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Expression of resistance gene and prognosis of chemotherapy in primary epithelial ovarian cancer

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Abstract

The sensitivity of tumor cells to chemotherapy drugs may become attenuated accounts for various reasons. Reduced drug sensitivity may cause the failure of chemotherapy and affect the prognosis of patients with cancer. This study investigates the relationship between the expression levels of lung resistance protein (LRP) and placental glutathione S-transferase-P1 (GSTP1), the resistance of primary epithelial ovarian cancer (PEOC) to chemotherapy, and the prognosis of patients with platinum drug-resistant PEOC.

Quantitative PCR (QT-PCR) was used to detect the mRNA level of the resistance genes *LRP, GSTP1* in all tissue and cell lines.

The expression levels of resistance gene (*LRP*, *GSTP1*) in PEOC were the highest, followed by borderline adenoma tissues, and the lowest levels found in benign tumor tissues, the difference of genes expression between different tissues was statistically significant; the difference between the expression rates and relative expression level of drug resistance genes was statistically significant in platinum sensitive group compare with the platinum resistant group. The difference between resistant gene negative-expression and positive-expression of chemotherapy efficiency, disease free survival time, and recurrence time were statistically significant. The resistant genes expression in the PEOC patients of the negative-group survival curves was higher than that in the positive group. With ascites non-cellular component (ANCC) stimulated SKOV3 cells, the cell proliferation inhibition rate (CPIR) increased, and with ANCC stimulated SKOV3/DDP, the expression of LRP and GSTP1 also increased.

ANCC may promote the expression of drug resistance genes, and the expression of genes may predict the poorly prognosis of epithelial ovarian cancer.

Abbreviations: ANCC = ascites non-cellular component, EOC = epithelial ovarian cancer, GSTP1 = placental glutathione S-transferase-P1, LRP = lung resistance protein, PEOC = primary epithelial ovarian cancer, QT-PCR = quantitative PCR.

Keywords: chemotherapy, drug-resistant, epithelial ovarian cancer, lung resistance protein, placental glutathione S-transferase-P1

1. Introduction

Epithelial ovarian cancer (EOC) is a malignant gynecological tumor. Although the global incidence rate of EOC ranks third, its mortality rate ranks first among female genital maligancies.[1] EOC is mainly treated by surgery combined with chemotherapy, radiotherapy, and some immune modulators.[2] However, most of patients are diagnosed in advanced stage, platinum is the first line for chemothrapy, some EOC types have developed resistance to platinum.[3,4] Patients with drug-resistant EOC will suffer a relapse within 6 months of receiving platinum-based chemotherapy or will remain in a stable state during the period of chemotherapy.[5] Chemo-resistance is related to the decrease in drug concentration or increase in drug metabolism and drug efflux pump activity.[6,7] Lung resistance protein (LRP) and placental glutathione S-transferase-P1 (GSTP1) play an important role in chemotherapy-resistant EOC and are associated with decreased drug concentration and drug efflux pump activity. This study investigates the relationship among the expression levels of LRP and GSTP1, the drug resistance of EOC, and the prognosis of patients with EOC. This work is crucial for studying the mechanisms of platinum resistance in EOC, guiding the rational clinical application of chemotherapy, predicting the prognosis of patients, and improving the curative effect of chemotherapy.

2. Materials and methods

2.1. Patients and specimens

A total of fresh surgical tissue (57 cases of PEOC, 34 cases of borderline adenoma, and 21 cases of benign adenoma) were collected from March 2009 to July 2011 in which Taihe hospital stored in liquid nitrogen for future use. Patients were aged between 35 and 71 years. Histologic cell types included 27 cases of serous adenocarcinoma, 20 cases of mucinous adenocarcinoma, and 10 cases of endometrioid carcinoma. Clinical staging was as follows: Stage I, 25 cases; stage II, 19 cases; and stage III,

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Table 1

The demographic and clinical information about all cases.

	PEOC	Borderline adenoma	Benign adenoma
Age			
<50	19	12	9
≥50	38	22	12
Smoking			
Yes	5	3	2
No	51	31	19
Menstruation			
Regular	44	24	17
Irregular	13	10	4
Dysmenorrhea			
Yes	35	20	13
No	22	14	8
Menarche age			
≥13	16	11	6
<13	41	23	15
Menstrual cycle			
>30	18	10	5
≤30	39	24	16
Uterine fibroid			
Yes	12	11	7
No	45	23	14
Gravidity			
≥2	22	10	7
<2	35	24	14
Family history			
Yes	4	2	1
No	53	32	20

PEOC = primary epithelial ovarian cancer.

13 cases. Of these cases, 12 were well differentiated, 20 were moderately differentiated, and 25 were poorly differentiated carcinomas. Patients were recruited in the study having the following criteria: without receive preoperative radiotherapy or chemotherapy, gotten 4 to 6 cycles of platinum-based chemotherapy postoperative, no serious complications, had good compliance over 6 to 60 months of follow-up. The 57 patients were divided into a platinum-sensitive group (35 cases) and a platinum-resistant group (22 cases). The complete demographic and clinical information was showed in Table 1. In accordance with the Declaration of Helsinki, this study was approved by the ethics committee of Taihe Hospital.

Drug efficacy judgment platinum-sensitive: The initial use of platinum-based chemotherapy completely relieves the symptoms of EOC as confirmed in clinical practice. The time to recurrence is >6 months since the last course of chemotherapy. Platinum-resistant: the initial treatment is effective but the time to recurrence is <6 months since the last course of chemotherapy. Chemotherapy is ineffective, and the best treatment response during the course of chemotherapy or after a minimum of 6 courses of treatment is partial pain relief or arrested tumor growth.

2.2. Acquisition of ANCC and cell culture

Thirty-three cases of ovarian cancer ascites were obtained by ultrasound guided puncture, and the ascites non-cell component were obtained by high speed centrifuged and filtrated. The obtained ANCC were divided into 15 mL centrifuge tubes and 2 mL cryopreserved tubes at a temperature of −80 °C. After thawing, the 2 mL cryopreserved tubes from all patients' ascites were mixed and used as culture conditions for ovarian cancer cell SKOV3. The SKOV3 cell line was stored in our laboratory and cultivated at 37 °C and 5% CO_2 in RPMI 1640 medium containing 10% FBS (fetal bovine serum), 1.5% L-glutamine, and 1% penicillin/streptomycin. The SKOV3/DDP (Cisplatin, DDP, Shanghai, China) was established from SKOV3 cells as previously described.[8]

2.3. Detection of SKOV3 proliferation

MTT method was used to detect SKOV3 proliferation. About 2×10^3 logarithmic phase cells (about 200 μL of the culture solution) were obtained and inoculated onto the culture plate. After single-layer adherent growth of cells for 24 hours and culture plate coverage of about 50% to 60%, the supernatant was discarded. After ANCC stimulated SKOV3, the culture was terminated, and the supernatant was discarded. DMSO was added to each hole for shaking and mixing, and absorbance A at 570 nm for each hole was recorded. Cell proliferation inhibition rate (CPIR) was used to determine cell proliferation activity in the 2 groups. $CPIR = (A_{Contro\ group} - A_{Test\ group}/A_{Control\ group}) \times 100\%$. Each experiment was repeated 5 times.

2.4. RNA extraction and reverse transcription

Total RNA was extracted using TRIzol Reagent (Invitrogen, CA) according to the manufacture's protocol. The concentration and purity of total RNA was determined by measuring the absorption with NanoDrop-2000 (Thermo Fisher, CA) at 260 and 280 nm. First-strand cDNA was prepared from total RNA using Promega reverse transcription system (Promega, CA) based on the manufacturer's instructions. cDNA was used immediately or stored at −80 °C until use.

2.5. Real-time PCR detected the expression of gene

The primers were used for the polymerase chain reactions (PCR) as follows: forward, 5′-CCA GAA CCA GGG AGG CAA GA-3′ and reverse, 5′-GAG GCG CCC CAC ATA TGC T-3′ for human GSTP1; forward, 5′-GTC TTC GGG CCT GAG CTG GTG TCG-3′ and reverse, 5′-CTT GGC CGT CTC TTG GGG GTC CTT-3′ for human LRP; and forward, 5′-GAA GGT GAA GGT CGG AGT C-3′ and reverse, 5′- GAA GAT GGT GAT GGG ATT TC-3′ for human GAPDH. LRP, GSTP1, and GAPDH primers yielded products of 240, 325, and 226 bp, respectively. PCR amplification system: Mg^{2+} 2.4 μL, 2 μL each of 5′ and 3′ primer, Taq 0.3 μL, 2 mmol/L dNTP 1.5 μL, 10× SYBR-Green I 1 μL, 10× Buffer 3 μL, cDNA 5 μL, with sterile water total volume filled 30 μL. Reaction conditions: 95 °C denaturation for 5 minutes; 94 °C 30 seconds, 60 °C 30 seconds, 72 °C 1 minute with 35 cycles. At the end point of 35 PCR cycles, dissociation curve analysis was performed, the reaction products were separated electrophoretically on a 2% agarose gel and stained with ethidium bromide for further confirmation of the PCR products. The mRNA expression levels of LRP, GSTP1 were expressed as a ratio relative to GAPDH in each sample, the level of genes expression were normalized to that of the internal glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and were determined by the $2^{-\Delta\Delta Ct}$ method.

2.6. Statistical analysis

Statistical analyses were performed using SPSS software version 16.0 (SPSS Inc. Chicago, IL), and $P < .05$ was used to indicate

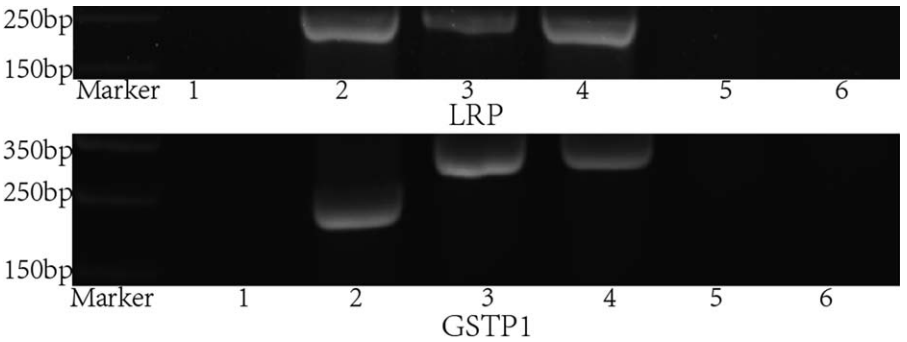

Figure 1. Representation of expression product of LRP, GSTP1 (Note: 1, water; 2, GAPDH; 3, PEOC; 4, borderline adenoma; 5–6, benign adenoma). GSTP1 = placental glutathione S-transferase-P1, LRP = lung resistance protein, PEOC = primary epithelial ovarian cancer.

statistically significant difference. The measured data were expressed as the mean ± standard deviation. Fisher exact test rather/the chi-squared test was used for comparing the chemotherapy efficiency between positive expression and negative expression patients. A Student *t* test/analysis of variance (ANOVA) was used to determine the expression differences between the different groups, if the data were non-normally distribution, the Mann–Whitney *U* test of non-parametric method was used. Gene expression levels and chemotherapeutic effect of PEOC were investigated using Pearson chi-squared test. Pearson correlation analysis was used to analyze the correlation between LRP and GSTP1 gene expression. Kaplan–Meier method with log-rank test was performed to estimate overall survival time.

3. Results

3.1. LRP, GSTP1 mRNA were highly expressed in PEOC compare with borderline and benign adenoma

The resistance genes LRP, GSTP1 in PEOC were highly expressed, and the positive expression rates were 78.9% and 57.9%, respectively. And the positive expression rates were 35.3% and 26.5% in borderline adenoma, respectively. Benign adenoma was either poorly or not expressed, with positive expression rates of 9.52% and 4.76%. The expression levels of the resistance genes were higher in PEOC tissues/borderline adenoma tissues than in benign adenoma tissues; the difference was statistically significant ($P < .001$). Both genes were positive in 28 cases, and there was a correlation between LRP and GSTP1 expression ($r = 0.72$, $P < .001$). The LRP, GSTP1 gene expression levels were presented in Figs. 1 and 2. The correlation between LRP and GSTP1 expression was presented in Fig. 3.

3.2. mRNA expression in different clinical pathological data of PEOC

The expression of the resistance genes were higher in well and moderately poorly differentiated carcinoma than that in the poorly differentiated carcinomas, besides, the expression of the resistance genes were higher in ascites positive than that in ascites negative. The difference in expression was statistically significant ($P < .05$), whereas the difference in other clinic-pathological factors (age, pathological type, clinical stage) were not statistically significant. The relationships between the expression levels of the resistance genes and the clinic-pathological features are presented in Table 2.

3.3. Gene expression and chemotherapeutic effect of PEOC

From the 45 cases of patients with positive expression of LRP, 25 patients were effective chemotherapy, chemotherapy efficiency rate was 55.6% (25/45); 12 cases of patients with negative expression of LRP, 11 patients were effective chemotherapy, chemotherapy efficiency rate was 91.7% (11/12), the difference

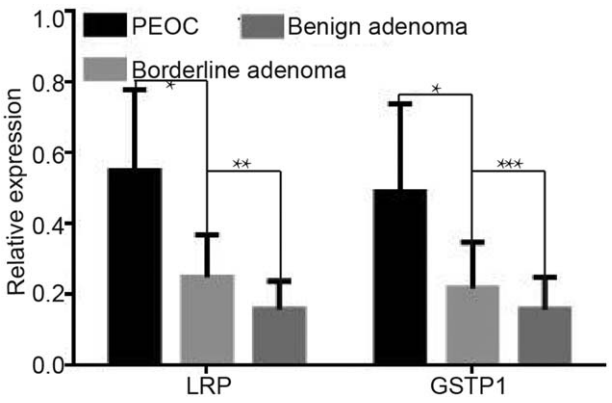

Figure 2. The expression level of LRP, GSTP1 mRNA in all samples. *, $P < .001$; **, $P = .006$; ***, $P = .034$. GSTP1 = placental glutathione S-transferase-P1, LRP = lung resistance protein.

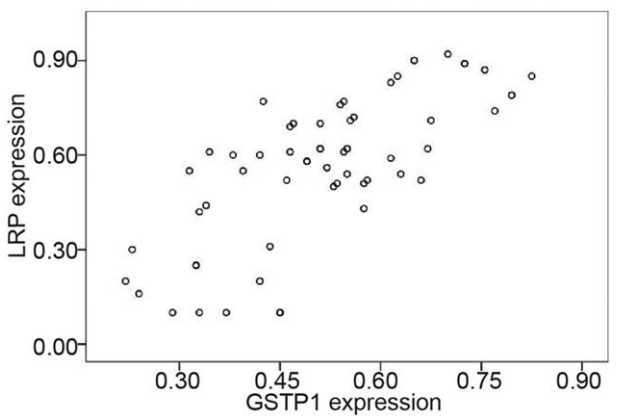

Figure 3. The correlation between LRP and GSTP1 expression. GSTP1 = placental glutathione S-transferase-P1, LRP = lung resistance protein.

Table 2

Relationship between the expression of gene and clinicopathologic paramenters in PEOC.

Study groups	N	LRP	GSTP1
Age, y			
<50	19	0.61 ± 0.25	0.50 ± 0.24
≥50	38	0.52 ± 0.22	0.43 ± 0.26
Histologic types			
Serous adenocarcinoma	30	0.61 ± 0.26	0.54 ± 0.21
Mucinous + Endometrioid	27	0.50 ± 0.19	0.43 ± 0.28
Stage			
I + II	25	0.62 ± 0.24	0.54 ± 0.23
III + IV	32	0.51 ± 0.22	0.45 ± 0.27
Differentiation			
Well + Moderately	32	0.61 ± 0.25*	0.56 ± 0.23**
Poorly	25	0.48 ± 0.18	0.41 ± 0.27
Ascites			
Yes	33	0.65 ± 0.20#	0.63 ± 0.15##
No	24	0.41 ± 0.20	0.30 ± 0.24

Note: Gene expression data are expressed as the mean ± standard deviation. LRP = lung resistance protein; GSTP1 = placental glutathione S-transferase P1.

* $Z = 2.61$, $P = .009$.

** $Z = 1.97$, $P = .042$.

$Z = 4.17$, $P < .001$.

$Z = 4.34$, $P < 0.001$.

was statistically significant (**x03C7;$^2_{\text{Fisher}} = 5.31$, $P = .04$**). Thirty-six cases of patients with positive expression of GSTP1, 23 patients were effective chemotherapy, chemotherapy efficiency rate was 63.9% (23/36); 21 cases of patients with negative expression of GSTP1, 19 patients were effective chemotherapy, chemotherapy efficiency rate was 90.5% (19/21), the difference was statistically significant ($\chi^2 = 4.84$, $P = .028$).

3.4. Gene expression and chemotherapy resistance of PEOC

In the platinum resistant group, 21 cases of patients with positive expression of LRP, the positive rate was 95.5% (21/22), and in sensitive groups, 26 cases of patients with positive expression of LRP, the positive rate was 74.3% (26/35), the difference was not statistically significant ($P = .071$, Fisher exact test). In the resistant group, 18 cases of patients with positive expression of GSTP1, the positive rate was 81.8% (18/22), and in sensitive groups, 18 cases of patients with positive expression of GSTP1, the positive rate was 51.4% (18/35), the difference was statistically significant ($\chi^2 = 5.36$, $P = .021$).

3.5. Effect of ANCC on cell proliferation and resistance gene expression

To study the proliferation of SKOV3 cells stimulated by ANCC, there were divided into 2 study groups, experimental group is the cell cultured by ANCC and control group that cultured by FBS. The CPIR in the experimental group was higher than that in the control group (Fig. 4A). And after stimulation of SKOV3/DDP cells with ANCC, the expression of drug resistance genes increased to varying degrees (Fig. 4B).

3.6. mRNA expression levels of LRP, GSTP1, and survival rate of patients

According to the expression of resistance gene, it was divided into positive and negative groups. The cancer samples were categorized into LRP-positive (median survival = 32.0, n = 45) and LRP-negative (n = 12) groups, GSTP1-positive (median survival = 30.0, n = 36), and GSTP1-negative (n = 21) groups, expression negative group survival curve were higher than the positive group, the difference were statistically significant ($P = .024$, $P < .001$), shown in Fig. 5. During the follow-up period, 42 patients relapsed, including 35 in the LRP-positive group and 28 in the GSTP1-positive group. The difference between the survival time/recurrence time of positive expression and negative expression was statistically significant, shown in Fig. 6.

4. Discussion

In-depth research and advances in surgery, radiotherapy, and chemotherapy have considerably improved the effectiveness of EOC treatment. However, the early clinical symptoms of EOC are not obvious, and resistance to chemotherapy drugs, particularly to platinum-based drugs, is an important factor that affects the prognosis of patients with EOC.[9,10] A high percentage of patients with EOC suffer relapse and cancer metastasis within 2 years of receiving surgical treatment combined with chemotherapy.[11] Therefore, studying the expression of genes associated with drug-resistant EOC and their involvement in platinum resistance may have important

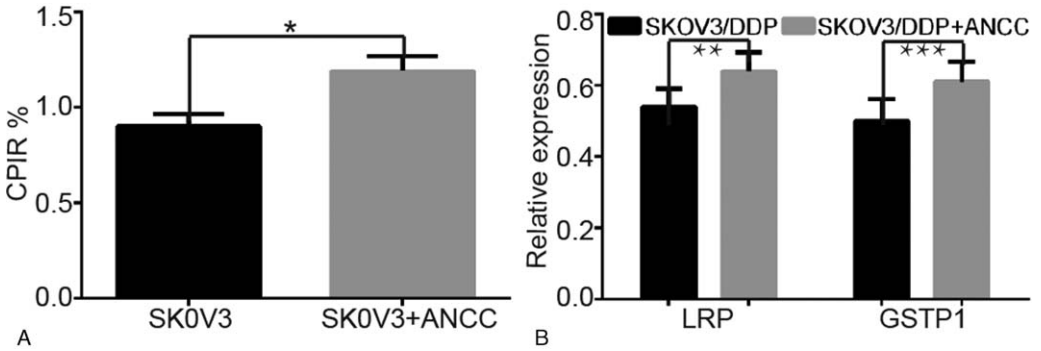

Figure 4. Effect of ANCC on cell proliferation and resistance gene expression. A: SKOV3 proliferation with culture different conditions; B: Gene expression in SKOV3/DDP under different culture conditions. ANCC = ascites non-cellular component, CPIR = cell proliferation inhibition rate. *, $P < .001$; **, $P = .013$; ***, $P = .021$.

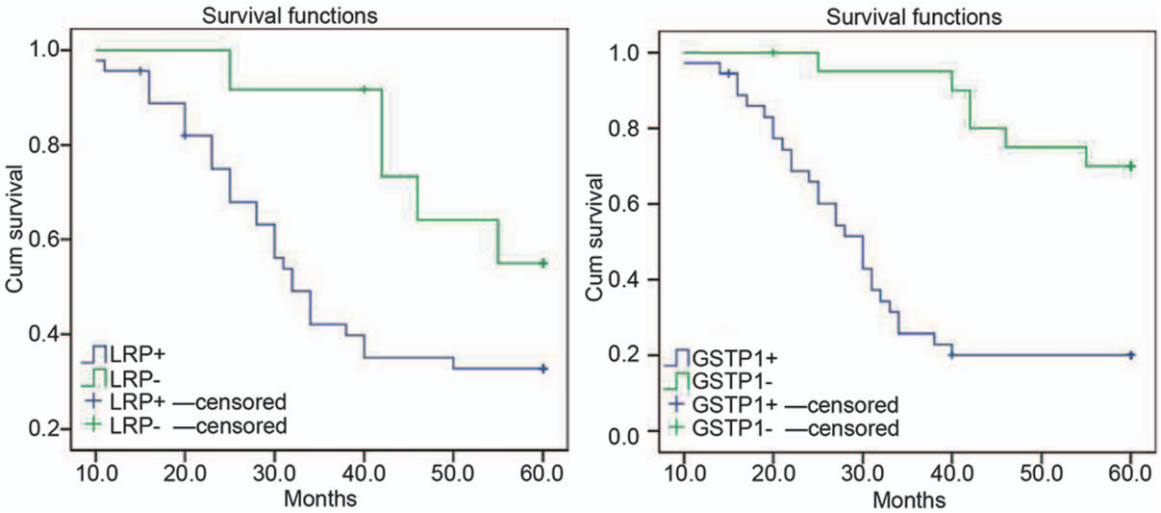

Figure 5. Survival curves of LRP, GSTP1 mRNA-positive and negative patients. A: LRP; B: GSTP1; LRP+: LRP-positive; LRP-: LRP-negative; GSTP1+: GSTP1-positive; GSTP1-: GSTP1-negative. GSTP1 = placental glutathione S-transferase-P1, LRP = lung resistance protein.

clinical significance for optimizing EOC chemotherapy regimens and judging the drug resistance of tumor types.

LRP was first observed in lung cancer cell strains. It competitively binds with platinum drugs to prevent their entry into the nucleus. Moreover, the LRP–drug complex can be translocated into the cytoplasm even it enters the nucleus, thereby decreasing the concentration of drugs that can reach the target cancer cells.[12] LRP is highly expressed in a variety of tumors.[13–15] GST is a drug-metabolizing enzyme, and GSTP1 is closely related with the platinum resistance of tumors. In a reaction that is catalyzed by GST, platinum combines with small-molecule substances to form chelates. Relevant membrane proteins recognize the chelates and prevent their entry into the cell, thus decreasing the concentration of platinum drugs that reaches cancer cells.[16] The present work investigated the expression of LRP and GSTP1 in different EOC groups and analyzed the effect of gene expression on the prognosis of patients with platinum drug-resistant EOC. It provides a theoretical basis for the rational selection of chemotherapy in the treatment of EOC.

LRP and GSTP1 expression in the drug-resistant group is significantly higher than that in the drug-sensitive group, and the effective rate of chemotherapy in patients with negative drug resistance is significantly higher than that in patients with positive drug resistance. These results indicated that LRP and GSTP1 may be involved in the development of platinum resistance in EOC and may be connected with the therapeutic effect of recent chemotherapy. Therefore, the expression levels of LRP and GSTP1 could be used as indices for predicting the resistance of tumors to platinum drugs and evaluating the therapeutic effect of recent chemotherapy. The expression level of LRP is negatively correlated with the sensitivity of the tumor to cisplatin and cyclophosphamide; thus, it is a highly valuable index for predicting cisplatin sensitivity.[17] LRP and GSTP1 were expressed by 28 cases. LRP expression is correlated with GSTP1 expression, indicating that the development of drug resistance is a process that involves multiple genes. The high expression of LRP and GSTP1 may play an important role in the development of platinum resistance in EOC.

The tumor microenvironment is very important for the development of tumors.[18] Ascites, as a part of the tumor microenvironment, is closely related to the prognosis of ovarian cancer.[19] Mo et al[20] found that ascites can significantly

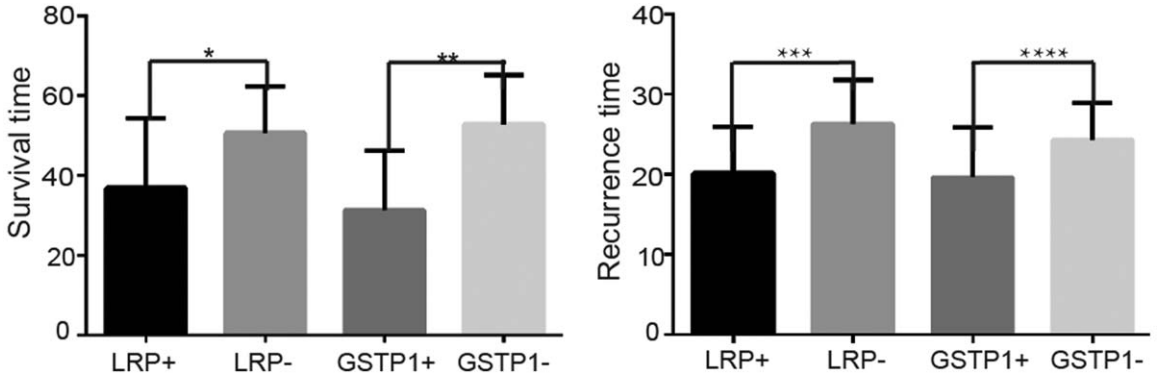

Figure 6. The survival time and recurrence time in the PEOC. A: survival time; B: recurrence time; LRP+: LRP-positive; LRP-: LRP-negative; GSTP1+: GSTP1-positive; GSTP1-: GSTP1-negative. *, $P = .012$; **, $P < .001$; ***, $P = .014$; ****, $P = .018$. GSTP1 = placental glutathione S-transferase-P1, LRP = lung resistance protein, PEOC = primary epithelial ovarian cancer.

enhance tumor migration ability. In this study, ANCC in ovarian cancer can promote the proliferation of tumor cells, and ANCC may decrease the sensitivity to DDP by promoting the expression of drug resistance genes, leading to the occurrence of drug resistance. The high expression of this resistance gene may also be one of the causes of poor prognosis in ascites. In subsequent trials, we will use different drugs to treat SKOV3/DDP, and further study this resistance mechanism.

Yang et al[21] found that the MDR1 expression in the cervical cancer patients of the negative-group survival curves was higher than that in the positive group. In this study, high LRP and GSTP1 genes expression were associated with epithelial ovarian cancer survival rates. The gene expression of the negative group survival curve was higher than that of the positive group, suggesting that the expression of the resistance gene in patients with epithelial ovarian cancer is a high-risk prognostic factor. High expression of resistance genes is the main tumor cell resistance to chemotherapy. Reduced resistance gene expression was likely to reverse the drug resistance. Hou et al[22] found that the drug resistance of P-gp high expression in EOC drug-resistant strain is proportional. Curcumin can reduce P-gp biosynthesis and inhibit P-gp biological activity to enhance the cytotoxicity of drugs for tumor cell and reduce the drug resistance of tumor cells. Furthermore, Cao et al[23] demonstrated that after curcumin acts on the liver cancer cell-resistant drug, the LRP expression is reduced. Chemotherapy drugs increase the intracellular concentration and toxicity significantly, thereby reversing drug resistance. Therefore, reduced drug-resistant gene expression may reverse drug resistance.

In conclusion, the high expression of LRP and GSTP1 gens in patients with EOC were related to the platinum-resistant, short-term to relapse and poorly prognosis of EOC, and may be a molecular marker for predicting the drug resistance and prognosis of EOC patients.

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Investigation: Fengmei Yang, Wei Chen, Yong Liang.
Methodology: Bo Gao, Xiuxue Hu.
Resources: Yong Liang.
Software: Enfu Du, Xiuxue Hu.
Writing – original draft: Fengmei Yang, Xiaofeng Yang.
Writing – review & editing: Fengmei Yang, Bo Gao, Xiaofeng Yang.

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