reference) | | 1.00 (Reference) | |
| III+ IV | 4.13 (2.57–6.38) | **0.015** | 2.14 (0.92–3.47) | **0.001** |
| **Tumor size** (cm) | | | | |
| ≤5 | 1.00 (Reference) | | 1.00 (Reference) | |
| >5 | 2.27 (1.83–4.05) | **0.004** | 0.89 (0.64–1.52) | 0.623 |
| **Lymph node metastasis** | | | | |
| No | 1.00 (Reference) | | 1.00 (Reference) | |
| Yes | 4.248 (2.03–6.17) | **0.002** | 3.05 (2.13–4.76) | **0.005** |
| **HSP60 expression** | | | | |
| Low | 1.00 (Reference) | | 1.00 (Reference) | |
| High | 5.37 (2.24–7.24) | **0.001** | 4.23 (2.25–6.17) | **0.001** |

**Notes**: Adjusted for potential confounding factors, including age, tumor differentiation, FIGO stage, tumor size, and lymph node metastasis. A $p < 0.05$ was considered statistical significance and highlighted in bold text.
**Abbreviations**: CI, Confidence interval; HR, hazard ratio.

important as a mitochondrial molecular chaperone that facilitates protein folding and prevents aggregation under stress conditions.[17,18] This study adds to the growing body of evidence suggesting that HSP60 is not only overexpressed in ovarian cancer but also plays a critical role in the prognosis of ovarian cancer patients.

Our findings showed that HSP60 expression was significantly higher in ovarian cancer tissues compared to normal ovarian tissues, with 91.54% of cancerous tissues exhibiting positive HSP60 staining versus only 11.15% of normal tissues (Table 1). Elevated HSP60 levels have been reported in other malignancies, such as colorectal cancer, non-small cell lung cancer, and breast cancer.[9–11] For instance, a study by Vocka et al found that serum HSP60 levels were higher in metastatic colorectal cancer and correlated with tumor progression and poor prognosis.[10] Similarly, Tang et al demonstrated that HSP60 overexpression predicted poor outcomes in non-small cell lung cancer patients.[9] These findings suggest that HSP60 may be a tumor biomarker associated with tumor progression.[9–12] The significant difference in HSP60 expression between cancerous tissues and normal ovarian tissues highlights its potential as a diagnostic tool for ovarian cancer, aiding in earlier detection and improved disease management.

Additionally, our study revealed that high HSP60 expression is associated with more aggressive clinicopathological features of ovarian cancer, including larger tumor size, advanced FIGO stage, and increased lymph node metastasis (Table 2). These findings indicate that high HSP60 expression serves as a marker for more aggressive disease characteristics in ovarian cancer. Incorporating high HSP60 expression into risk stratification models may help identify patients at a higher risk of disease progression. This could enable oncologists to tailor follow-up schedules, such as reducing intervals between imaging and tumor marker assessments, to facilitate earlier detection of recurrence in high-risk patients.[19] Moreover, patients with high HSP60 expression may benefit from more aggressive initial treatment strategies, including optimal cytoreductive surgery combined with adjuvant therapies.

More importantly, our study found that patients with high HSP60 expression had a poorer overall survival compared to those with low HSP60 expression (Figure 2). Similarly, the disease-free survival was significantly shorter for patients with high HSP60 expression compared to those with low HSP60 expression (Figure 3). Previous studies have also highlighted the prognostic value of HSP60 in gastric and prostate cancers. Li et al reported that high HSP60 expression in gastric cancer tissues was linked to reduced overall survival and disease-free survival.[20] Beyene et al found that elevated HSP60 expression predicted disease progression and worse survival in prostate cancer patients.[21] These findings suggest the universal prognostic significance of HSP60 across various malignancies. Future research should focus on translating these findings into clinical applications, including targeted therapies and personalized treatment strategies for ovarian cancer patients.

Our multivariate Cox regression analysis further underscores the independent prognostic value of HSP60 expression in ovarian cancer. Even after adjusting for potential confounding variables such as age, tumor differentiation, tumor size, lymph node metastasis, and FIGO stage, high HSP60 expression remained an independent risk factor for both overall survival and disease-free survival (Tables 3 and 4). This finding strengthens the potential of HSP60 as a prognostic biomarker in clinical settings, where it could be used to identify high-risk patients who may require more aggressive treatment and closer monitoring.

The mechanisms for this association likely involve several pathways. HSP60 interacts with key regulatory proteins such as p53 and survivin, both of which play central roles in cancer cell survival and apoptosis.[22,23] The interaction with p53, a well-known tumor suppressor, may inhibit its pro-apoptotic functions, enabling cancer cells to evade programmed cell death.[24] Additionally, HSP60 upregulates the expression of survivin and promotes cell survival by inhibiting caspase activation, a critical step in apoptosis.[25] The elevated expression of HSP60 in ovarian cancer may therefore create an environment that promotes tumor cell survival and resistance to apoptosis, contributing to the poorer survival outcomes observed in patients with high HSP60 expression.

Several potential therapeutic strategies could be explored based on the overexpression of HSP60 in ovarian cancer. One approach is the development of HSP60 inhibitors that could disrupt its chaperone function, thereby restoring apoptosis in cancer cells. Small molecule inhibitors targeting the ATPase activity of HSPs have shown promise in preclinical studies for other cancer types, and similar strategies could be applied to ovarian cancer.[26–28] Alternatively, HSP60 could be targeted indirectly by modulating its interacting partners, such as p53 and survivin,

to enhance apoptotic signaling. Given that HSP60 is primarily localized in the mitochondria, another potential strategy could involve disrupting mitochondrial function to sensitize cancer cells to chemotherapy.[12,29]

Despite the promising implications of our findings, it is important to acknowledge the limitations of this study. First, the study was carried out on a relatively homogenous population from a single healthcare center, which could potentially restrict the generalizability of the findings. Second, the subjectivity of pathologists in evaluating HSP60 expression through immunohistochemical staining cannot be completely ruled out. Third, while our study focused on HSP60 expression in ovarian cancer tissues, the molecular mechanisms through which HSP60 contributes to tumor progression remain incompletely understood. Further research is required to elucidate these pathways and assess whether targeting HSP60 could provide therapeutic benefits.

## Conclusion

Our study underscores the clinical significance of HSP60 as both a prognostic biomarker and a potential therapeutic target in ovarian cancer. The strong association between high HSP60 expression and poor survival outcomes highlights the need for further research into the mechanisms by which HSP60 promotes tumor progression. Additionally, developing targeted therapies against HSP60 could offer new strategies to improve the prognosis of patients with ovarian cancer, particularly those with advanced disease or resistance to conventional treatments. Future studies should focus on validating these findings in larger cohorts and exploring the feasibility of incorporating HSP60-targeted therapies into the clinical management of ovarian cancer.

## Ethics Approval

This study was approved by the Ethics Committee of The First Affiliated Hospital of Chengdu Medical College (No. 23423727). All the participants provided written informed consent.

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## Disclosure

We declare no conflict of interest.

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