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Original Research

The Chemokine CXCL7 is Correlated with LDH-A and Predicts the Prognosis of Patients with Colorectal Cancer

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Abstract

Objective: The aims of this study were to evaluate the correlation between chemokine (C-X-C) ligand 7 (CXCL7) expression and glycolysis and to explore the prognostic significance of CXCL7 in colorectal cancer (CRC). **Methods**: The expression of CXCL7 and lactate dehydrogenase A (LDH-A) was measured by immunohistochemistry in tissue from 158 CRC patients. Patients were divided into high expression and low expression groups based on receiver operating characteristic curves and a cut-off value. The correlation between CXCL7 and LDH-A expression was evaluated. The overall survival (OS) times of CRC patients were explored. The risk factors related to prognosis were assessed. **Results**: Significantly higher expression of CXCL7 and LDH-A was detected in CRC tissue than in non-CRC tissue, and was associated with N stage and tumor-node-metastasis (TNM) stage. CXCL7 expression was strongly correlated with LDH-A expression in CRC tissue. High expression of CXCL7 was validated as an independent risk factor for OS. **Conclusion**: Increased expression of CXCL7 was positively correlated with LDH-A expression and was an independent risk factor for CRC prognosis.

Keywords: colorectal cancer; CXCL7; glycolysis; LDH-A; prognosis

1. Introduction

Colorectal cancer (colorectal carcinoma, CRC) is a commonly occurring malignant intestinal tumor that poses a serious threat to public health owing to its high incidence (ranking third among reported cancers worldwide) and mortality (ranking fourth) [1]. Over recent decades, 10% of all annually diagnosed tumor cases were attributed to CRC [2]. About 1.9 million CRC cases were newly diagnosed and 880,000 CRC-related deaths occurred in 2018 [3]. The incidence of CRC has declined over the past decade in some developed regions; however, it remains high in some developing countries, and new cases are expected to rise to 2.5 million in 2035 worldwide [2,4]. Risk factors including aging, lifestyle, and genetic and environmental influences play important roles in the malignant transformation processes of CRC [4,5]. About 10–20% of CRC patients have family history of the disease [6]. Both genetic factors (various oncogenes such as carcinoembryonic antigen [CEA], carbohydrate antigen 19-9 and carbohydrate antigen 724, cytokines, and chemokines) and epigenetic factors (such as non-coding RNAs) have vital roles in the biological activities of CRC [7,8]. Although various treatments (including surgical resection, radiotherapy, chemotherapy, and, most recently, immune-targeted therapy) are available for CRC patients, the 5-year survival rate (around 50–65%) has shown no substantial change in recent years, owing to local tissue relapse and distant metastasis [9]. Therefore, it is extremely important to understand the mechanisms involved in the occurrence and development of CRC so as to improve prevention, early diagnosis, and treatment.

Chemokines are a group of small soluble proteins released in pathological circumstances that play an essential role in immune reactions (for example, recruitment of Th1 lymphocytes, wound healing, cell differentiation, metabolism, and prostaglandin synthesis) by binding to their specific chemokine receptors [10]. One chemokine can have several receptors, and a receptor normally has several ligands [10]. Chemokines can be expressed in many cell types, including fibroblasts, neutrophils, macrophages, and endothelial cells [10–12]. Chemokines such as chemokine (C-X-C) ligand 17 (CXCL17) and chemokine (C-X-C) ligand 16 (CXCL16) were found to be produced by tumor cells in colon cancer, and shown to be associated with bad prognosis [13–16]. Chemokines originating from the tumor microenvironment promote the signal transduction of tumor cells by activating related signal pathways [17–19]. The chemokine ligand 7 (CXCL7), also named NAP-2, is released mostly by platelets, and exerts effects in diverse cancers by activating its specific CXCR1 and CXCR2 receptors [20].

Metabolic reprogramming, a common feature of malignant tumors, can accelerate cancer progression and

metastasis [21]. To sustain the growth of tumor tissue, cells must take in more nutrients to support rapid and sustained metabolism. Carbohydrates are an important energy source, so glucose metabolism has biological roles in various cellular physiological and pathological processes [22]. Glycolysis is a series of enzymatic reactions that can generate lactic acid and produce energy (adenosine triphosphate) in the cytoplasm [23]. Many studies have shown that even under aerobic conditions, tumor cells preferentially rely on glycolysis to meet the needs of cells; this phenomenon is known as the Warburg effect or aerobic glycolysis [23]. The acidic tumor microenvironment, which depends on lactic acid, can promote tumor tissue invasion and distant metastasis [24]. Lactate dehydrogenase (LDH), a key enzyme in glycolysis, is related to the occurrence, development, and prognosis of various tumors and is highly expressed in multiple cancers [21,23,25]. Depending on differences in its coding genes, LDH has six isozymes. Lactate dehydrogenase A (LDH-A), one of the most important subunits of LDH, is mainly expressed in skeletal muscle and preferentially converts pyruvate to lactate [26]. Moreover, LDH-A has been found to be highly expressed in a variety of tumors, and its expression level is closely related to clinical stage and prognosis [27].

Many studies have shown that chemokines play vital roles, via aerobic glycolysis, in tumor glucose metabolism and function in various aspects of proliferation, metastasis, and other physiological activities [13–19,28,29]. Our previous work also found that overexpression of CXCL7 led to worse survival in CRC patients [20]. However, the relationship between CXCL7 and glycolysis has remained unclear. In the present study, we used immunohistochemistry (IHC) to measure the expression of CXCL7 and LDH-A in 158 CRC patients, and comprehensively explored the relationship of the two proteins. We also investigated the prognostic value of CXCL7 and LDH-A in CRC patients by constructing Cox regression models and a nomogram.

2. Materials and Methods

2.1 Patients and Tissue Processing

CRC patients first diagnosed in Bozhou Hospital of Anhui Medical University from January 2013 to December 2018 were included in the study. The inclusion criteria were as follows: (1) date of diagnosis of the patient was consistent with the designated time interval in this study; (2) patients received intestinal resection; (3) postoperative (pathological) diagnosis was consistent with the preoperative (clinical) diagnosis of CRC; (4) no preoperative radiotherapy, chemotherapy, or other treatment had been administered; (5) basic clinical information had been completely collected; (6) patient provided written informed consent to participate. Other related criteria were as in our previous study [20]. On the basis of these criteria, 195 patients were included in this study for follow-up; however, 37 patients withdrew from the study, so survival information for 158 CRC patients was finally acquired. The study was approved by the Institutional Research Ethics Committee of Bozhou Hospital of Anhui Medical University (No.202298). The clinicopathological staging of CRC patients was based on the tumor-node-metastasis (TNM) staging method of the American Joint Committee on Cancer guidelines (7th version) [20]. After intestinal resection, cancer tissue and adjacent paracancerous tissue of 158 CRC patients was collected. Then, 316 tissue samples were harvested and snap-frozen with liquid nitrogen. Tissue blocks were fixed in formalin (10%) and embedded in paraffin.

2.2 IHC Assay

All processed tissue was cut into 4-µm-thick sections by pathology technicians. The tissue was incubated with rabbit polyclonal antibodies against CXCL7 (# DF6695, 1:200, Affinity Biosciences, Cincinnati, OH, USA) and LDH-A (# DF6280, 1:200, Affinity Biosciences, Cincinnati, OH, USA) according to the operating instructions, with phosphate-buffered saline as a negative control. All processes related to IHC were conducted using an automatic staining machine [20]. Images of IHC tissue were captured from all thicknesses by a pathologist. IHC scores were obtained consistent with procedures in our previous study [20]. Finally, a receiver operating characteristic (ROC) curve was used to obtain a cut-off value for distinguishing high expression and low expression tissue for all staining thicknesses.

Each participant was followed up until either death or the end date of the study. The follow-up method was similar to that used in our previous study [20]. Detailed data of CRC patients, including pathologic stage, survival status, and time, were prospectively captured by two special researchers.

2.3 Statistical Analysis

All data analyses were performed with the SPSS 22.0 software package (IBM; Armonk, NY, USA); GraphPad Prism 7.0 software was also used for constructing graphs (GraphPad Software; La Jolla, CA, USA). Data for categorical variables are shown as frequencies (n) with percentages (%) and were analyzed by chi-square statistical tests (x^2), Fisher's exact probability test, or Mann–Whitney U-test. Quantitative data are expressed as mean and standard deviation (SD) and were analyzed by Student's t-test unless otherwise specified. Spearman's rank-correlation analysis was used to evaluate the correlation between CXCL7 and LDH-A expression. The last follow-up was carried out in January 2022, after which survival times were estimated. Kaplan–Meier analysis and log-rank test were used to explore the overall survival (OS) times of CRC patients. Cox regression models and hazard ratios (HR) with 95% confidence intervals (95% CI) were also used to evaluate the risk factors related to prognosis. A nomogram and correspond-

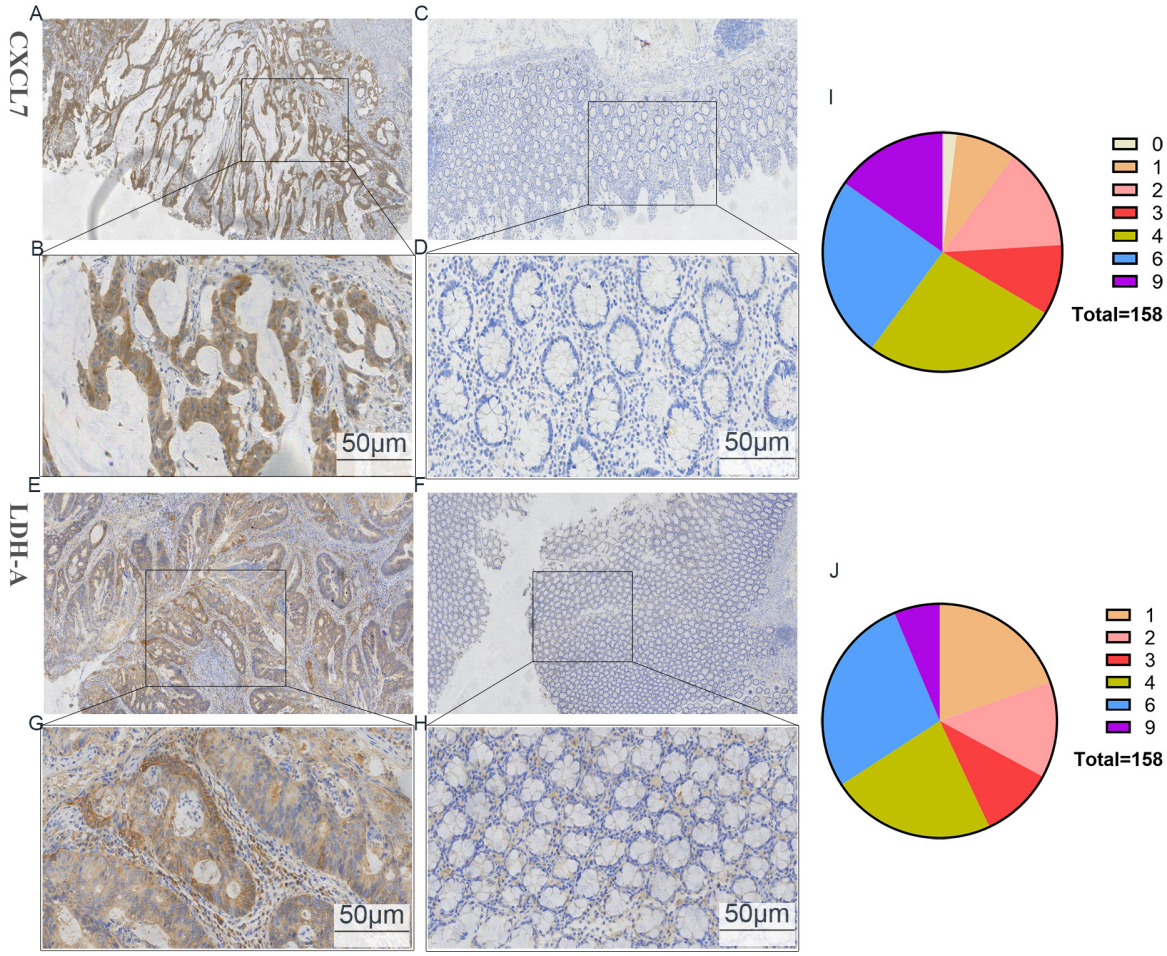


Fig. 1. Expression of CXCL7 and LDH-A in CRC tissue. (A,B) Expression of CXCL7 in 158 CRC tissue (magnification: 40× and 200×). (C,D) Expression of CXCL7 in normal tissue (40× and 200×). (E,G) LDH-A expression in CRC tissue (40× and 200×). (F,H) LDH-A expression in normal tissue (40× and 200×). (I) Numbers of patients with different IHC scores related to CXCL7. (J) Numbers of patients with different IHC scores related to LHD-A. (Scores from 0 to 9). Scale bar: 50 μm. CRC, colorectal cancer; IHC, immunohistochemistry.

ing indexes were used to assess the value of the established prognostic models. $p \leq 0.05$ was considered to be significant.

3. Results

3.1 Basic Information of CRC Patients

One hundred and fifty-eight CRC patients met the study criteria and included 86 men (54.4%, 86/158) and 72 women (45.6%, 72/158). The mean age was 58.74 (10.37) years. To better analyze the data, patients were divided into two subgroups based on age (≤60 and >60 years old). The cohort included 2 stage I (1.3%), 65 stage II (41.1%), 69 stage III (43.7%), and 22 stage IV (13.9%) patients. Patient details are shown in Table 1.

3.2 Elevated Expression of CXCL7 and LDH-A in CRC Tissue

Cancer tissue and para-tumoral tissue from 158 CRC patients were stained by IHC to analyze the expression of CXCL7 and LDH-A. CXCL7 was significantly higher in CRC tumor cells than in adjacent non-cancer cells (65.82%, 104/158 *vs.* 22.78%, 36/158; $p < 0.001$; Fig. 1A,B *vs.* Fig. 1C,D). As this result was similar to that of our previous study [20], a score of 3.5 was regarded as the cut-off value for CXCL7 expression on the basis of the ROC curve. The protein level of LDH-A was also higher in cancer cells than in normal tissue cells (56.96%, 90/158 *vs.* 18.99%, 30/158; $p < 0.001$; Fig. 1E,G *vs.* Fig. 1F,H). Using ROC curve analysis, a cut-off value of 3.6 was chosen to divide the cases into high-expression and low-expression subgroups for further analysis. The numbers of different IHC score groups are listed in Fig. 1I,J.

3.3 Expression of CXCL7 and LDH-A in Different CRC Subgroups

In order to investigate the relationships of CXCL7 and LDH-A expression with clinical features more deeply, the ICH scores of the two markers were compared in different

Table 1. Expression of CXCL7 and LDH-A associated with different subgroups of CRC patients and correlation between two markers.

Characteristics	Case (n = 158)	CXCL7 expression		*p*-value	LDH-A expression		*p*-value	r	*p*-value
		Low	High		Low	High			
Total	158	54	104		68	90		0.696	<0.001
Gender				0.895			0.997		
Male	86	29	57		37	49		0.720	<0.001
Female	72	25	47		31	41		0.658	<0.001
Age				0.357			0.641		
≤60	87	27	60		36	51		0.662	<0.001
>60	71	27	44		32	39		0.732	<0.001
Tumor location				0.427			0.231		
Colon	75	28	47		36	39		0.720	<0.001
Rectum	83	26	57		32	51		0.656	<0.001
Cancer site				0.573			0.355		
Left	124	41	83		51	73		0.679	<0.001
Right	34	13	21		17	17		0.688	<0.001
Tumor size				0.383			0.673		
<4 cm	69	21	48		31	38		0.781	<0.001
≥4 cm	89	33	56		37	52		0.620	<0.001
Depth of tumor invasion				0.123			0.174		
T1–T2	49	21	28		25	24		0.575	<0.001
T3–T4	109	33	76		48	66		0.764	<0.001
Lymph node metastasis				<0.001			<0.001		
N0	74	38	36		45	29		0.630	<0.001
N1–N2	84	36	68		23	61		0.499	<0.001
Distant metastasis				0.376			0.187		
M0	135	48	87		61	74		0.643	<0.001
M1	23	6	17		7	16		0.667	<0.001
TNM stage				<0.001			<0.001		
I–II	67	35	32		42	25		0.606	<0.001
III–IV	91	19	72		26	65		0.529	<0.001
Neural invasion				0.607			0.448		
Yes	54	37	67		47	57		0.704	<0.001
No	104	17	37		21	33		0.640	<0.001
Vascular invasion				0.686			0.896		
Yes	59	19	40		25	34		0.641	<0.001
No	99	35	64		43	56		0.727	<0.001
Differentiation				0.659			0.492		
Well	77	25	52		31	46		0.725	<0.001
Moderate-Poor	81	29	52		37	44		0.663	<0.001

CXCL7, chemokine ligand 7; LDH-A, lactate dehydrogenase A; TNM, tumor-node-metastasis.

clinical subgroups. CXCL7 was differentially expressed by N stage (N1–N2 *vs.* N0; $p < 0.001$; Fig. 2G) and TNM stage (III–IV *vs.* I–II; $p < 0.001$; Fig. 2I), as was LDH-A (N1–N2 *vs.* N0 [$p < 0.001$; Fig. 2S] and TNM III–IV *vs.* I–II [$p < 0.001$; Fig. 2U]). No other variables were significantly connected with expression of CXCL7 or LDH-A (Fig. 2A–F,H,J–R,T,V–X). Details are shown in Fig. 2 and Table 1. In the logistic regression analysis, increased CXCL7 and LDH-A expression levels were positively associated with N stage (CXCL7: N1–N2 *vs.* N0, OR = 4.486, 95% CI: 2.205–9.127, $p < 0.001$; LDH-A: N1–N2 *vs.* N0, OR = 4.115, 95% CI: 2.108–8.036, $p < 0.001$), TNM stage (CXCL7: III–IV *vs.* I–II, OR = 4.145, 95% CI: 2.065–8.319, $p < 0.001$; LDH-A: III–IV *vs.* I–II, OR = 4.200, 95% CI: 2.144–8.227, $p < 0.001$). No significant statistical correlations were found with other variables. Details are shown in Fig. 2 and Table 2.

3.4 Correlation between CXCL7 and LDH-A in CRC Tissue

The non-parametric Spearman's test was used to assess the correlation between CXCL7 and LDH-A expression and was described by the correlation coefficient (r). As

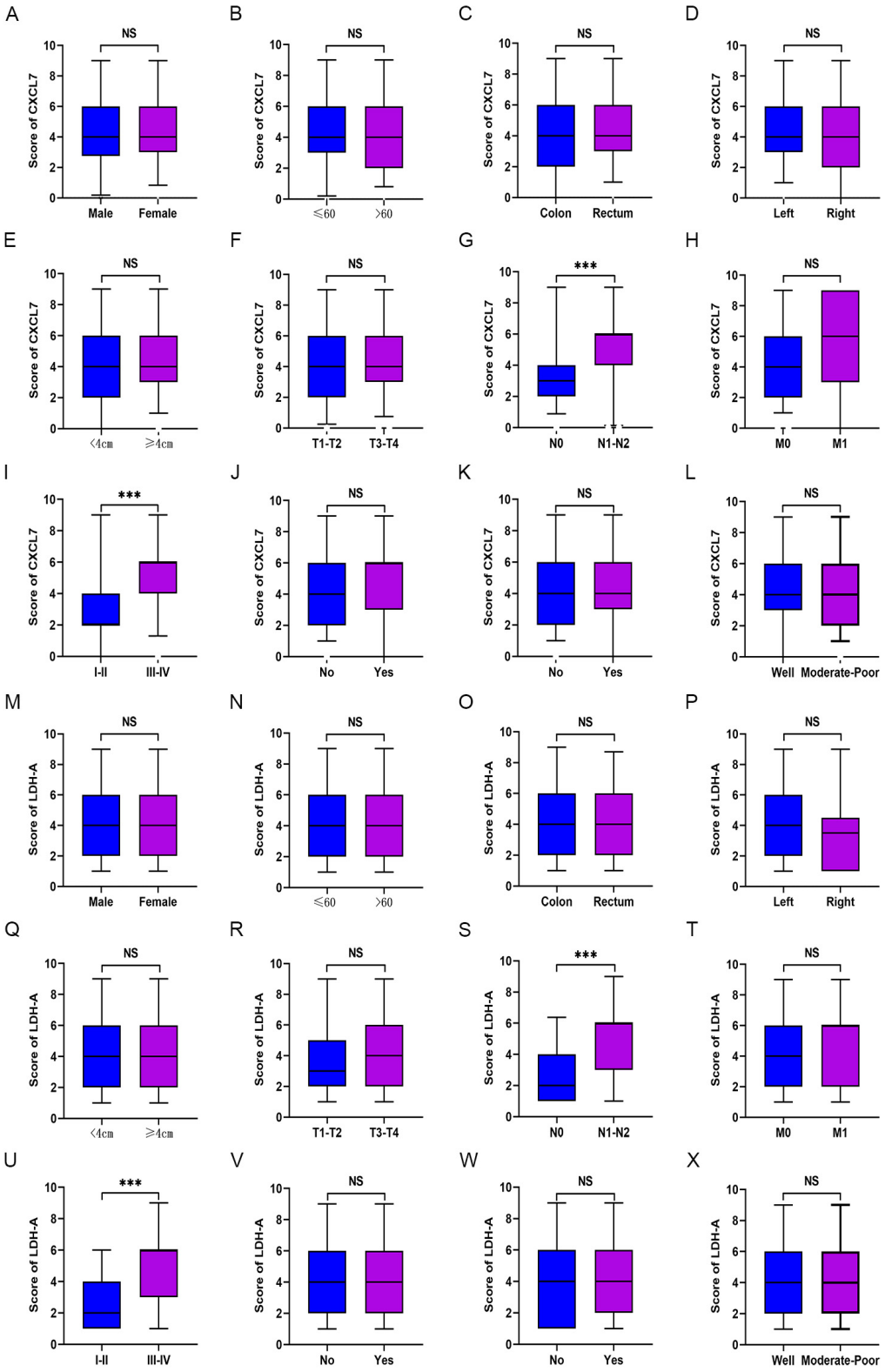


Fig. 2. Expression of CXCL7 and LDH-A in different CRC patient groups. (A) CXCL7 expression stratified by sex. (B) CXCL7 expression at different ages. (C) CXCL7 expression for different tumor location sites. (D) CXCL7 expression for different cancer sites. (E) CXCL7 expression for different tumor sizes. (F) CXCL7 expression at different T stages. (G) CXCL7 expression at different N stages. (H) CXCL7 expression at different M stages. (I) CXCL7 expression at different TNM stages. (J) CXCL7 expression in different neural invasion groups. (K) CXCL7 expression in different vascular invasion groups. (L) CXCL7 expression in different differentiation groups. (M–X) LDH-A expression in different subgroups. ***$p < 0.001$, NS: no statistical significance. Comparisons were tested by Mann–Whitney U-test ($n = 2$).

Table 2. Logistic regression analysis to make a thorough inquiry of the relationship between CXCL7 and LDH-A and clinical features in CRC tissues.

Characteristics	CXCL7		LDH-A	
	Odds Ratio (OR)	*p*-value	Odds Ratio (OR)	*p*-value
Gender (Male *vs*. Female)	1.045 (0.541–2.022)	0.895	1.001 (0.532–1.884)	0.997
Age (>60 *vs*. ≤60)	0.733 (0.379–1.419)	0.357	0.860 (0.457–1.620)	0.641
Tumor location (Rectum *vs*. Colon)	1.306 (0.676–2.524)	0.427	1.471 (0.781–2.770)	0.232
Cancer site (Right *vs*. Left)	0.798 (0.363–1.752)	0.798	0.699 (0.326–1.496)	0.356
Tumor size (≥4 cm *vs*. <4 cm)	0.742 (0.380–1.450)	0.383	1.147 (0.608–2.163)	0.673
Depth of tumor invasion (T3–T4 *vs*. T1–T2)	1.727 (0.860–3.471)	0.125	1.599 (0.811–3.153)	0.176
Lymph node metastasis (N1–N2 *vs*. N0)	4.486 (2.205–9.127)	<0.001	4.115 (2.108–8.036)	<0.001
Distant metastasis (M1 *vs*. M0)	1.563 (0.578–4.229)	0.379	1.884 (0.728–4.875)	0.192
TNM stage (III–IV *vs*. I–II)	4.145 (2.065–8.319)	<0.001	4.200 (2.144–8.227)	<0.001
Neural invasion (Yes *vs*. No)	1.202 (0.596–2.422)	0.607	1.296 (0.663–2.531)	0.448
Vascular invasion (Yes *vs*. No)	1.151 (0.581–2.282)	0.686	1.044 (0.544–2.004)	0.896
Differentiation (Moderate-Poor *vs*. Well)	0.862 (0.446–1.666)	0.862	0.801 (0.426–1.507)	0.492

shown in the scatter plot in Fig. 3, CXCL7 expression was significantly correlated with LDH-A expression in CRC tissue (all $p < 0.001$). The coefficient of correlation between CXCL7 and LDH-A expression was 0.696 across all 158 CRC patients ($p < 0.001$; Fig. 3A). In subgroup analysis, the highest r value was obtained for the tumor size group <4 cm (0.781; $p < 0.001$; Fig. 3J), whereas the lowest r was obtained for the N1–N2 group (0.499; $p < 0.001$; Fig. 3O). It is important to note that all r values were greater than 0.500 except in the N1–N2 subgroups (Fig. 3, Table 1). These results demonstrate that CXCL7 is strongly correlated with LDH-A in CRC tissue.

3.5 Association between Survival Time and CXCL7 and LDH-A Expression

Patients were followed and OS was recorded. At the last follow-up, 80 CRC patients had died. To evaluate the predictive value of CXCL7 and LDH-A in CRC prognosis, Kaplan–Meier analysis and Cox regression methods were used. The median OS was 67.00 months (95% CI: 61.60–72.40), and the 5-year survival rate was 68.50% (Fig. 4D, Table 3). The 5-year OS rate was significantly lower in the CXCL7 high-expression group than in the low-expression group. Similarly, patients with high LDH-A expression had worse outcomes than did the low LDH-A expression group. We conducted a series of univariate analyses to evaluate the prognostic value of various risk factors in CRC. Kaplan–Meier survival curves showed that OS was positively related to T stage (T3–T4 *vs*. T1–T2; HR: 1.963, 95% CI: 1.191–3.237; $p = 0.007$; Fig. 4J), N stage (N1–N2 *vs*. N0; HR: 3.567, 95% CI: 2.075–6.134; $p < 0.001$; Fig. 4K), M stage (M1 *vs*. M0; HR: 3.609, 95% CI: 1.944–6.698; $p < 0.001$; Fig. 4L), TNM stage (III–IV *vs*. I–II; HR: 4.341, 95% CI: 2.517–7.485; $p < 0.001$; Fig. 4M), CXCL7 expression (high *vs*. low; HR: 2.407, 95% CI: 1.466–3.953; $p = 0.001$; Fig. 4A), LDH-A expression (high *vs*. low; HR:1.953, 95% CI: 1.231–3.100; $p = 0.005$; Fig. 4B), and CXCL7 and LDH-A expression (CXCL7 high +VEGF high *vs*. CXCL7 low +VEGF low; HR: 2.529, 95% CI: 1.484–4.310; $p < 0.001$; Fig. 4C). No statistical differences were found in other terms (Fig. 4E-I and 4N-P). Next, multivariate Cox regression analysis was used to further investigate the effects of CXCL7 and LDH-A in CRC; the data revealed that OS was influenced by M stage (HR: 3.128; 95% CI: 1.746–5.605; $p = 0.003$), TNM stage (HR: 2.746; 95% CI: 1.424–5.279; $p < 0.001$), and CXCL7 level (HR: 2.066; 95% CI: 1.223–3.490; $p = 0.007$), which illustrated that CXCL7 level was an independent risk factor in CRC patients. The results are shown in Table 3 and in the Forest plots in Fig. 5A (univariate analysis) and B (multivariate analysis).

3.6 Construction and Evaluation of Nomograms in CRC Patients

A nomogram and calibration curve were constructed using the prognostic factors from the univariate analysis, including T stage, N stage, M stage, TNM stage, CXCL7 expression, and LDH-A expression, to evaluate the ability of these risk factors to predict prognosis in CRC. The score range of CXCL7 was calculated to be from about 0 to 2.2 in the nomogram, which was consistent with the results of the univariate Cox regression (Fig. 6A, Table 3). The area under the ROC curve (AUC) was 0.799 (95% CI:0.721–0.877; Fig. 6B), which showed that the nomogram was a good model in this study. The concordance index was 0.735 (95% CI: 0.551–0.919; $p < 0.001$). Moreover, the calibration curve was close to the ideal line, meaning that the nomogram was a suitable model (Fig. 6C). In sum, the nomogram could be used as a model for assessing long-term OS in CRC patients.

4. Discussion

CRC is one of the most common lethal tumors of the digestive system and represents a serious threat to hu-

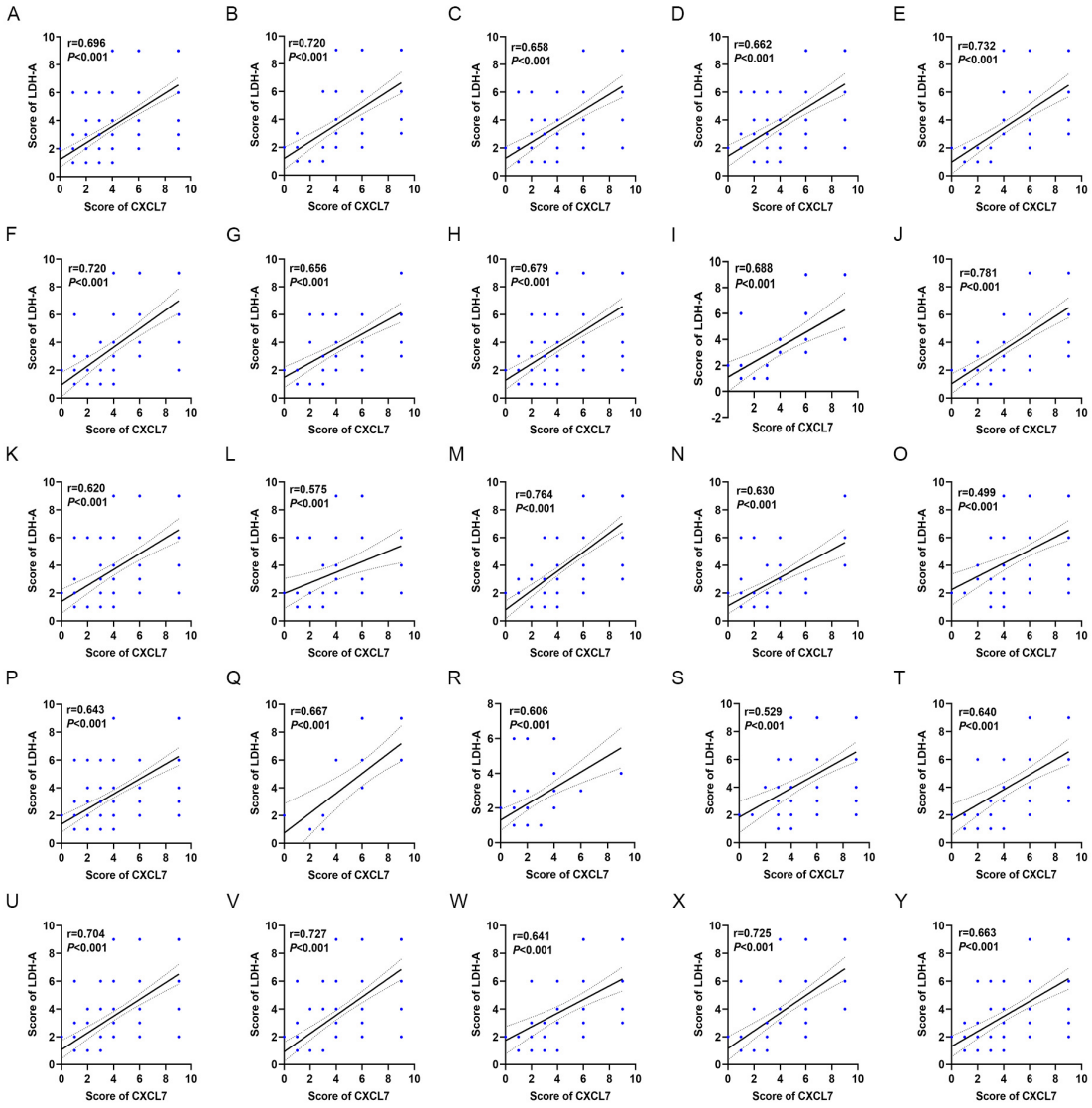


Fig. 3. Scatter plot of CXCL7 and LDH-A in CRC patients. (A) All CRC patients (n = 158). (B) Male patients (n = 86). (C) Female patients (n = 72). (D) Patients aged ≤60 years (n = 87). (E) Patients aged >60 years (n = 71). (F) Colon cancer patients (n = 75). (G) Rectum cancer patients (n = 83). (H) Patients with left tumor location (n = 124). (I) Patients with right tumor location (n = 34). (J) Patients with tumor size <4 cm (n = 69). (K) Patients with tumor size ≥4 cm (n = 89). (L) Stage T1–T2 patients (n = 49). (M) Stage T3–T4 patients (n = 109). (N) Stage N0 patients (n = 74). (O) Stage N1–N2 patients (n = 84). (P) Stage M0 patients (n = 125). (Q) Stage M1 patients (n = 23). (R) TNM stage I–II patients (n = 67). (S) TNM stage III–IV patients (n = 91). (T) Patients without neural invasion (n = 104). (U) Patients with neural invasion (n = 54). (V) Patients without vascular invasion (n = 99). (W) Patients with vascular invasion (n = 59). (X) Patients with well differentiated tumors (n = 77). (Y) Patients with moderately or poorly differentiated tumors (n = 81). Analyses were tested by non-parametric Spearman's test.

man health and a heavy burden on families and society. The morbidity and mortality of CRC are increasing year by year, and in recent years, its incidence has been increasing in developing countries, especially in China [30]. Early accurate diagnosis is extremely important for CRC patients. Clinically, a diagnosis is based on the patient's symptoms and signs and the results of auxiliary examinations [31]; however, early symptoms are often not obvious or representative, which may easily lead to missed diagnosis [32]. Laboratory examinations, such as conventional CEA, can facilitate patient screening to some extent [33]. Computed tomography, ultrasonography, and magnetic resonance imaging are all helpful for early diagnosis [34–36]. However, these methods and the diagnostic gold standard, tissue biopsy, have certain limitations. Appropriate treatments should be selected according to the clinical diagnosis of CRC patients. These treatments, which include surgery, neoadjuvant therapy, adjuvant therapy, targeted therapy, and comprehensive treatment [37], can extend patients' survival time and improve postoperative quality of life. Re-

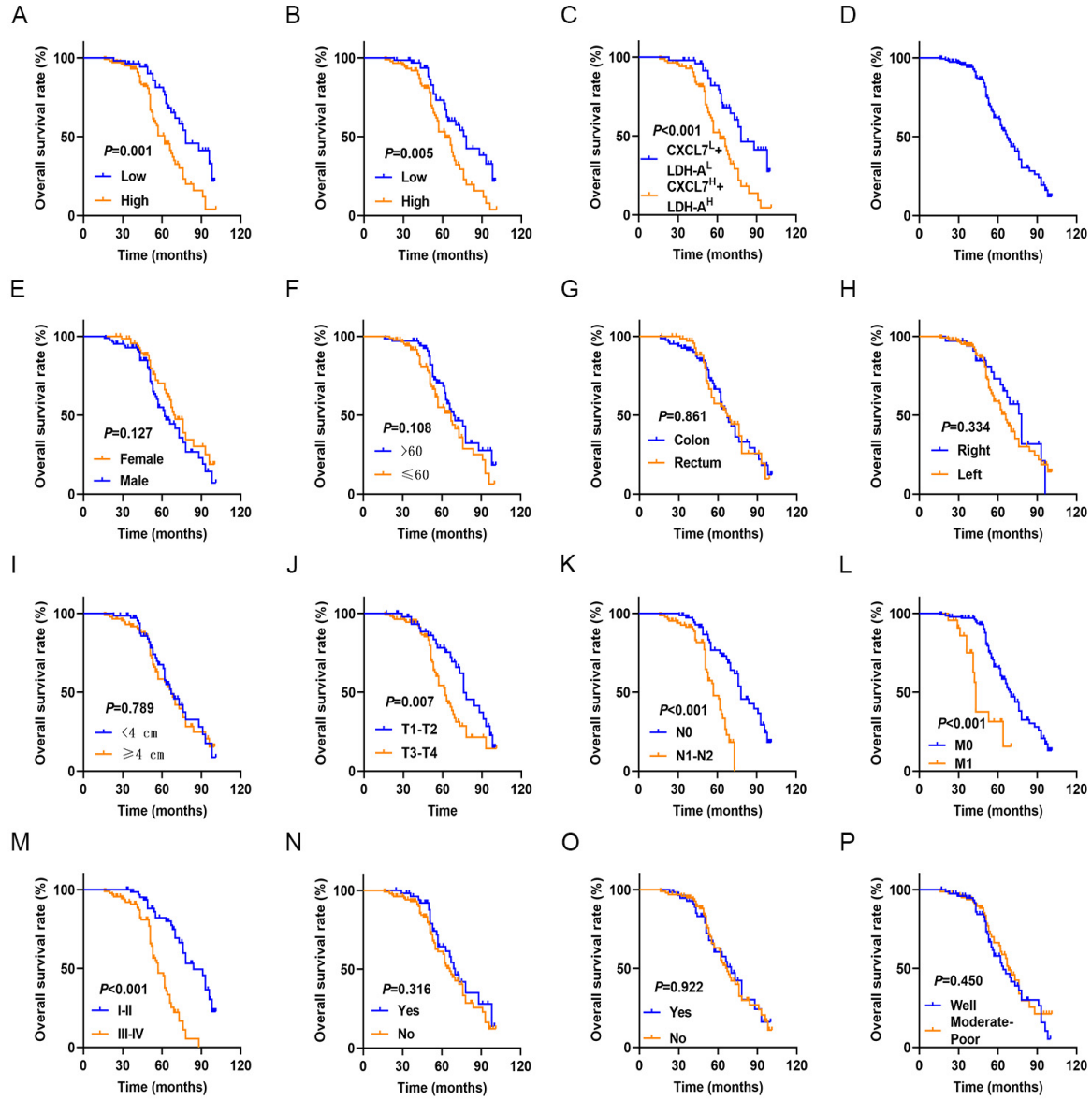
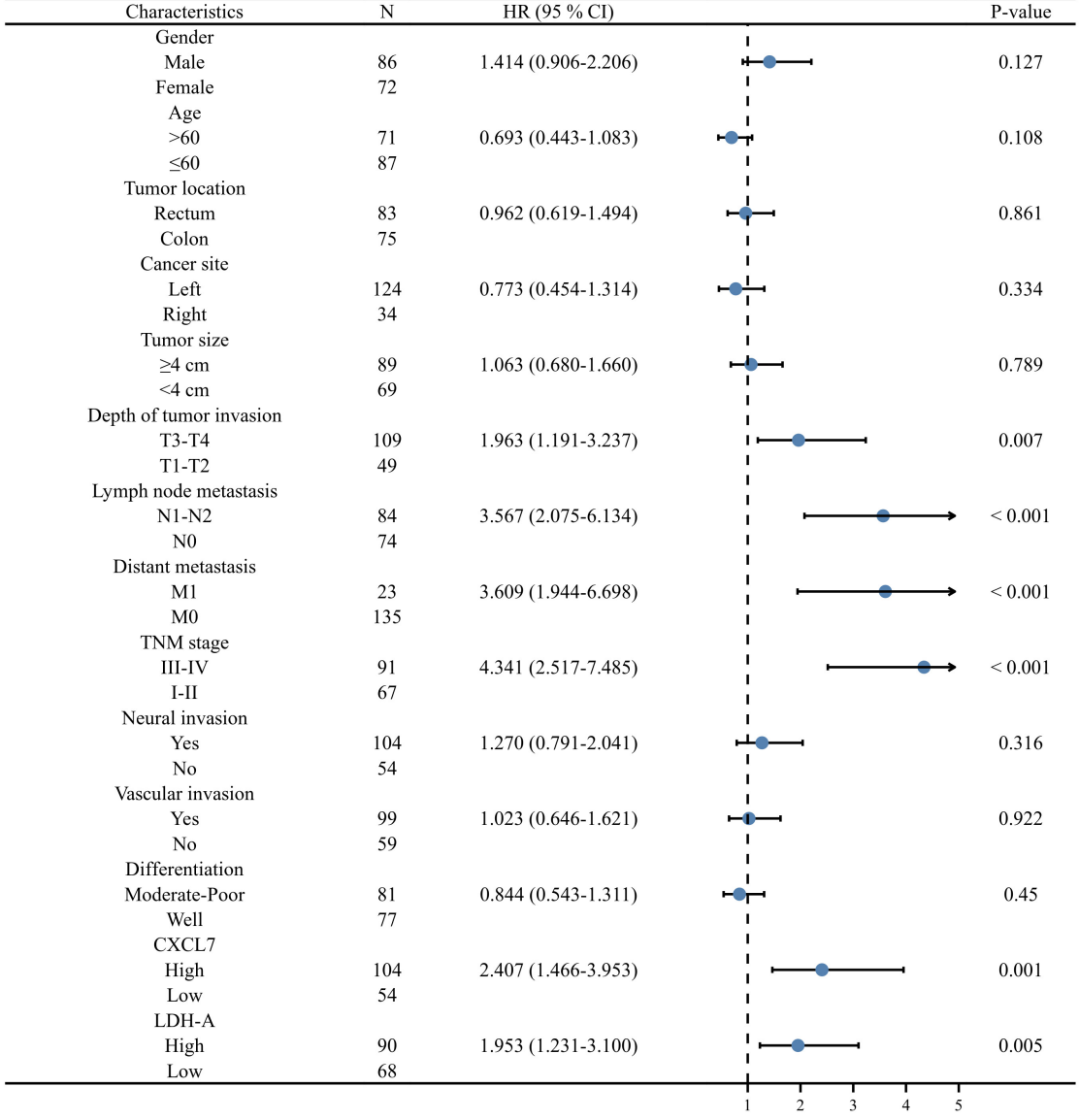


Fig. 4. High CXCL7 and LDH-A expression were correlated with worse outcomes in CRC patients. (A) OS rates according to CXCL7 expression (high [$CXCL7^H$] *vs.* low [$CXCL7^L$]; $p = 0.001$). (B) OS rates according to LDH-A expression (high [$LDH\text{-}A^H$] *vs.* low [$LDH\text{-}A^L$]; $p = 0.005$). (C) OS rates according to CXCL7 and LDH-A expression ($CXCL7^H$ + $VEGF^H$ *vs.* $CXCL7^L$ + $VEGF^L$; $p < 0.001$). (D) OS rates in 158 CRC patients. (E) OS rates according to sex (male *vs.* female; $p = 0.127$). (F) OS rates according to age (>60 *vs.* ≤60; $p = 0.108$). (G) OS rates according to tumor location (rectum *vs.* colon; $p = 0.861$). (H) OS rates according to cancer site (left *vs.* right; $p = 0.334$). (I) OS rates according to tumor size (≥4 cm *vs.* <4 cm; $p = 0.789$). (J) OS rates according to T stage (T3–T4 *vs.* T1–T2; $p = 0.007$). (K) OS rates according to N stage (N1–N2 *vs.* N0; $p < 0.001$). (L) OS rates according to M stage (M1 *vs.* M0; $p < 0.001$). (M) OS rates according to TNM stage (III–IV *vs.* I–II, $p < 0.001$). (N) OS rates according to neural invasion (yes *vs.* no; $p = 0.316$). (O) OS rates according to vascular invasion (yes *vs.* no; $p = 0.922$). (P) OS rates according to differentiation (moderate-poor *vs.* well; $p = 0.450$). OS, overall survival.

currence and metastasis are the most important causes of cancer-related deaths. Numerous oncogenes, tumor suppressor genes, cytokines, and chemokines have been shown to play important roles in the processes of recurrence and metastasis [8,13,20,23]. Previous studies have shown that glycolysis plays critical parts in tumor progression, especially in recurrence and metastasis [24,38]. Although many molecules and pathways are involved in the regulation of glycolysis in CRC [39,40], the association between CXCL7 and glycolysis has not yet been well explored. Therefore, the present study evaluated the relationship between CXCL7 and glycolysis, and the prognostic value of CXCL7 level in CRC.

A

Characteristics	N	HR (95 % CI)	P-value
Gender			
Male	86	1.414 (0.906-2.206)	0.127
Female	72		
Age			
>60	71	0.693 (0.443-1.083)	0.108
≤60	87		
Tumor location			
Rectum	83	0.962 (0.619-1.494)	0.861
Colon	75		
Cancer site			
Left	124	0.773 (0.454-1.314)	0.334
Right	34		
Tumor size			
≥4 cm	89	1.063 (0.680-1.660)	0.789
<4 cm	69		
Depth of tumor invasion			
T3-T4	109	1.963 (1.191-3.237)	0.007
T1-T2	49		
Lymph node metastasis			
N1-N2	84	3.567 (2.075-6.134)	< 0.001
N0	74		
Distant metastasis			
M1	23	3.609 (1.944-6.698)	< 0.001
M0	135		
TNM stage			
III-IV	91	4.341 (2.517-7.485)	< 0.001
I-II	67		
Neural invasion			
Yes	104	1.270 (0.791-2.041)	0.316
No	54		
Vascular invasion			
Yes	99	1.023 (0.646-1.621)	0.922
No	59		
Differentiation			
Moderate-Poor	81	0.844 (0.543-1.311)	0.45
Well	77		
CXCL7			
High	104	2.407 (1.466-3.953)	0.001
Low	54		
LDH-A			
High	90	1.953 (1.231-3.100)	0.005
Low	68		



B

Characteristics	N	HR (95 % CI)	P-value
Depth of tumor invasion			
T3-T4	109	1.548 (0.923-2.594)	0.097
T1-T2	49		
Lymph node metastasis			
N1-N2	84	0.842 (0.384-1.848)	0.668
N0	74		
Distant metastasis			
M1	23	3.128 (1.746-5.605)	0.003
M0	135		
TNM stage			
III-IV	91	2.746 (1.424-5.279)	< 0.001
I-II	67		
CXCL7			
High	104	2.066 (1.223-3.490)	0.007
Low	54		
LDH-A			
High	90	0.958 (0.452-2.031)	0.91
Low	68		

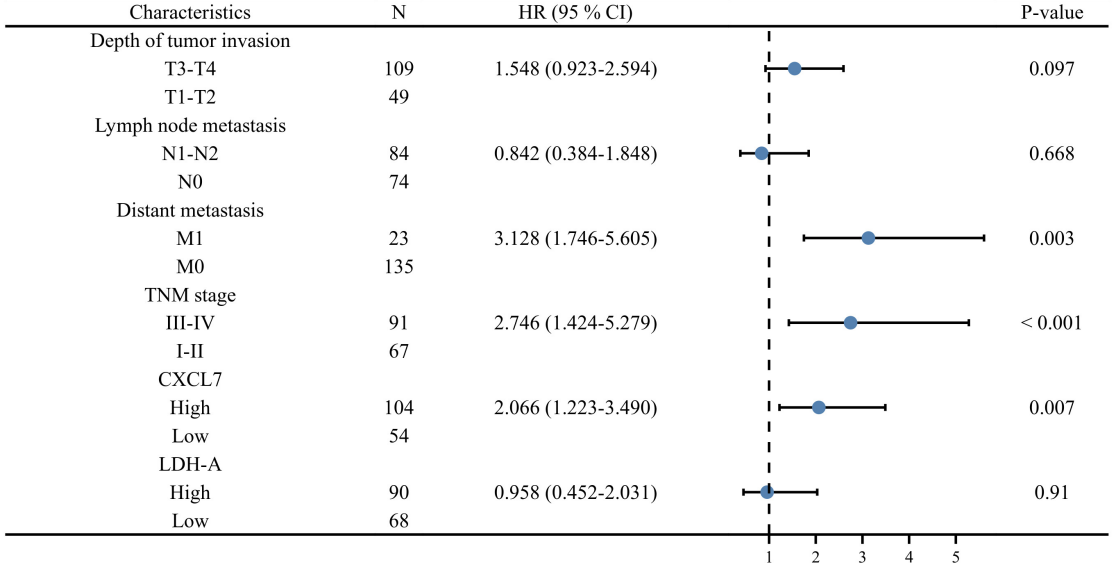


Fig. 5. Forest plots for Cox regression model in CRC patients. (A) Univariate survival analyses. (B) Multivariate survival analyses.

Table 3. Cox proportional hazards regression analysis for patients with CRC.

Clinicopathologic parameters		Median of OS (95% CI)	5-year OS (%)	Univariate analysis		Multivariate analysis	
				HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Total		67.00 (61.60–72.40)	68.50				
Gender	Male	62.08 (51.70–72.45)	65.20	1.414 (0.906–2.206)	0.127		
	Female	69.00 (62.24–75.76)	72.10				
Age	≤60	67.00 (56.01–77.99)	66.60	0.693 (0.443–1.083)	0.108		
	>60	69.00 (57.03–80.97)	70.70				
Tumor location	Colon	67.00 (57.71–76.29)	66.60	0.962 (0.619–1.494)	0.861		
	Rectum	67.00 (59.83–74.17)	72.00				
Cancer site	Left	66.00 (60.99–71.00)	67.20	0.773 (0.454–1.314)	0.334		
	Right	78.00 (70.45–85.55)	69.50				
Tumor size	<4 cm	67.00 (56.22–77.78)	74.00	1.063 (0.680–1.660)	0.789		
	≥4 cm	67.00 (60.51–73.49)	66.10				
Depth of tumor invasion	T1–T2	76.00 (66.38–85.63)	75.40	1.963 (1.191–3.237)	0.007	1.548 (0.923–2.594)	0.097
	T3–T4	62.00 (55.61–68.39)	64.00				
Lymph node metastasis	N0	78.00 (69.56–86.44)	72.80	3.567 (2.075–6.134)	<0.001	0.842 (0.384–1.848)	0.668
	N1–N2	59.92 (50.61–62.23)	64.40				
Distant metastasis	M0	69.00 (62.58–75.47)	71.50	3.609 (1.944–6.698)	<0.001	3.128 (1.746–5.605)	0.003
	M1	42.93 (41.17–44.70)	62.60				
TNM stage	I–II	84.00 (72.08–75.92)	79.80	4.341 (2.517–7.485)	<0.001	2.746 (1.424–5.279)	<0.001
	III–IV	56.92 (49.37–64.47)	65.80				
Neural invasion	No	69.00 (61.70–76.30)	69.40	1.270 (0.791–2.041)	0.316		
	Yes	66.00 (60.19–71.81)	68.10				
Vascular invasion	No	70.00 (59.72–80.28)	72.40	1.023 (0.646–1.621)	0.922		
	Yes	66.00 (58.76–73.24)	64.40				
Differentiation	Well	64.00 (56.01–71.99)	65.20	0.844 (0.543–1.311)	0.450		
	Moderate–Poor	68.00 (61.11–74.89)	70.10				
CXCL7	Low	78.00 (62.54–93.47)	73.50	2.407 (1.466–3.953)	0.001	2.066 (1.223–3.490)	0.007
	High	62.00 (54.31–9.69)	66.90				
LDH-A	Low	76.00 (67.63–84.37)	71.10	1.953 (1.231–3.100)	0.005	0.958 (0.452–2.031)	0.910
	High	62.18 (52.72–71.64)	68.30				
CXCL7 high + VEGF high		62.00 (54.37–69.63)	65.10	2.529 (1.484–4.310)	<0.001		
CXCL7 low + VEGF low		78.00 (62.44–93.56)	76.90				

Chemokines are gradually being recognized as important agents in tumor progression, with regulatory roles in tumor activity in addition to the traditional chemotaxis [14–16]. They function in both anti-cancer and cancer-promoting processes and can regulate proliferation, metastasis, communication between cells, and other activities of cancer cells [14,41,42]. In the present study, the results, which were similar to those of our previous study [20], showed that CXCL7 levels are higher in CRC tissue than in non-CRC tissue, and overexpression of CXCL7 was positively linked to N stage and TNM stage, as well as to worse outcomes for CRC patients. What is more important is that CXCL7 level was shown to be an independent risk factor in CRC prognosis by Cox regression analysis. Comprehensively, analysis of the results of this study, and of our previous study [20], demonstrate that increased levels of CXCL7 may be a good prognostic marker in CRC.

Cells require glycolysis for survival under hypoxic conditions and in certain physiological or pathological circumstances [43]. In the 1920s, Otto Warburg found significantly higher levels of glycolysis in tumor cells than in normal cells. Even under aerobic conditions, tumor cells tend to maintain high levels of glycolysis, whereas the glycolytic pathway is often inhibited in normal cells [44]. Several studies have identified glycolysis as a mediator of tumorigenesis in different types of tumors, and high levels of glycolysis are associated with a poor prognosis for patients [43,45]. Various molecules, substances, and metabolic pathways are involved in the process of glycolysis. Notably, LDH-A is a catalytic enzyme that is highly expressed in a variety of tumor cell types and is associated with prognosis [21,25–27,46]. In the present study, we found that LDH-A was significantly more highly expressed in CRC tumor cells than in normal cells, and that this high

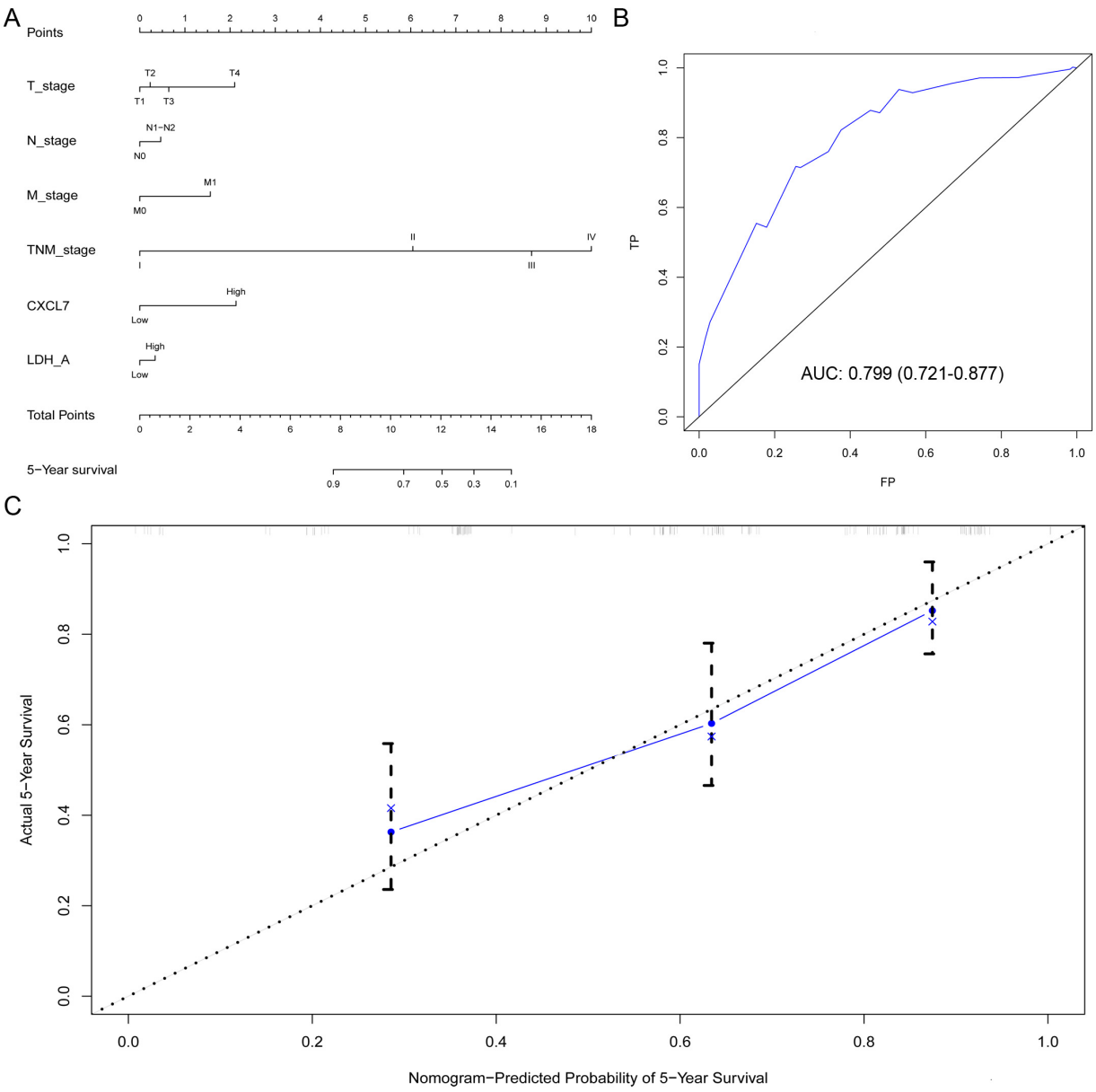


Fig. 6. Nomogram to predict the status of CRC patients by stratification of risk factors. (A) Nomogram prognostic models in CRC patients. (B) Area under the ROC curve. (C) Calibration curve. ROC, receiver operating characteristic.

level of expression was associated with poor survival time of CRC patients. These results were consistent with those of previous studies [46,47].

Numerous chemokine receptors and ligand networks play crucial roles in the occurrence and development of tumors, especially in CRC [42,48]. Our previous studies showed that CXCL7 was highly expressed in the serum of CRC patients [49,50]. In addition, several noteworthy studies have revealed a relationship between chemokines and glycolysis [51,52]. Therefore, the function of CXCL7 in glycolysis was explored in the present study using CRC tissue. First, LDH-A was selected as a biomarker of aerobic glycolysis owing to its vital roles in the catalytic process of glycolysis [52]. Then, the expression of CXCL7 and LDH-A was investigated by IHC staining, and a positive correlation was found between CXCL7 and LDH-A expression. Next, Cox regression analysis revealed that CXCL7 and LDH-A levels were correlated with OS according to univariate analysis. However, in the multivariate analysis, although CXCL7 level was still correlated with OS, LDH-A level was not found to be an independent risk factor. In view of the fact that receptors of CXCL7, CXCR1, and CXCR2 are important for tumor progression [53,54], we speculate that there may exist a receptor-dependent process related to the prognostic value in the relationship between CXCL7 and LDH-A. Last, a nomogram was constructed and evaluated; the results showed that CXCL7 is an independent risk factor in CRC. In addition, in view of the high ROC curve of CXCL7 and LDH-A, multiple-biomarker dependent logistic regression model may have high value in clinical ap-

plications. In view of these results, we assume that CXCL7 may act on glycolysis by altering levels of LDH-A in CRC; this is consistent with the findings of several studies that the process of glycolysis in cancers may be promoted by chemokines [53–55].

Surgical methods, postoperative treatments, nursing methods, patient's mental state, and other factors can all affect prognosis [56–59], therefore these general factors will be included in our future study. The reason that the combination of high levels of LDH-A and CXCL7 did not increase the median OS, compared to CXCL7 alone, should be also explored. The numbers of CRC patients enrolled in future studies should be increased to better identify the connection between CXCL7 and LHD-A, and the correlation of CXCL7 score and LDH-A score may involve certain confounding factors, which should be thoroughly studied in future. In addition, future studies might include different methods of measuring the expression of CXCL7 and LHD-A (e.g., Western blot) to ensure the stability of results, and the decimal scale of scoring could be narrowed to 0.1. It is important that the mechanism by which CXCL7 affects glycolysis should be further explored by constructing cell and animal models. Further clarification is needed on the specific forms of regulation between CXCL7 and LDH-A. In future, series studies will be designed to determine whether targeting CXCL7 and LDHA expression proves to be beneficial in treating CRC patients.

5. Conclusion

In summary, this study offers firm evidence that CXCL7 expression is positively correlated with LDH-A expression, and that CXCL7 level is an independent risk factor in CRC prognosis.

Abbreviations

CRC, colorectal cancer; LDH, lactate dehydrogenase; LDH-A, lactate dehydrogenase A; IHC, immunohistochemistry; TNM, tumor-node-metastasis; ROC, receiver operating characteristic; OS, overall survival time; HR: high risk factor; 95% CI, 95% confident intervals; T, depth of tumor invasion; N, nodal involvement; M, distant metastasis; r, correlation coefficient; AUC, area under the ROC curve.

Availability of Data and Materials

All data are available from the authors for reasonable purposes.

Author Contributions

HL, Conceptualization, Funding acquisition and Writing-review & editing; LL, Conceptualization, Formal analysis, Methodology, Supervision and Writing-review & editing; BH, Funding acquisition, Data curation, Investigation and Project administration; RJ, Software, Supervision and Writing-original draft; GC, Resources and Visualization; JA, Formal analysis and Validation; SH, Conceptualization, Formal analysis and Funding acquisition. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The CRC samples were obtained with informed consent from patients and approved by the Institutional Research Ethics Committee of Bozhou Hospital of Anhui Medical University (No.202298).

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Conflict of Interest

The authors declare no conflict of interest.

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