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Original Article

Serous and Exosomal LDH-C4 as a Potential Diagnostic and Prognostic Biomarker of Cervical Carcinoma

Fengxia Zhang[1], PhD; Zengguang Ma[2], PhD; Fengqin Zhang[3], PhD; Yucui Li[1], PhD; Xiaojie Liu[1], PhD; Jiandong Zhang[4], PhD

[1]Medical Laboratory Center, Hengshui Health Technology Vocational College, Hengshui, China;
[2]Respiratory and Critical Care Medicine Department, Hengshui Third People's Hospital, Hengshui, China;
[3]Department of Pathology, Hengshui people's Hospital of Hebei Medical University, Hengshui, China;
[4]Clinical Laboratory, The Third Hospital of Hebei Medical University, Shijiazhuang, China

Correspondence:
Jiandong Zhang, PhD;
Ziqiang Road 139, Postal code: 050000, Shijiazhuang, China
Tel: +86 15 833917703
Email: zhangjian2221993@126.com
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Abstract

Background: Exosomal molecules derived from cancer cells have been recognized as candidate biomarkers for cancer diagnosis and prognosis. This study aimed to evaluate the potential of the LDH-C4 expression level in cervical carcinoma.

Methods: A retrospective study was conducted on patients with cervical carcinoma at the Third Hospital of Hebei Medical University, in Shijiazhuang, China, between July 2021 to September 2023. Peripheral blood was obtained, and serum and exosomes were extracted. Lactate dehydrogenase (LDHC) gene expression levels were quantified using reverse transcription-quantitative polymerase chain reaction (PCR), and these were compared with protein expression levels in cervical carcinoma tissues. Statistical analyses, including independent *t* tests, Chi square tests, receiver operator characteristic (ROC) curves, Kaplan-Meier analysis, and subsequent log-rank tests, were performed with the SPSS software version 21. Univariate and multiple analyses were used to analyze independent prognostic risk factors. $P<0.05$ was considered statistically significant.

Results: A total of 220 individuals were recruited, including 120 with cervical carcinoma and 100 healthy controls. In patients with cervical carcinoma, the LDHC gene expression levels were 5.58% and 11.28% in serum and exosomes of healthy donors and were 79.38% and 66.27% in patients with cervical carcinoma. There was a statistically significant difference in the LDHC expression between the patient group and the control group ($P=0.008$, in serum; $P=0.011$, in exosomes). In addition, LDH-C4 protein expression was associated with histology grade ($P=0.022$), tumor stage ($P=0.019$), and lymph node metastasis ($P=0.016$). The overall survival of patients with cervical carcinoma with positive LDH-C4 expression was 83.54%; patients with a higher LDH-C4 expression exhibited a poorer overall survival rate than those with lower LDH-C4 expression. Multiple Cox regression analysis demonstrated that LDH-C4 expression is a poor independent prognostic factor for patients with cervical carcinoma.

Conclusion: LDH-C4 levels in serum and exosomes may exhibit potential in identifying patients with cervical carcinoma, thus providing a novel approach for the early screening of cervical carcinoma.

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Keywords ● Lactate dehydrogenase C4 ● Biomarkers ● Gene expression ● Uterine cervical neoplasms

What's Known

- LDH-C4, a member of the cancer-testis antigen (CTA) family, is the focus of research at present, due to the aberrant transcription in a broad spectrum of human neoplasms. LDH-C4 is frequently expressed in several human cancers.

What's New

- The expression of LDH-C4 in patients with cervical carcinoma remains to be fully elucidated. In this study, LDH-C4 levels in serum and exosomes exhibited potential in identifying patients with cervical carcinoma, thus providing a novel approach for the early screening of cervical carcinoma.

Introduction

Cervical carcinoma is one of the most common female malignancies and the fourth leading cause of cancer-related mortality in women worldwide. The latest statistics indicate that cervical carcinoma accounts for 300,000 deaths worldwide, with 0.5 million women being diagnosed every year.[1] In China, there are 132,300 new cases of cervical carcinoma and 60,000 deaths each year.[2] With the rapid development of medical technology, cervical cancer screening technology has been developed. Previously, the clinical diagnosis of cervical lesions was mainly based on Papanicolaou (PAP) cytology technology.[3] Due to poor sampling methods and smears, its sensitivity is relatively low, and it has a certain false positive. The quality of cervical thin-layer liquid-based cytology specimens has improved, which may improve sensitivity. However, during the testing process, it is easily influenced by the subjective factors of the inspection operators. Compared to PAP, human papillomavirus (HPV) examination has higher sensitivity but relatively lower specificity.[4] Due to differences in viral load and pathogenicity, there are differences in HPV infection among different subtypes. For example, inaccuracies in patient age and infection subtypes during screening may lead to over-treatment of benign cervical lesions. The diagnostic criteria of cervical carcinoma mainly rely on colposcopy with biopsy,[5] which is an invasive examination. Early diagnosis and treatment of cervical carcinoma are critical for achieving higher levels of treatment success rates and better prognosis.[6, 7] Therefore, current research is focused on developing improved medical strategies, including the identification of novel and efficient biomarkers.

Exosomes are small membrane-bound vesicles, with a diameter of 30-100 nm, which are secreted from various cell types into bodily fluids, such as blood and urine.[8] Exosomes derived from cancer cells carry RNA, DNA, and proteins that play a pivotal role in cell communication in cancer.[9] Therefore, exosomes play key roles as mediators for primary tumor cells,[10] and exhibit potential as tumor biomarkers.[11] Lactate dehydrogenase C4 (LDH-C4) is a unique lactate dehydrogenase (LDH) isoenzyme.[12] Initially, LDH-C4 expression was observed in mature testis, playing a critical role in sperm motility, captivation, and fertilization.[13] Due to the aberrant expression in various tumor types, results of a previous study implicated LDH-C4 as a cancer-testis antigen (CTA).[14] However, the expression and prognostic significance of LDH-C4 in patients with cervical carcinoma are yet to be fully elucidated.

In the present study, *LDH-C4* gene expression was determined in the peripheral blood of patients with cervical carcinoma, and the potential association between LDH-C4 expression and clinicopathological risk factors was determined. In addition, LDH-C4 protein expression levels were determined in cervical carcinoma tissues using immunohistochemistry, and the 5-year overall survival of patients with cervical carcinoma was analyzed. Therefore, the present study evaluates the expression of LDH-C4 in patients with cervical carcinoma and assesses their association with diagnostic and prognostic value.

Materials and Methods

Patients and Clinical Data

This retrospective study was conducted on patients with cervical carcinoma at the Third Hospital of Hebei Medical University, in Shijiazhuang, China, between July 2021 to September 2023.

The control group included healthy subjects referred to clinicians for cervical carcinoma screening, and clinical cervical exams confirmed their health. The target group was patients diagnosed with cervical carcinoma, without restricting age or histological type. The exclusion criteria were a history of any type of malignancy or receiving any form of therapy. The present study was approved by The Third Hospital of Hebei Medical University (ethics approval no. 2021-034-5). Written informed consent was obtained from each participant prior to the study.

The sample size estimation is based on the equation of detection sensitivity: $N=Z^2\times[p(1-p)]/E^2$, E represents the margin of error (set to 10% in this study), and p represents the assumed sensitivity. If P is set to 0.5 in this study, a minimum sample size of 96 cervical cancer patients is required. The ratio of cervical cancer patients to healthy individuals is at least 1:1; then, at least 88 healthy individuals are required. Therefore, this study recruited a total of 120 cervical cancer patients and 100 healthy individuals.

Blood and Tissue Specimen Collection

Blood samples of patients were collected before any treatment from the clinical laboratory of the Third Hospital of Hebei Medical University, in Shijiazhuang, China. In total, 5 mL of peripheral blood samples were obtained from volunteer donors and patients, and serum was centrifuged at 4,000 ×g for 10 min following coagulation. An ExoRneasy Serum/Plasma

ExoEasy Maxi kit (Qiagen GmbH, Germany) was used to extract exosomes from serum. Briefly, the serum was centrifuged at 8,000 ×g at 4 °C for 15 min. Supernatants were precipitated with ExoQuiekTC reagent (Qiagen GmbH, Germany) at a ratio of 4:1, and mixed at 4 °C for 12 hours. Subsequently, samples were centrifuged at 1,500 ×g for 30 min. Samples were washed with phosphate-buffered saline (PBS) (Sunncell, China), and the dissolved solution was collected. Pathological tissue samples of patients were collected from the histopathology laboratory of the Third Hospital of Hebei Medical University in Shijiazhuang, China. All cervical carcinoma samples were confirmed by two pathologists and classified according to the World Health Organization (WHO) classification for each type of cancer.[15] The adjacent specimens were obtained from individuals with cervical carcinoma.

Reverse Transcription Quantitative (RT-q) PCR

Total RNA was extracted from samples using an miRNeasy Serum/Plasma Advanced kit (Baoxin, China) and the exoRNeasy Serum/Plasma Midi kit (Univ, China), according to the manufacturer's instructions. Extracted RNA was reverse transcribed into cDNA using the Mir-XTM miRNA first-strand synthesis kit (Takara Bio, Japan). RT-qPCR was performed using the following thermocycling conditions: Initial denaturation at 95 °C for 10 min; 40 cycles of 95 °C for 15 sec and 60 °C for 1 min. mRNA levels were quantified using the $2^{-\Delta\Delta Cq}$ method[16] and normalized to the internal reference gene GAPDH. The following primers were used for RT-qPCR: LDH-C4F, 5'-TCATTCCTGCCATAGTCCA-3', and LDH-C4R, 5'-CAATTACACGAGTTACAGGTA-3'; and GAPDH forward, 5'-ACCTGACCTGCCGTCT AGAA-3' and reverse 5'-TCCACCACCCT GTTGCTGTA-3'.

Immunohistochemistry

Tissue sections were dried, dehydrated, and rehydrated. Subsequently, sections were blocked for 5 min and incubated with rabbit anti-human LDH-C4 antibody (1:100; Abcam, Britain) at 4 °C overnight. Following washing with PBS for 10 min, sections were incubated in biotinylated goat anti-rabbit antibody and streptavidin labeled with horseradish peroxidase (Abcam, Britain). After a 10-minute wash in PBS, samples were incubated in a substrate solution containing diaminobenzidine (DAB) (Haoran Bio, China). Sections were counterstained with hematoxylin (Haoran Bio, China) and observed under a light microscope (Olympus, Japan).

Statistical Analysis

SPSS statistical software (version 21.0; IBM Corp, USA) was used for statistical analysis. Data are expressed as the mean±SD. Descriptive statistics were determined for all variables. Quantitative and qualitative variables were compared between groups using independent *t* tests and Chi square tests, respectively. The receiver operating characteristic (ROC) curve was used to evaluate diagnostic value. Kaplan-Meier analysis was used to calculate the survival rates of patients, and the log-rank test was employed to analyze the difference. Binary logistic regression analysis was performed to assess the association between SNPs and the risk of cervical cancer. Multiple analysis was then undertaken for the baseline variables, with a $P<0.05$ found in the univariate analysis.

Results

The present study evaluated 120 patients with cervical carcinoma. Their age ranged between 40 and 85 years, with a mean value of 63.15±21.43 years. The clinical stages of the tumor, (56.67%) and 52 (43.33%) patients were in I and II-IV, respectively. Histologically, 77 (64.16%) had tumor stage G1-G2, and 43 (35.84%) had G3. 55 (45.83%) had lymph node metastasis, 63 (52.5%) had vascular invasion, and 86 (71.66%) had HPV infection. The demographic characteristics of the patients are presented in table 1.

Table 1: Demographic characteristics of patients

Variable		Patients (n, %) (n=120)
Age		63.15±21.43
Tumor stage	I	68 (56.67%)
	II-□	52 (43.33%)
Histology Grade	G1-G2	77 (64.16%)
	G3	43 (35.84%)
Lymph node metastasis		55 (45.83%)
Vascular invasion		63 (52.5%)
HPV infection		86 (71.66%)

Data are expressed as mean±SD. HPV: Human papillomavirus

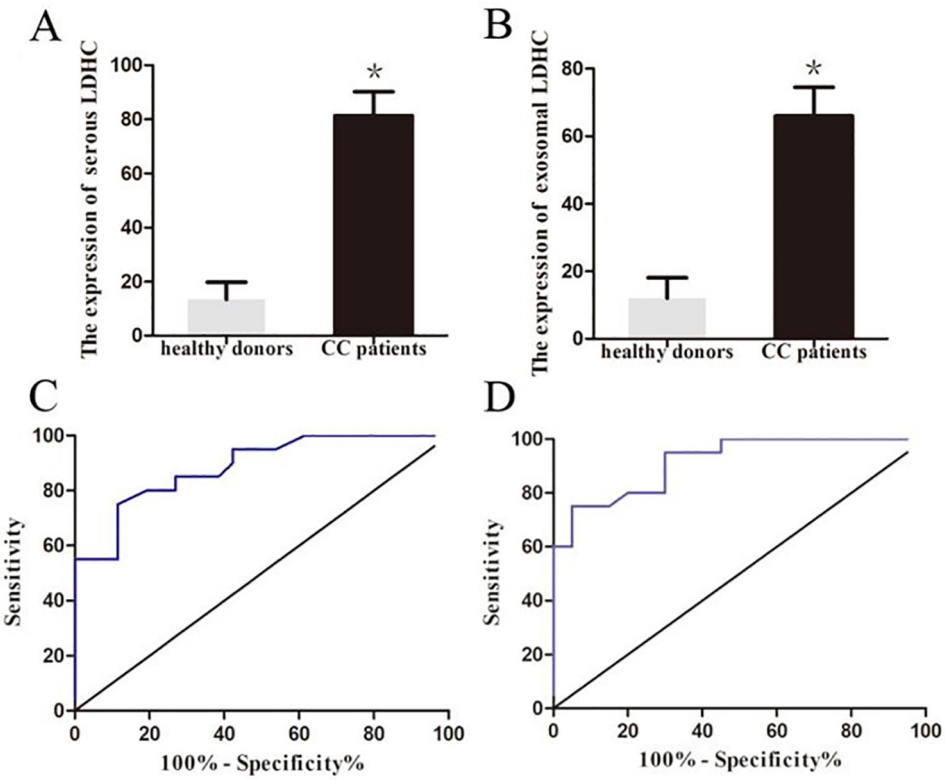

Figure 1: LDH-C4 exhibited satisfactory diagnostic value in cervical carcinoma. (A) Quantitative RT-PCR was used to assess serous LDHC expression in cervical carcinoma and healthy control specimens (*P=0.008). (B) Quantitative RT-PCR was used to assess exosomal LDHC expression in cervical carcinoma and healthy control specimens (*P=0.011). (C) A ROC curve was used to assess the diagnostic efficacy of LDH-C4 in serum. (D) A ROC curve was used to assess the diagnostic efficacy of LDH-C4 in exosomes. CC: Cervical carcinoma; LDHC: Lactate dehydrogenase; ROC: Receiver operating characteristic

LDH-C4 mRNA Expression in the Serum and Exosomes of Patients with Cervical Carcinoma

The expression of LDHC genes in the serum and exosomes of 120 patients with cervical carcinoma and 100 healthy donors was determined using RT-qPCR. Results of the present study revealed that positive expression levels of LDHC were 15.58% and 11.28% in the serum and exosomes of healthy donors, respectively, and were 79.38% and 66.27% in patients with cervical carcinoma. LDHC expression levels were significantly higher in patients with cervical carcinoma than those in healthy donors (P=0.008, in serum; P=0.011, in exosomes) (figures 1A and 1B). Results obtained using ROC curves demonstrated that the area under the curve (AUC) values of serum LDHC in cervical carcinoma and healthy groups were 0.851 (95% confidence interval [CI], 0.733-0.969), with a cut-off value of 0.925, and a sensitivity and specificity of 72.9% and 83.1%, respectively (figure 1C). AUC values of LDHC exosomes in cervical carcinoma and healthy groups were 0.916 (95% CI, 0.834-0.998), with a cut-off value of 1.038, and a sensitivity and specificity of 82.3% and 88.7% (figure 1D).

Association of Clinicopathological and Outcome Parameters with LDH-C4 Expression. In total, 120 patients with cervical carcinoma were divided into LDH-C4-positive and LDH-C4-negative groups according to LDH-C4 expression levels in the cervical carcinoma group, with an optimal cut-off value. As shown in table 2, the expression of LDH-C4 in patients with cervical carcinoma was highly correlated with histology grade (P=0.022), tumor stage (P=0.019), and lymph node metastasis (P=0.016). However, there was no significant association between LDH-C4 expression and age, tumor size, vascular infiltration, infiltrating depth, or HPV infection in patients with cervical carcinoma.

Association between LDH-C4 mRNA Expression in Serum and Exosomes, and Protein Expression in Cervical Carcinoma Tissues

Notably, *LDH-C4* positive expression was not detected in adjacent specimens; however, *LDH-C4* expression was observed in 97 of 120 cervical carcinoma specimens (80.8%; table 3). In the majority of sections, LDH-C4 expression was present in the cytoplasm and nuclei of cervical carcinoma cells (figure 2). The association between LDH-C4 mRNA expression in serum and exosomes, and protein expression in cervical carcinoma tissues are presented in table 4.

Table 2: Association between the expression of *LDH-C4* and the clinicopathological factors of cervical carcinoma patients

Clinical pathological parameters		N	Serum LDH-C4		P value	Exosomal LDH-C4		P value
			High n (%)	Low n (%)		High n (%)	Low n (%)	
Age (year)	<50	42	34 (80.95)	8 (19.05)	0.403	27 (64.28)	15 (35.72)	0.336
	≥50	78	61 (78.20)	17 (11.80)		52 (66.66)	26 (33.34)	
Tumor size (cm)	≤4	84	68 (80.95)	16 (19.05)	0.691	66 (78.57)	28 (21.43)	0.578
	>4	36	27 (75.00)	9 (25.00)		23 (63.88)	13 (36.12)	
Histology Grade	G1-G2	77	58 (75.32)	19 (24.68)	0.037	44 (57.14)	33 (42.86)	0.022
	G3	43	37 (86.04)	6 (13.96)		35 (81.39)	8 (18.61)	
Tumor stage	I	68	50 (73.52)	18 (26.48)	0.023	38 (55.88)	30 (44.12)	0.019
	II-□	52	45 (86.53)	7 (13.47)		41 (78.84)	11 (21.16)	
Lymph node metastasis	Without	75	59 (78.66)	16 (21.34)	0.009	47 (62.66)	28 (37.34)	0.016
	With	55	46 (83.63)	9 (16.37)		42 (76.36)	13 (23.64)	
Vascular invasion	Without	57	46 (80.70)	11 (19.30)	0.438	39 (68.42)	18 (31.58)	0.315
	With	63	49 (77.77)	14 (22.23)		40 (63.49)	23 (36.51)	
Infiltrating depth	<1/2	48	38 (79.16)	10 (20.84)	0.357	30 (62.50)	18 (37.50)	0.441
	≥1/2	72	57(79.16)	15(20.84)		49 (68.05)	23 (31.95)	
HPV infection	Negative	34	27 (79.41)	7 (20.59)	0.172	22 (64.71)	12 (35.29)	0.262
	Positive	86	68 (79.06)	18 (20.94)		57 (66.27)	29 (33.73)	

Data analysis was performed using the Chi square test. P≤0.05 was considered statistically significant.

Table 3: Expression of LDH-C4 protein in cervical carcinoma and adjacent non-neoplastic tissues

Type of tissue	LDH-C4$^-$ n (%)	LDH-C4$^+$ n (%)	P value
Cervical carcinoma	23 (19.16)	97 (80.84)	<0.001
Adjacent tissues	92 (92)	8 (8)	

Data analysis was performed using independent *t* tests. P≤0.05 was considered statistically significant.

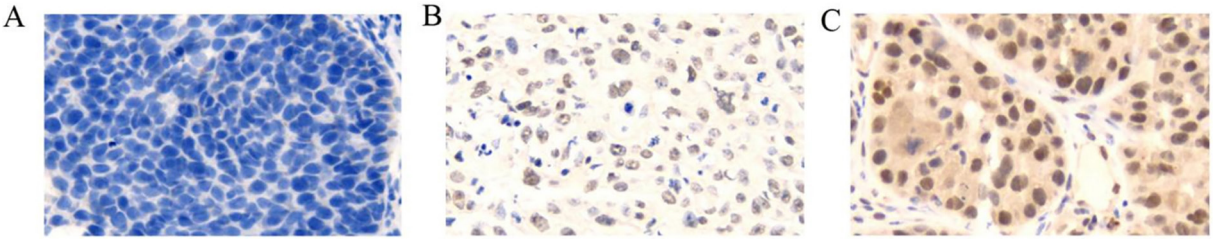

Figure 2: Immunohistochemistry staining for the cervical carcinoma and adjacent healthy tissues. (A) Negative staining in adjacent healthy tissues, ×20. (B) Negative staining in adjacent healthy tissues, ×40. (C) Positive staining in cervical carcinoma specimens, ×20. (D) Positive staining in cervical carcinoma specimens, ×40.

Table 4: Association between LDH-C4 mRNA expression in serum and exosomes and protein expression in cervical carcinoma tissues

Variable		LDH-C4 protein Low	LDH-C4 protein High	P value
Serous LDH-C4	High	6 (5%)	89 (74.1%)	<0.001
	Low	17 (14.1%)	8 (6.8%)	
Exosomal LDH-C4	High	8 (6.8%)	71 (59.2%)	<0.001
	Low	15 (12.5%)	26 (21.5%)	

Data analysis was performed using independent *t* tests. P≤0.05 was considered statistically significant.

Results of the present study revealed that LDH-C4 protein expression in cervical carcinoma tissues was positively correlated with *LDH-C4* gene expression in serum ($\chi2$=22.471, P<0.001) and *LDH-C4* gene expression in exosomes ($\chi2$=16.3874, P<0.001). These results suggested that LDH-C4 mRNA expression in serum and exosomes were associated protein expression in cervical carcinoma tissues.

LDH-C4 Expression in Serum and Serum-Derived Exosomes is Associated with a Poor Prognosis in Patients with Cervical Carcinoma

All 120 cases of cervical carcinoma were followed up for 4-120 months, and the 5-year survival rate for these patients was 83.54%. Kaplan-Meier analysis revealed that patients with cervical carcinoma with a higher *LDH-C4* expression

exhibited a poorer overall survival rate than those with lower *LDH-C4* expression (P=0.031, in serum; P=0.041, in exosomes), using the median *LDH-C4* expression level as the cut-off (figure 3).

The Impact of Clinical Factors on the Prognosis of Patients with Cervical Cancer

As displayed in table 5, histology grade, tumor stage, lymph node metastasis, and *LDH-C4* expression were significant risk factors for patient prognosis. Results of the multiple analysis revealed that histology grade, tumor stage, lymph node metastasis, and *LDH-C4* expression were associated with the poor prognosis of patients with cervical carcinoma, and these are considered independent prognostic factors (table 6).

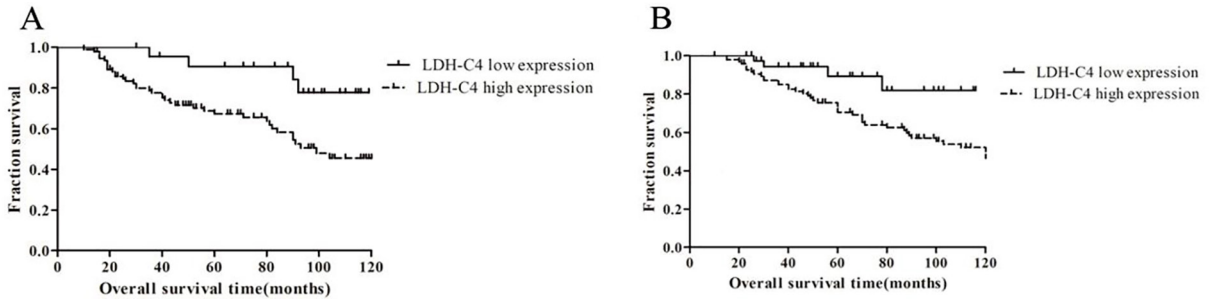

Figure 3: Kaplan-Meier survival analysis was used to assess the association of LDH-C4 expression with overall survival. (A) Patients with high LDH-C4 expression levels in serum exhibited poor overall survival. (B) Patients with high LDH-C4 expression levels in exosomes exhibited poor overall survival. LDH: lactate dehydrogenase.

Table 5: Univariate analyses of prognostic factors for overall survival of cervical carcinoma

Variable	Categories	95% CI	P value
Age	<50	Reference	0.574
	≥50	1.024-3.367	
Tumor size (cm)	≤4	Reference	0.352
	>4	0.736-2.538	
Histology Grade	G1-G2	Reference	0.003
	G3	0.741-1.696	
Tumor stage	I	Reference	
	II-IV	1.816-3.668	
Lymph node metastasis	Without	Reference	<0.001
	With	1.021-4.660	
Vascular invasion	Without	Reference	0.453
	With	0.661-2.167	
Infiltrating depth	<1/2	Reference	0.127
	≥1/2	0.798-2.639	
HPV infection	Negative	Reference	0.512
	Positive	1.359-4.226	
Serum LDH-C4	Low	Reference	0.002
	High	1.134-3.051	
Exosome LDH-C4	Low	Reference	<0.001
	High	1.092-2.876	

Univariate analysis was used to analyze the data. P<0.05 was considered a significant difference.

Table 6: Multiple analyses of prognostic factors for overall survival of cervical carcinoma

Variable	Categories	95% CI	P value
Histology Grade	G1-G2	Reference	<0.001
	G3	1.651-4.338	
Tumor stage	I	Reference	0.001
	II-IV	1.461-4.017	
Lymph node metastasis	Without	Reference	0.003
	With	0.997-4.135	
Serum LDH-C4	Low	Reference	<0.001
	High	1.541-4.114	
Exosome LDH-C4	Low	Reference	<0.001
	High	1.272-3.461	

Multiple analysis was used to analyze the data. P<0.05 was considered a significant difference.

Results of the present study indicated that *LDH-C4* expression may act as a marker for the prediction of survival of patients with cervical carcinoma.

Discussion

Our findings indicated that LDH-C4 was highly expressed in the exosomes of patients with cervical cancer. There was a significant relationship between LDH-C4 expression in tumor tissues and histology grade, tumor stage, lymph node metastasis, and overall survival. Moreover, LDH-C4 expression is a poor independent prognostic factor for patients with cervical carcinoma.

Although the prognosis of cervical cancer patients has improved with the popularization of cancer screening and HPV vaccines, limited treatment options and high recurrence rates often indicate a poor prognosis for patients with advanced or recurrent and metastatic cervical cancer.[17] Immunotherapy exhibits the potential to improve the survival and clinical outcomes of patients with cancer.[18, 19] LDH-C4, a member of the CTA family, is the focus of research at present, due to the aberrant transcription in a broad spectrum of human neoplasms.

Studies on the patterns of LDH-C4 expression in different cancers reported different results. In a multi-center study, LDH-C4 expression was observed in 81.8% of patients with lung adenocarcinoma (LUAD) tissues,[20] in 91.55% of patients with breast cancer tissues,[21] and in 22.3% of patients with renal cell carcinoma (RCC) tissues.[22] Koslowski and others confirmed the expression of LDHC mRNA in the following tested tumor types: melanoma (7/16), breast (7/20), colon (3/20), prostate (3/8), lung (8/17), renal (4/7), ovarian (3/7), thyroid (1/4), cervical cancers (5/6), and lung cancer cell lines (2/6).[23] In addition, LDHC mRNA was detected in serum and serum-derived exosomes of patients with breast cancer,[21] HCC,[24] and LUAD,[25] and the source may be associated with the vesicle encapsulation of tumor cells and the release of necrotic tumor cells into the peripheral blood. As an important cell-to-cell communication tool, exosomes have received extensive attention in recent studies. In the field of tumor liquid biopsy, exosomes have exhibited a high level of potential.[26] In the present study, LDH-C4 gene expression was determined in both the serum and exosomes of patients with cervical carcinoma. To the best of our knowledge, the present study is the first to evaluate the association between LDH-C4 expression and the clinicopathological characteristics of patients with cervical carcinoma. Results of the present study highlighted that 79.38% of cervical carcinoma serum specimens expressed LDH-C4, and 66.27% of cervical carcinoma exosome specimens expressed LDH-C4. LDH-C4 expression was positively associated with histology grade, tumor stage, and lymph node metastasis. These results indicated that LDH-C4 expression may represent an important biological marker to evaluate prognosis in patients with cervical carcinoma. Immunohistochemistry is a common method for detecting protein expression in tumor tissues. Our results demonstrated that LDH-C4 gene expression in plasma exosomes is similar to protein expression in tumor tissues. It is speculated that information contained within exosomes is derived from parent tumor cells. Thus, the characteristics of exosomes may better reflect the characteristics of their parent cells. Notably, this forms the theoretical basis for exosome liquid biopsy. Therefore, plasma exocrine LDH-C4 exhibits potential as a biological indicator for early diagnosis, dynamic monitoring, precise treatment, and evaluation of the prognosis of tumors.

Further survival analysis revealed that the overall survival of patients with LDH-C4 expression in serum and exosomes was significantly lower than in patients without the corresponding expression. Multiple regression analysis was performed using factors that were filtered via binary logistic regression. LDH-C4 expression, histology grade, tumor stage, and lymph node metastasis may exhibit potential as independent prognostic factors for determining the five-year survival of patients with cervical carcinoma. Results of the present study highlight the significance of LDH-C4 expression in the serum and exosomes of patients with cervical carcinoma. LDH-C4 expression may act as a novel and reliable prognostic marker for patients with cervical carcinoma. The cost of screening methods is a factor of concern for patients. This study focuses on the molecular detection of LDH-C4 and preliminarily evaluates that its cost is lower than HPV detection and higher than PAP. Considering the cost and loss brought by each occurrence of cervical cancer, it is better to choose a relatively high sensitivity and moderate cost scheme, which can prolong the screening interval and reduce the total screening cost.

Although the detection of LDH-C4 markers in tumor specimens has great potential for the detection of cervical carcinoma, the sample size, especially for survival analysis, is the main limitation of our study.

Conclusion

The results of the present study revealed that LDH-C4 expression is a poor prognostic marker for patients with cervical carcinoma. Further investigations into the specific role and mechanism of *LDH-C4* in cervical carcinoma are needed to assess its potential as a target in tumors.

Acknowledgment

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Authors' Contribution

F.Z: Study concept, study design, and drafting; Z.M: Data analysis and drafting: F.Zh: Performing the experiments and drafting; Y.L: Performing the experiments and drafting; X.L: Performing the experiments and drafting, J.Zh: Study concept, study design, and drafting; All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest: None declared.

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