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Downregulated Long Noncoding RNA DGCR5 Acts as a New Promising Biomarker for the Diagnosis and Prognosis of Ovarian Cancer

Hongxiao Chen, MM[1], Xiufang Tian, MM[1], Yajing Luan, MM[2], and Hui Lu, MM[1]

Abstract

Emerging evidence have indicated that dysregulated long noncoding ribonucleic acids act as a novel diagnostic and therapeutic target in the progression of ovarian cancer. Long noncoding RNA DiGeorge syndrome critical region gene 5 has been reported to participate in some types of human cancer progresses, but its clinical roles in ovarian cancer had been rarely reported. This study aimed to explore the expression, clinicopathological features, diagnostic, and prognostic values of DiGeorge syndrome critical region gene 5 in ovarian cancer. The total levels of DiGeorge syndrome critical region gene 5 transcript variant 1 (NR_002733.2) and 2 (NR_045121.1) in patients with ovarian cancer were determined by quantitative reverse transcription polymerase chain reaction. The correlation of DiGeorge syndrome critical region gene 5 expression with clinicopathological factors was statistically analyzed by χ^2 test. Overall survival analysis was carried out with the Kaplan–Meier curves with the log-rank test. Univariate and multivariate Cox regression analyses were performed to identify the prognostic significance of DiGeorge syndrome critical region gene 5 expression. Receiver operating characteristic curves were constructed to estimate the diagnostic and prognostic usefulness of DiGeorge syndrome critical region gene 5 in ovarian cancer. Results showed that relative DiGeorge syndrome critical region gene 5 expression was reduced by 36.81% and 65.79% in ovarian cancer tissues of patients and Gene Expression Omnibus DataSets (GSE119056) in contrast to normal tissues, respectively. Patients with lymph node metastasis and distant metastasis exhibited lower levels of DiGeorge syndrome critical region gene 5 in contrast to those patients with non-lymph node metastasis and non-distant metastasis, respectively. Low expression of DiGeorge syndrome critical region gene 5 was significantly associated with large tumor size, more lymph node metastasis, present distant metastasis, advanced clinical stage, and short overall survival in patients with ovarian cancer. Low expression of DiGeorge syndrome critical region gene 5 was an independent unfavorable prognostic factor for overall survival in patients with ovarian cancer. Receiver operating characteristics curves for prognosis yielded significant area under curves for lymph node metastasis, clinical stage, and overall survival. In conclusion, our study demonstrated that downregulated DiGeorge syndrome critical region gene 5 may be a new promising biomarker for predicting clinical progression and prognosis in patients with ovarian cancer.

Keywords

OC, DGCR5, biomarker, expression, overall survival

Abbreviations

AUC, area under curve; CI, confidence interval; DGCR5, DiGeorge syndrome critical region gene 5; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; lncRNAs, long noncoding ribonucleic acids; miRNA, microRNA; OC, ovarian cancer; qRT-PCR, quantitative reverse transcription–polymerase chain reaction; ROC, receiver operating characteristic.

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[1] Department of Gynaecology and Obstetrics, Tianjin Fifth Central Hospital, Tianjin, China
[2] Teaching Center, School of Basic Medical Sciences, Tianjin Medical University, Tianjin, China

Corresponding Author:
Hui Lu, Department of Gynaecology and Obstetrics, Tianjin Fifth Central Hospital, No. 41 Zhejiang Road, Tanggu Street, Binhai New Area, Tianjin 300450, China.
Email: goodlucktjwzx@aliyun.com

Introduction

Ovarian cancer (OC) is acknowledged as the sixth most common malignant gynecological tumor around the world.[1] According to the Cancer statistics in China, a significantly increasing incidence trend of OC is observed, which leads to a serious threat to female health.[2] With the development of surgery, chemotherapy, immunotherapy, as well as radiotherapy, patients with OC at stage I and II have a favorable prognosis.[3,4] However, because of the lack of explicit early diagnostic symptoms, the overall 5-year overall survival rate for patients with OC at stages III and IV is less than 30%.[5] Unlike lung and breast cancer, the effective molecular targets for diagnosis and prognosis have yet to be identified in OC.[6] Simultaneously, the unclear pathophysiologic mechanisms have limited its clinical treatment options for patients with OC with an advanced or recurrent stage. Therefore, it is urgently needed to identify sensitive, noninvasive biomarkers to improve early detection and to guide therapy for OC treatment.

Long noncoding RNA (lncRNAs) are evolutionarily conserved non-protein coding RNAs that are longer than 200 nucleotides in length and can regulate gene expression at transcription or post-transcription level.[7] According to chromosome region to the nearby coding genes, lncRNAs can be classified into 5 types, including sense, antisense, bidirectional, intronic, and intergenic lncRNAs.[7,8] Although not translated to proteins, lncRNAs act critical roles in regulating cellular and physiologic processes, such as viability, differentiation, apoptosis, invasion, and metastasis.[8,9] Recent studies have demonstrated that lncRNAs are differentially expressed in tumor cells and are involved in tumor initiation and development via endogenous-sponging microRNAs (miRNAs) or direct-binding miRNAs.[10,11] In addition, lncRNAs may be used as diagnostic and/or prognostic biomarkers in various types of human cancers.[12] For instance, Li *et al*[13] found that lncRNA downregulated in liver cancer stem cells acts as a potentially useful biomarker for the diagnosis and prognosis of colorectal cancer. Zhang *et al*[14] reported that lncRNA differentiation antagonizing non-protein coding RNA is associated with aggressive clinical features and may serve as a diagnostic biomarker for detecting papillary thyroid cancer. Wang *et al*[15] demonstrated that lncRNA MIR210 host gene (MIR210HG) predicts poor prognosis and functions as an oncogenic gene in hepatocellular carcinoma.

Previous studies have reported that the total levels of lncRNA DiGeorge syndrome critical region gene 5 (DGCR5) transcript variant 1 (NR_002733.2) and 2 (NR_045121.1) expression are downregulated in cancer tissues, and DGCR5 acts as a tumor suppressor in papillary thyroid carcinoma, cervical cancer, and gastric cancer.[16-18] However, the clinical roles of DGCR5 in OC remain unknown. This study aimed to explore the expression, clinicopathological features, diagnostic, and prognostic values of DGCR5 in OC. Our data showed that the relative DGCR5 (transcript variant 1 and 2) expression was downregulated in OC tissues and was associated with large tumor size, more lymph node metastasis, present distant metastasis, advanced clinical stage, and short overall survival in patients with OC. Based on these findings, DGCR5 may be a promising novel biomarker for screening and predicting the diagnosis and prognosis of patients with OC.

Table 1. The Association Between lncRNA DGCR5 Expression and Clinicopathological Characteristics in Patients With Ovarian Cancer.

Parameters	No. of Cases (n)	DGCR5 Expression		*P* value
		Low	High	
Age (years)				.135
<55	38	16	22	
≥55	28	17	11	
Histological subtype				.786
Mucinous	47	23	24	
Serous	19	10	9	
Tumor size (cm^3)				.022
<10	16	4	12	
≥10	50	29	21	
Tumor location				.757
Unilateral	53	27	26	
Bilateral	13	6	7	
Differentiation				.284
Well and moderate	20	8	12	
Poor	46	25	21	
Clinical stage				.007
I/II	35	12	23	
III/IV	31	21	10	
Lymph node metastasis				<.001
No	30	6	24	
Yes	36	27	9	
Distant metastasis				.008
Absent	51	21	30	
Present	15	12	3	
Recurrence				.453
No	27	12	15	
Yes	39	21	18	

Materials and Methods

Patients and Specimens

The purpose of the study was explained to all patients and written informed consent was obtained prior to enrolment. The research was approved by the Institutional Ethics Committee at Tianjin Fifth Central Hospital (no. 2017542160). From January 2011 to December 2017, a total of 66 patients with OC who underwent surgical treatment at Tianjin Fifth Central Hospital were recruited for this study. None of the patients received chemotherapy or radiotherapy before the collection of the specimens. The OC tissues and paired adjacent normal tissues (≥3 cm away from tumor) were collected and were immediately snap-frozen in liquid nitrogen and stored at −80°C prior to RNA isolation. All tissues were confirmed diagnosis based on hematoxylin–eosin and immunohistochemical staining by 2 pathologists. Related clinical data were retrieved from the medical records of each patient and were listed in Table 1. The

median age of study participants was 49.4 ± 6.72 years and ranged from 29 to 73 years. Based on International Federation of Gynecology and Obstetrics and World Health Organization standards,[19] the 66 patients with OC were 35 cases in early stage (stages I and II) and 31 cases in late stage (stages III and IV).

RNA Extraction

Tissue RNA was extracted from tissues (1 mm^3 size) or cells (10^6) using TRIzol reagents (Invitrogen, Carlsbad, California), following the manufacturer's instructions. 10 U DNase (Takara, Beijing, China) was used to hydrolyze residuary DNA in each RNA sample for 30 minutes at 37°C. The concentration of the extracted RNA was measured by using NanoDrop 2000c Spectrophotometer (Thermo Fisher Scientific, Waltham, Massachusetts). The extracted RNA was determined to be used only when the A260/A280 ratio is 1.8 to 2.1. In addition, 1.5% agarose gel electrophoresis was used to assess the quality and integrity of RNA. After that, the RNA was stored at −80°C for further experiments.

Quantitative Reverse Transcription Polymerase Chain Reaction

Total RNA (1 μg) was reverse transcribed into complementary DNA using random primers under standard protocols for the PrimeScript RT reagent Kit (TaKaRa). Quantitative reverse transcription–polymerase chain reaction (qRT-PCR) reaction was performed to amplify DGCR5 transcript variant 1 (NR_002733.2) and 2 (NR_045121.1) with the GoTaq qPCR Master Mix (Promega, Madison, Wisconsin) on the ABI Prism 7300 Sequence Detection System (Applied Biosystems, Foster City, California) under the following PCR conditions: an initial cycle at 95°C for 20 minutes, 1 cycle at 95°C for 10 seconds, followed by 40 cycles of 98°C for 30 seconds, 55°C for 30 seconds, and 72°C for 30 seconds. The primers for DGCR5 and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) were as follows: DGCR5 forward primer: 5′-CCAAGCCT GTCTGTGTGTTC-3′, reverse primer: 5′-GGGAGACACAG ACCACAAGA-3′; GAPDH forward primer: 5′-ACCCAC TCCTCCACCTTTGAC-3′, reverse primer: 5′-TGTTGCTGT AGCCAAATTCGTT-3′. The relative expression of DGCR5 was normalized to the endogenous gene GAPDH. We used the Schmittgen TD and Livak KJ' equation to calculate the relative expression of DGCR5: $2^{-\Delta\Delta Ct}$ = [(Ct gene of interest − Ct internal control) sample A − (Ct gene of interest − Ct internal control) sample B].[20] Experiments were repeated in triplicates.

Statistical Analysis

The statistical analysis in this study was performed using Statistical Program for Social Sciences (SPSS) software, version 19.0 (SPSS, Chicago, Illinois). Each experiment was performed in triplicate. GraphPad Prism 5.0 (GraphPad Software, San Diego, California) software was used to draw graphs. Comparisons between 2 independent groups were analyzed using 2-tailed Student *t* test. The χ^2 test was applied to determine the association between the DGCR5 expression and the clinicopathological features of patients with OC. Overall survival defined as the time between the initial diagnosis and death or the last follow-up was compared to show any significant associations between DGCR5 expression and the overall survival of the patients with OC according to Kaplan–Meier method and log-rank test. Univariate and multivariate Cox regression analyses were performed to determine the prognostic parameters in predicting overall survival. Receiver operating characteristic (ROC) curves were constructed to estimate the diagnostic and prognostic usefulness of DGCR5 in OC. Receiver operating characteristic curves were produced according to the 2-category method, the true positive rate (sensitivity) was plotted on the ordinate, and the false-positive rate (1-specificity) was plotted on the abscissa. A 2-tailed *P* value <.05 was considered to indicate statistically significant.

Results

The Expression Pattern of DGCR5 in Patients With OC

To determine DGCR5 (transcript variant 1 and 2) expression levels in OC, 66 pairs of human OC tissues and adjacent normal tissues were conducted to qRT-PCR analysis. As shown in Figure 1A, DGCR5 expression was decreased by 36.81% in OC tissues compared with adjacent normal tissues ($P < .001$). Meanwhile, we also calculated the expression of DGCR5 (transcript variant 1 and 2) in the Gene Expression Omnibus (GEO) DataSets (GSE119056)[21] and found that DGCR5 expression was reduced by 65.79% in OC tissues compared with adjacent normal tissues (Figure 1B, $P < .001$). Furthermore, we showed that patients with OC with lymph node metastasis exhibited lower levels of DGCR5 expression by 12.31% in contrast to patients with non-lymph node metastasis (Figure 1C, $P = .031$). The expression levels of DGCR5 in patients with distant metastasis were downregulated by 19.95% than those patients with non-distant metastasis (Figure 1D, $P = .003$). All these data hinted that decreased DGCR5 is associated with the progression of OC.

Decreased DGCR5 Expression in Relation to Clinicopathological Features of Patients With OC

To further identify the clinicopathological relationship of DGCR5 expression in patients with OC, DGCR5 expression levels in 66 OC tissues were divided into high (n = 33) or low (n = 33) expression subgroup based on the median value (Figure 2A). We evaluated the association between DGCR5 expression and clinicopathological characteristics of patients with OC by using χ^2 test. As summarized in Table 1, we found that the low expression of DGCR5 was obviously associated with large tumor size ($P = .022$), more lymph node metastasis ($P < .001$), present distant metastasis ($P = .008$), and advanced clinical stage ($P = .007$). However, there was no significant association of the DGCR5 expression levels between the

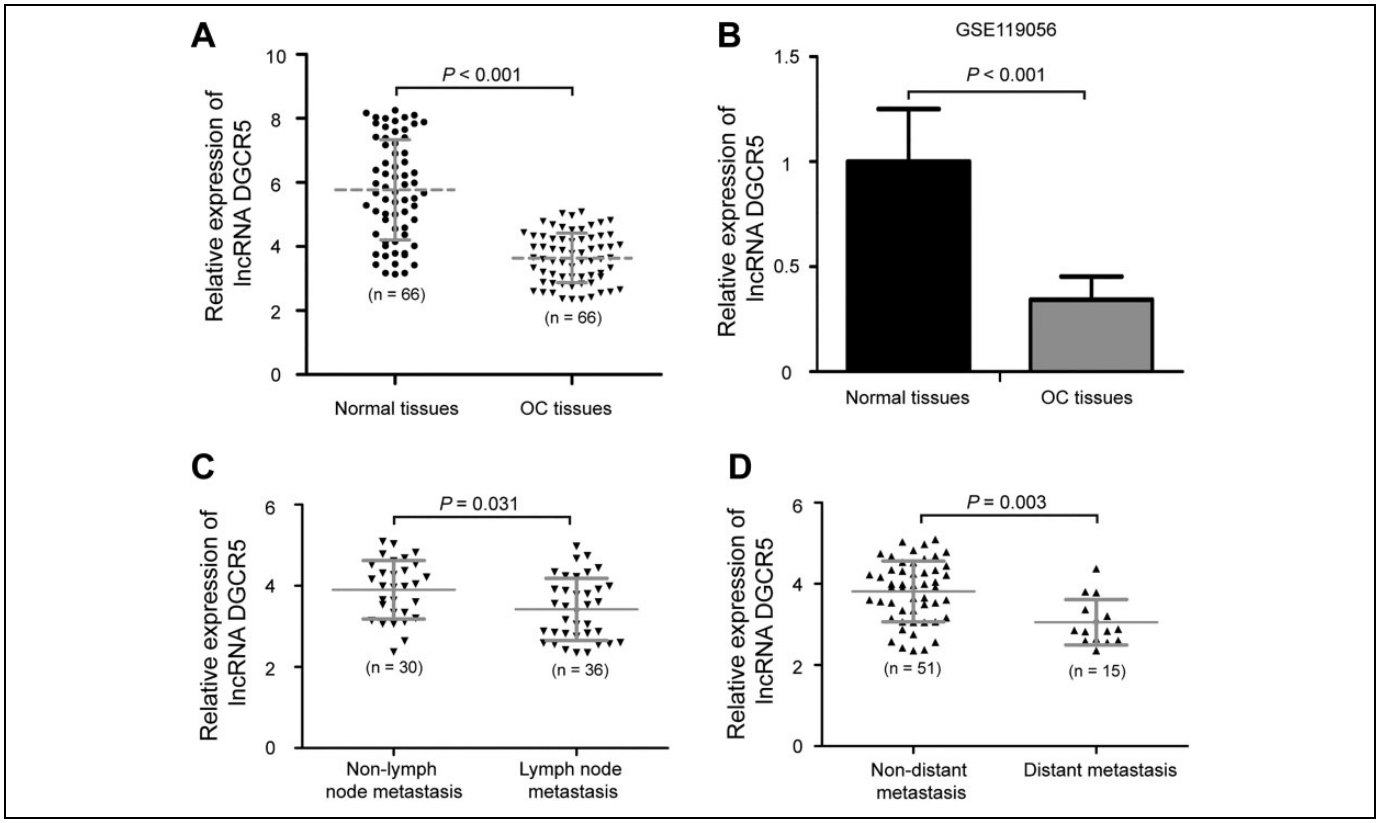

Figure 1. Long noncoding RNA (lncRNA) DGCR5 expression in patients with ovarian cancer (OC). A, Quantitative reverse transcription–polymerase chain reaction was applied to detect DGCR5 expression levels. Glyceraldehyde-3-phosphate dehydrogenase was an endogenous gene. The DGCR5 expression levels were downregulated in OC tissues (n = 66) compared with the adjacent non-tumorous tissues (n = 66). B, The levels of DGCR5 in OC tissues and adjacent normal tissues from GSE119056 DataSets. C, The patients with lymph node metastasis had a lower levels of DGCR5 expression than patients with non-lymph node metastasis. D, The patients with distant metastasis had a lower expression of DGCR5 in contrast to those patients with non-distant metastasis. DGCR5 indicates DiGeorge syndrome critical region gene 5.

2 subgroups in other clinical features including age, histological subtype, tumor location, differentiation, and recurrence. These data implied that DGCR5 is closely associated with the growth and metastasis during the carcinogenesis of OC.

Overall Survival Analysis and Prognostic Values of DGCR5 in Patients With OC

Then, we explored the prognostic values of DGCR5 in patients with OC. The survival analysis through the Kaplan–Meier method and log-rank test revealed that patients with low DGCR5 expression was correlated with a shorter overall survival than those patients with high DGCR5 level (Figure 2B, $P = .015$), suggesting that the low expression of DGCR5 predicted a poor prognosis in patients with OC. Moreover, the univariate and multivariate Cox regression analyses were used for assessing whether DGCR5 expression could be identified as a prognostic predictor for overall survival in patients with OC. As shown in Table 2, lymph node metastasis ($P = .002$), distant metastasis ($P = .037$), clinical stage ($P < .001$), and DGCR5 expression ($P = .015$) were suggested by univariate Cox regression analysis to be potential risk factors for overall survival in patients with OC. In addition, multivariate Cox regression analysis confirmed that low DGCR5 expression was an independent predictor for unfavorable prognosis in patients with OC (Table 3, $P = .047$).

ROC Curves Analysis of Diagnostic and Prognostic Usefulness of DGCR5 in OC

Finally, ROC curves were used to investigate characteristics of the DGCR5 as potential diagnostic markers of OC from all subjects, including 66 OC tissues and 66 adjacent normal tissues. The results showed a strong separation between the OC tissues and adjacent normal tissues, with an area under curve (AUC) of 0.876 (95% confidence interval [CI]: 0.817-0.934), sensitivity was 74.81%, and specificity was 83.26% (Figure 3A, $P < .001$). Interesting, ROC curve for the expression of DGCR5 and lymph node metastasis revealed a significant AUC of 0.819 (95% CI: 0.719-0.920) with a sensitivity of 64.30% and specificity of 75.45% (Figure 3B, $P < .001$). Receiver operating characteristic curve for DGCR5 expression and clinical stage yielded an AUC of 0.757 (95% CI: 0.637-0.876) with a sensitivity and specificity of 60.14% and 73.22%, respectively (Figure 3C, $P < .001$). Moreover, DGCR5 expression could discriminate poor overall survival patients from good

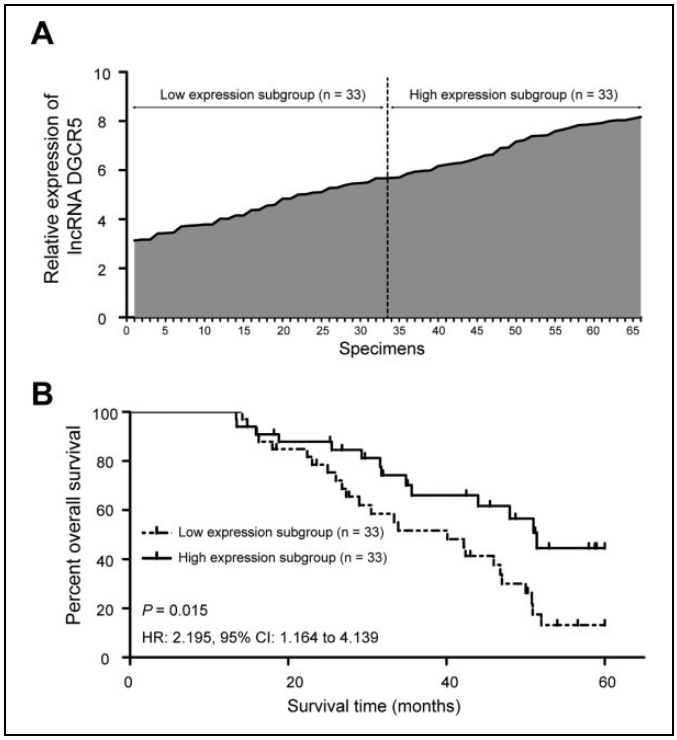

Figure 2. Kaplan–Meier curves analysis of the association between DGCR5 expression and overall survival in 66 patients with OC. A, DGCR5 expression levels in 66 OC tissues were divided into high (n = 33) or low (n = 33) expression subgroup based on the median value. B, Overall survival rate in patients with low DGCR5 expression was significantly shorter than that in those patients with high DGCR5 expression. DGCR5 indicates DiGeorge syndrome critical region gene 5.

Table 2. Univariate Cox Regression Analysis of Prognostic Parameters Patients With Ovarian Cancer.

	Univariate	
Parameters	HR (95% CI)	*P* value
Age (<55 vs ≥55 years)	0.612 (0.447-1.260)	.751
Histological subtype (mucinous vs serous)	1.343 (0.864-1.952)	.367
Tumor size (<10 vs ≥10 cm^3)	0.817 (0.504-1.329)	.932
Tumor location (unilateral vs bilateral)	1.657 (0.912-2.350)	.086
Differentiation (well and moderate vs poor)	0.949 (0.675-1.536)	.534
Clinical stage (I/II vs III/IV)	2.476 (1.385-4.934)	<.001
Lymph node metastasis (no vs yes)	2.382 (1.341-4.805)	.002
Distant metastasis (absent vs present)	1.940 (1.055-3.428)	.037
Recurrence (no vs yes)	0.867 (0.533-1.416)	.443
DGCR5 expression (low vs high)	2.195 (1.164-4.139)	.015

Abbreviations: CI, confidence interval; DGCR5, DiGeorge syndrome critical region gene 5; HR, hazard ratio.

overall survival patients with AUC of 0.692 (95% CI: 0.565-0.818), sensitivity was 58.39%, and specificity was 70.80% (Figure 3D, $P < .05$). Therefore, DGCR5 may provide a promising diagnostic and prognostic values for the detection of OC.

Table 3. Multivariate Cox Regression Analysis of Prognostic Parameters Patients With Ovarian Cancer.

	Multivariate	
Parameters	HR (95% CI)	*P* value
Age (<55 vs ≥55 years)	0.554 (0.391-1.074)	.621
Histological subtype (mucinous vs serous)	0.912 (0.734-1.482)	.210
Tumor size (<10 vs ≥10 cm^3)	0.690 (0.564-1.123)	.425
Tumor location (unilateral vs bilateral)	1.216 (0.833-1.902)	.167
Differentiation (well and moderate vs poor)	0.450 (0.317-0.894)	.905
Clinical stage (I/II vs III/IV)	1.377 (0.915-2.430)	.083
Lymph node metastasis (no vs yes)	1.006 (0.786-1.658)	.542
Distant metastasis (absent vs present)	1.480 (0.942-2.136)	.135
Recurrence (no vs yes)	0.714 (0.528-1.227)	.369
DGCR5 expression (low vs high)	2.113 (1.082-2.895)	.047

Abbreviations: CI, confidence interval; DGCR5, DiGeorge syndrome critical region gene 5; HR, hazard ratio.

Discussion

Ovarian cancer, as a lethal gynecological malignancy, has become the leading cause of cancer-related deaths among women worldwide.[22] An increasing number of discoveries have reported that lncRNAs can be served as promising prognostic and therapeutic targets in the progression of OC.[23,24] For example, downregulated lncRNA cancer susceptibility candidate 2 and growth arrest-specific 5 confirm to be used as a promising prognostic biomarkers and therapeutic targets in OC.[25,26] LncRNA TP73 antisense RNA 1 facilitates the growth of OC cells and is an effective therapeutic target in patients with OC.[27] LncRNA metastasis-associated lung adenocarcinoma transcript 1 is a new therapeutic target of human OC via regulating cell migration and invasion governing hallmarks of metastasis.[28] Thus, discovering more lncRNAs associated with the diagnosis and prognosis of OC is essential. LncRNA DGCR5, also known as Linc00037, is located at human chromosome 22q11.21 with a length of 60745 bp, which is originally found in Huntington's disease neurodegeneration.[29] However, the roles of DGCR5 in the clinicopathology and prognosis in OC have not been reported. Our data suggested that downregulated DGCR5 may be a new promising biomarker for predicting clinical progression and prognosis in patients with OC.

In a recent study, DGCR5 has been shown to be a participator in liver cancer and can serve as a potential biomarker for the diagnosis and prognosis.[30] The results of our study indicated that DGCR5 was significantly downregulated in OC tissues compared with that in adjacent non-tumor tissues, which was consistent with the previous GEO DataSets (GSE119056).[21] In addition, patients with OC with lymph node metastasis and distant metastasis exhibited lower levels of DGCR5 expression. DiGeorge syndrome critical region gene 5 expression has a high sensitivity and specificity for discriminating OC tissues from adjacent normal tissues. More

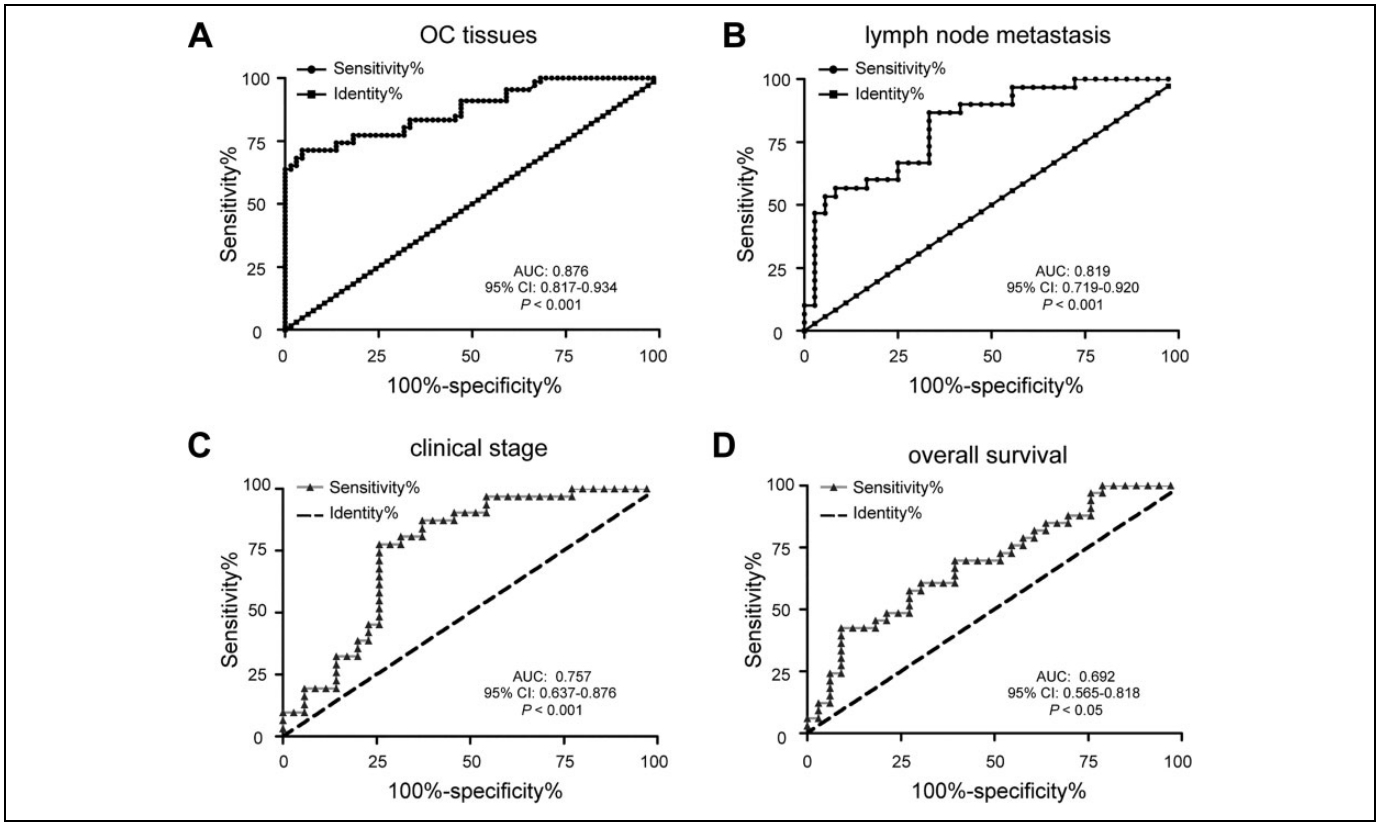

Figure 3. Receiver operating characteristic (ROC) curves and area under curve analysis of DGCR5 expression for discriminating OC tissue from adjacent normal tissues and for differentiating clinicopathological features. A, The diagnostic specificity and sensitivity of DGCR5 expression in OC tissues and adjacent normal tissues. B, The ROC analysis for detection of patients with ovarian cancer (OC) with positive lymph node metastasis from those with negative lymph node metastasis using DGCR5 expression. C, The diagnostic specificity and sensitivity of DGCR5 expression in clinical stage. D, DGCR5 expression could discriminate poor overall survival patients from good overall survival patients.

importantly, we proved that low expression of DGCR5 was obviously associated with large tumor size, more lymph node metastasis, present distant metastasis, and advanced clinical stage. Similarly, Huang *et al*[30]observed that DGCR5 expression is obviously associated with hepatitis B surface antigen and vascular invasion in hepatocellular carcinoma. Dong *et al*[31]reported that downregulated DGCR5 expression is greatly associated with tumor size in lung adenocarcinoma. Besides, Luo *et al*[32] demonstrated that low expression of DGCR5 is significantly associated with large tumor size, high incidence of both lymph metastasis, and distant metastasis in lung cancer. The phenomenon indicated that downregulation of DGCR5 has a strong correlation with OC progression.

Up to now, more and more literatures have reported that decreased DGCR5 (transcript variant 1 and 2) acts as a tumor-suppressive gene to restrain the progression in several types of human cancer. In papillary thyroid carcinoma, DGCR5 inhibits tumor cell growth and invasion via sponging miR-2861.[16] In colorectal cancer, DGCR5 suppresses the proliferation of RKO and CR4 cells by downregulation of miR-21.[33] In non-small cell lung cancer, DGCR5 overexpression suppresses cell growth, migration, and invasion through regulating miR-211-5p/EPHB6 axis.[34] Inspired by these evidences of clinicopathological data, low DGCR5 expression was closely associated with OC growth and metastasis, thus we supposed DGCR5 may function as a tumor suppressor and its deficiency expression could contribute to OC progression. Therefore, future efforts will be devoted to exploring the potential effects and underlying mechanisms of DGCR5 on OC progression.

The prognostic values of DGCR5 expression have been reported in human cancers. In liver cancer patients, DGCR5 expression is found to be independent prognostic factors for prognosis.[30] In bladder cancer, lower expression of DGCR5 predicts a poor overall survival.[35] To more clearly define the prognosis of DGCR5 in OC, we generated the overall survival analysis. Consistent with the poor prognosis of low DGCR5 expression in liver and bladder cancer, our data indicated that patients with low DGCR5 expression was correlated with a shorter overall survival than those patients with high DGCR5 expression. Furthermore, DGCR5 expression acts as an independent poor prognostic factor for overall survival in patients with OC. DiGeorge syndrome critical region gene 5 could be served as a promising biomarker for diagnosing lymph node metastasis, clinical stage, and overall survival of patients with OC. Despite the diagnostic and prognostic significances of DGCR5 for OC progression, the results of the present study should be viewed cautiously because of the relatively small sample size. Larger prospective studies are needed to confirm our results.

In summary, our study offered the convincing evidence for the first time that the DGCR5 expression is downregulated in OC tissues and strongly associated with advanced tumor progression. More importantly, we preliminarily illustrated that low expression of DGCR5 is an independent poor prognostic factor for overall survival in patients with OC. As a result, the manipulation of DGCR5 may be a promising biomarker for the diagnosis and prognosis of patients with OC in the future.

Authors' Note

Hongxiao Chen and Xiufang Tian have contributed equally to this work. H.L. contributed to the study design, data analysis, manuscript writing and revision. H.C. contributed to sample collection, experiment, data analysis, manuscript writing and revision. X.T. contributed to sample collection, experiment, and data analysis. Y.L. contributed to sample collection. All authors read and approved the final manuscript. This study was approved by the Ethical Board of the Institutional Ethics Committee at Tianjin Fifth Central Hospital (no. 2017542160). Written informed consent was obtained from all participants. The patients have provided informed consent for publication.

Declaration of Conflicting Interests

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ORCID iD

Hui Lu https://orcid.org/0000-0003-1760-6749

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