mutant ovarian cancer to predict prognosis and efficiency of chemotherapy

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Running title
Two long non-coding RNAs to predict prognosis and efficiency of chemotherapy in BRCA Mutant ovarian cancer

Abstract

Background: Ovarian cancer (OV) is the most common type of primary female reproductive cancer. BRCA1/2 gene is an important biomarker for evaluating the risk of OV, breast cancer and other related tumors and influences patient choice of individualized treatment. A powerful signature to predict OV prognosis and improve treatment personalization is urgently needed.

This study aimed to identify a novel OV-related lncRNA prognostic biomarker.

Methods: A Univariate Cox proportional-hazards and multivariate Cox regression analyses were used to identifying prognostic factors from The Cancer Genome Atlas (TCGA) database.
The area under the curve (AUC) of the receiver operating characteristic (ROC) curve was assessed, and the sensitivity and specificity of the prediction model were determined.

**Results:** The signature consisting of two long noncoding RNAs (lncRNAs), Z98885.2 and AC011601.1, was selected as a criterion for classifying patients into high and low-risk groups (median survival: 7.2 years vs. 2.3 years). The 3-year overall survival (OS) rates for the high- and low-risk groups were approximately 38% and 100%, respectively. Chemotherapy treatment survival rates indicated that high-risk groups had significantly shorter OS rates with adjuvant chemotherapy than the low-risk groups. The OS of 1-, 3- and 5- years were 100%, 40%, and 15% in the high-risk groups respectively. The survival rate of the high-risk group declined rapidly after two years of OA chemotherapy treatment. In addition, multivariate Cox regression associated with other traditional clinical factors showed that the 2-lncRNA model could be used as an independent OV prognostic factor. Analyses of the Kyoto Encyclopedia of Genes and Genomes (KEGG) and Gene Ontology (GO) indicated that these signatures are pivotal to cancer development.

**Conclusion:** In conclusion, Z98885.2 and AC011601.1 comprise a novel prognostic signature for OV patients with in **BRCA1/2** mutations to predict prognosis and chemotherapy efficiency.

**Keywords**

ovarian cancer; long non-coding RNA; prognostic biomarker; mutations; **BRCA1/2** gene; chemotherapy; efficiency

**Introduction**
Ovarian cancer (OV) is one of the most severe gynecologic malignancies. Currently, OV is the fifth leading cause cancer and the second cause-related death to cervical cancer and uterine in malignancies worldwide [1]. Early symptoms are difficult to decipher correctly, and peritoneal metastasis often occurs before symptoms appear. As per reports, 60%–70% of patients are diagnosed at advanced stages. OV mortality rate has always been the highest among female reproductive tract malignancies [2]. According to statistics, the 5-year survival rate of stages I and II OV patients that have undergone surgery and chemotherapy can reach 80%–95%, whereas that for stages III and IV is only 20%–30% [3]. Therefore, early diagnosis and treatment are crucial to improving OV patients' quality of life and survival rate.

Breast cancer susceptibility genes, BRCA1/2, are critical tumor suppressor genes [4]. BRCA1/2 is a vital biomarker to evaluate the risk of OV and other related cancers, and also serves as a biomarker to personalize treatment for patients [5, 6]. Therefore, BRCA1/2 detection and screening of prognostic biomarkers for patients bearing BRCA mutations have important clinical significance in early diagnosis [7], drug development, and drug therapy guidance.

Long noncoding RNAs (lncRNAs) are a family of nonprotein-coding RNAs of 200–100,000 nucleotides[8] that regulate various genes during chromatin modification, transcription, or during post-transcriptional modifications. Additionally, lncRNAs are involved in various biological developmental pathways, regulating cell proliferation, invasion, and apoptosis [9]; events which are interlinked in tumor occurrence and development. Perez et al [10] has reported that lncRNA expression differs between OV and healthy tissues; however, the functional differences were not revealed. A separate study on 115 lncRNAs showed that in OV SKOV3 cells, estrogen could induce lncRNAs, regulating cell migration and invasion during estrogen
These studies indicate that lncRNA plays a vital role in the development of OV [11]. Emerging evidence suggests lncRNAs have the prognostic potential to act as multidimensional transcriptome. The aim of this study was to identify a novel lncRNA prognostic biomarker to potentially provide new and accurate biological indicators for early diagnosis and prognosis monitoring of ovarian cancer bearing BRCA1/2 mutation.

Materials and methods

Clinical cohorts and different types of molecular data

The Cancer Genome Atlas (TCGA; https://cancergenome.nih.gov/) was used to download the clinical cohorts and different types of molecular data, including 255 samples in the somatic mutation dataset and 379 samples in the mRNA expression and lncRNA expression dataset; clinical information was available for 375 patients. The technical route for selecting lncRNA signal signatures to predict prognostic outcomes is depicted in Figure 1.

Description of BRCA1/2 mutated dataset

The somatic mutation data in var scan format was downloaded. All genes harboring nonsynonymous or nonsense mutations were derived from within among these datasets. Infrequently mutated genes were excluded on the base of a 5% mutation frequency threshold, and data regarding mutated genes were curated into a binary matrix to identify 20 patients with BRCA1/2 mutations. GenVisR (http://bioconductor.org/packages/release/bioc/html/GenVisR.html) was used to visualize mutations graphically as a waterfall image.

Identification of the differentially expressed mRNAs and lncRNAs
Using the edgeR software to analyze 31 BRCA1/2 mutated patients vs. 224 non BRCA1/2 mutated patients, the differentially expressed mRNAs and lncRNAs were identified. Fold changes (log; absolute) ≥2, \( P < 0.05 \), FDR < 0.05 indicated statistical significance.

**Construction of a lncRNA signature in the BRCA1/2 mutated dataset**

The signature module was constructed as previously described [12-16]. The Univariate Cox regression analysis was used to assess the combination with survival time, and the constant expression degree of each lncRNA in the BRCA1/2 mutated data set. To filter out the most useful predictive prognostic lncRNAs, the Multivariate Cox regression analysis was subsequently performed to establish a model to evaluate the prognosis risk in accordance with the following equation:

\[
\text{Risk Score (RS)} = \sum_{i=1}^{N} E_{x_i} \times Coef_{i}
\]

Where, \( N \) is the representative number of lncRNAs in prognosis, \( E_{x_i} \) is the definition value of the lncRNAs, and \( Coef_{i} \) is a single factor of Cox regression coefficient. Risk Score (RS) is the multi-node weighted sum of risk scores.

**Statistical analysis**

LncRNAs were selected to established the risk model, and the BRCA1/2 mutation groups were divided into high- and low-risk groups using the median risk score and cut-off values. The effective prognostic potency and the chemotherapy treatment of the lncRNA signature was verified using Kaplan-Meier (KM) survival analysis and receiver operating characteristic (ROC) analysis. Multivariable Cox regression was performed to validate the signature during survival prediction. The RNAs package was used in the R program to map the Nomogram, including
grading and age, as they are typically included in the prognostic model for most BRCA1/2 mutant groups. Nomograms were described on the base of coefficients of the multivariate Cox regression model. All assessments were carried out using the R project (https://cloud.r-project.org/) (version 3.5.1) with pROC and survival packages downloaded from Bioconductor (https://bioconductor.org). For all analysis P<0.05 was considered significant.

Functional analysis of differentially expressed mRNAs

Gene Ontology (GO) analysis, comprising biological processes, molecular functions, and cellular component, was performed from Kyoto Encyclopedia of Genes and Genomes (KEGG). The functions associated with signatures of differentially expressed genes were predicted using the DAVID Bioinformatics Tool (https://david.ncifcrf.gov/, version 6.8).

Results

Patient characteristics

Herein, total of 375 patients were clinically and pathologically diagnosed with OV. In accordance with the International Federation of Gynecology and Obstetrics (FIGO) classification catalogue [17-19], grading of endometrioid carcinomas was identical to that of uterine endometrioid carcinomas and was of prognostic and therapeutic significance. In total, 6, 68, and 301 patients were at grades 1, 2, and 3, respectively. Clinical data of all patients is shown in Table 1. The flowchart for the analysis of selected lncRNA and mRNA signatures is shown in Figure 1.

Differentially expressed mRNAs and lncRNAs
A total of 20 BRCA1 mutated patients and 11 BRCA2 mutated patients were identified from 255 samples in somatic mutation data. A total of 19,495 mRNAs and 14,589 lncRNAs were identified from the 31 BRCA1/2 mutated patients (Table S1). Using fold |changes| ≥ 2 and $P<0.05$ as cutoffs, we identified 325 differentially expressed mRNAs (149 downregulated and 176 upregulated) and 117 differentially expressed lncRNAs (24 downregulated and 93 upregulated), as shown in the heatmap (Figure 2). The distribution of differentially expressed mRNAs and lncRNAs is indicated in the volcano plot map (Figure S1).

Construction of the prognostic BRCA1/2 lncRNA signature

Univariate Cox hazards regression analysis was performed on the base of differentially expressed lncRNA expression profiling data, considering the overall status and survival time as the dependent variables. Four lncRNAs were markedly associated with recurrence ($P < 0.05$, Table S2). To select the most effective diagnostic lncRNAs, we then performed multivariate Cox regression analysis (Figure 3) and constructed a 2-lncRNA model to estimate the survival risk. The risk score (Table S3) of the combination, comprising Z98885.2 and AC011601.1, was determined as follows:

$$RS = (-0.36 \times ev_{Z98885.2}) + (0.032 \times ev_{AC011601.1})$$

where RS is the risk score, and ev is the expression value.

Determining the survival power and adjuvant chemotherapy of the lncRNA gene signature in the dataset

LncRNA markers were selected, and risk scores were allocated for each OV patient. OV
patients were segregated into two groups according to the risk score: low-risk (n=9) and high-risk (n=9) groups. KM survival model analysis revealed that OS was remarkably higher in the low-risk group than in the high-risk group (median survival: 7.2 years vs. 2.3 years (Figure 4A, left)). The 3-year OS of high-risk patients was almost 38% relative to that of the low-risk patients, approaching 100%.

To further understand whether the risk signature could promote or reduce chemotherapy efficacy, the KM survival model analysis was conducted between the low-risk (n=5) and high-risk (n=9) groups (Figure 5). The results showed that the high-risk groups had significantly shorter OS with adjuvant chemotherapy compared to the low-groups. The overall 1-, 3- and 5-years survival rates were 100%, 40% and 15% in the high-risk groups respectively; however, the low-risk groups had the same 80% survival rate.

Based on the ROC analysis to confirm the prognostic potential of lncRNA markers, a greater area under the ROC curve denotes a greater the survival of patients harboring \( BRCA1/2 \) mutations. The dataset supports the premise that the predictive function of the 2-lncRNA signature was high (AUC Signature=0.952, Figure 4B). These results suggest this the signature as a novel, highly-accurate survival biomarker.

**Functional enrichment analysis**

KEGG and GO analyses were used to investigate the different mRNAs’ potential involvement in biological processes associated with \( BRCA1/2 \) mutated patients (Figure 6, Table S4). Results revealed mRNAs associated with DNA binding, cholinergic neurotransmission, lipid transport and so on. Additionally, mRNAs that participate in MAPK/RAS and PI3K-Akt
signaling pathways were identified, which are critical in tumor development.

Nomogram development

The aforementioned independence signatures, including tumor stage, age, each represented a point. Each point in the nomogram graph is indicated on the top scale (Figure 7). The corresponding of 1-, 2-, and 3-year survival rates were determined in accordance with the scale provided, and the predicted risk values of 1-, 2-, and 3-year survival rates were predicted. The total score was determined by adding these values. The respective point was determined to match the 1-, 2- and 3- survival rates on the base of the scale provided, predicting patients’ 1-, 2-, and 3-year survival rates of the risk prediction value, finally adding up to a total point. The C-index in the nomogram was 0.952 to predict the survival rate for the nomogram of OS patients.

Discussion

OV is one of the most common malignancies in the female reproductive system, which poses a serious threat to women’s health and their survival. It is associated with the highest mortality rate because the clinical symptoms of early OV are not evident, and in most cases, cancer has already advanced to late stages when diagnosed. Therefore, there is an urgent need to develop new targets for the treatment of OV [3, 20].

In this study, we used different statistical tests to assess the risk signature of two IncRNAs and found that this risk signature was an independent factor able to predict BRCA1/2 mutations in OV patients. A multivariate Cox regression model was applied to evaluate the independence
of signatures to predict the prognostic potential of OV patients with either BRCA1/2 mutations.

Age and tumor grade were considered covariables in accordance with the risk scores of OV patients and were found to be independently associated with recurrence. Thus, we selected two lncRNAs, Z98885.2 and AC011601.1 as a risk signature.

An increasing number of studies have suggested that lncRNAs play important roles in the pathophysiology of OV among several diseases and participate in various biological events and are known to regulate tumorigenic processes. To accurately predict the clinical outcome or chemotherapy resistance of OV patients and improve their long-term survival, the development of novel biomarkers for early OV detection by molecular testing holds the utmost priority [21].

Xu Meng et al [22] revealed and confirmed a progressive transcription signature to predict the prognostic potential in OV associated with protein-coding genes, lncRNAs, and miRNAs. Some lncRNAs were downregulated in OV cells and significantly associated with histological grading, FIGO staging, and lymph node metastasis, such as GAS5, rp11-190d6.2, and nbat-1.

As between Because 5%–10% of OV is hereditary, the above observations are based on germline mutation, with only a few studies having evaluated somatic mutant genes [23].

Collectively, our results suggest that the two lncRNAs, Z98885.2 and AC011601.1, may serve as biomarkers to predict the survival of patients with OV. To date, the functions of Z98885.2 and AC011601.1 are relatively unknown. A previous study [24] reported the use of a tiling-path chromosome for the identification of limited regions of genetic aberration in patients affected with Wilm’s tumor. Four cases presenting presented partial deletion or gain on chromosome 22 and Z98885–AC000036 was located on a telomeric gain on chromosome 22 array-CGH profile. However, the study provided minimal information on the above two
lncRNAs. In contract, in this study, we provide comprehensive insights into the function of these lncRNAs.

*BRCA1/2* are major players of the machinery that repair DNA double-strand breaks (DSBs) via homologous recombination (HR). Loss of *BRCA1/2* renders the cells HR-deficient, thus requiring alternative error-prone repair pathways to fix DSB, resulting in chromosome deletions, translocations, and subsequent cell death. Women with *BRCA1/2* gene germline mutations are under 39% and 11% higher lifetime risk of OV, respectively [25]. Currently, PARPi, a potent drug for cancer caused by *BRCA* mutation leading to *BRCA* pathway defect, gathered the attention of pharmaceutical industries. PARPi leads to unmodified single-chain rupture (SSB) by inhibiting PARP activity and induces DSB, while *BRCA* cascaded cells are unable to repair DSB through HR, resulting in cell death. PARPi also increases cell death by phosphorylating DNA-dependent proteases in non-homologous terminal junction pathways. PARPi has limited off-target side effects as it only targets tumor cells that simultaneously have *BRCA1/2* mutations, causing cell death [26]. Cells carrying *BRCA* mutations are up to 1,000 times more sensitive to PARPi than wild-type cells [27]. Moreover, Olaparib was identified in stage I and II clinical trials as a single-agent to treat OV with *BRCA* mutations [28]. However, predicting the prognosis of OV patients with *BRCA1/2* mutations remains a challenge. Signatures that serve not only as biomarkers in the occurrence and development of OV, but also as therapeutic agents are urgently needed [29].

To confirm the signature can serve as a prognostic biomarker in OV patients, we calculated the risk score of the selected signature of OV for each patient. The median risk score separated the low-risk and high-risk group. Our results showed that the high-risk group had significantly
higher disease progression rates than those for the low-risk group in BRCA1/2 mutation. From TCGA databases, the survival rate of the high-risk group declined rapidly after two years of OA chemotherapy treatment. Whereas, an 80% survival rate for five years was seen in the low-risk groups. These results indicated that chemotherapy resistance may develop in the high-risk groups. The low-risk groups were sensitive to the platinum-based chemotherapy treatment. Hence, the prognostic potential of lncRNA for OV patients harboring BRCA1/2 mutations was considered an independent signature apart from miscellaneous clinical factors.

For further evaluation of the differences between BRCA1/2 mutations, we performed the difference gene of 117 and 325 differentially mRNAs and lncRNAs from 19 BRCA1/2 mutation and non-different expression screen. GO and KEGG analyses indicated that these genes are involved in the MAPK/RAS and PI3K-Akt signaling pathways. MAPK and PI3K-Akt are responsible for sustained proliferative signaling, while RAS participates in the inflammatory response. Each of these pathways is closely associated with the tumorigenesis and tumor progression.

The nomogram model is considered an evidence-based, accurate treatment and prognosis assessment method, which has been widely used in studies on a variety of malignant tumors [30, 31]. The progressive potential of the clinical model was assessed using C-index by multivariate Cox regression analysis with matched OV patients [32]. Herein, the nomogram prediction model was successfully constructed on the base of independent risk factors determined through survival analyses. By incorporating independent risk factors into nomogram modeling to predict the survival rate, a C-index of 0.952 was achieved, indicating the excellent predictive ability of this method. The model can individually predict the survival
rate of patients and is helpful for clinical treatment decision-making and design of clinical research programs.

Furthermore, some limitations of this study should be acknowledged. First, we investigated only a fraction of the lncRNA expression dataset. Our data are not enough to validate the independent lncRNA signature for survival prediction to form a test group. Therefore, the prognostic lncRNAs defined here may be accompanied by other, yet unidentified, lncRNA candidates. Second, we only provided a limited mechanistic explanation of the roles played by the two lncRNAs in OV. Further experimental studies on the lncRNAs are needed to deepen our understanding of their functional mechanisms. Notwithstanding these limitations, the robust and consistent correlation observed in this study between 2 lncRNA biomarkers with overall survival indicates that it is a dominant independent signature for OV.

Conclusion

In conclusion, this study shows that the two lncRNAs signature has potential clinical application value for the early diagnosis and prognosis monitoring of ovarian cancer. Future studies evaluating the carcinogenic mechanisms involved in ovarian cancer will provide the theoretical basis for the development of successful targeted therapy.

Ethical approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.
Consent for publication

All of the authors have agreed to publish this article in your journal if it should be accepted

Availability of data and materials

The dataset supporting the conclusions of this article is included within the article

Competing for interests

The authors declare that they have no competing interests.

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Authors’ contributions:

The authors contributed in the following ways: Yinglian Pan: data collection, data analysis, LiPing Jia, Yuzhu Liu: study design, study supervision; Qian Li, Qin Zhou, Zhongpei Zhang: data collection, final approval of the manuscript; Jin Huang, Qingchun Deng: drafting, technical support and critical revision of the manuscript. All the authors read and approved the final manuscript.

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Figure legend

Figure 1
Study protocol. The order of analyses to develop the risk score model and validate the efficiency of the signature to predict prognostic outcomes.

Figure 2
The waterfall image of partial mutations in OV. GenVisR was used to visualize mutations graphically, using the waterfall image.

Figure 3
Identities of IncRNAs in the prognostic signature and their univariable cox association with prognosis.

Figure 4
The IncRNA signature predicts the overall survival of patients with OC. (A). Kaplan-Meier survival curves classified patients into high- and low-risk groups on the base of their IncRNA signatures in the sample datasets. P-values were determined through the log-rank test. (B). Results of receiver operating characteristic (ROC) analysis.

Figure 5
The IncRNA signature predicts the overall survival of chemotherapy treatment.
Figure 6  
**KEGG and GO analyses.** KEGG and GO analyses were performed to investigate the potential involvement of different mRNAs in biological processes occurring in patients harboring BRAC1 and BRAC2 mutations.

Figure 7  
**Multivariable Cox regression analysis and Nomogram to predict 3-year OS for OV patients.** Multivariable Cox regression analysis was performed to assess the independence of the signature in survival prediction, and P value < 0.05 was considered significant. The nomogram was plotted using the rms package in R, including information such as age and stage in the nomogram, as they are usually included in most prognostic models of BRAC1 and BRAC2 muted groups.

Figure S1  
**Volcano plot of mRNAs and IncRNAs.** Differentially expressed mRNAs and IncRNAs, Fold changes (log2 absolute) ≥ 2, P<0.05 and FDR<0.05 indicated a statistically significant difference.

Table 1  **Summary of patient demographics and characteristics**

Table S1  
Differentially expressed mRNAs and IncRNAs

Table S2  
Univariate Cox proportional hazards regression analysis (P <0.05) of the differentially expressed IncRNAs profiling data in the dataset

Table S3  
The signature risk score composed of 2 IncRNAs combinations in the dataset
Table S4

Functional enrichment analysis of different mRNAs