

Research Paper

Elevated baseline serum lactate dehydrogenase indicates a poor prognosis in primary duodenum adenocarcinoma patients

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Abstract

Purpose: Tumour cells produce energy through glycolysis and lactate dehydrogenase (LDH) is a key part of glycolysis. Elevation of serum LDH may indicate poor prognosis in primary duodenum adenocarcinoma. We aim to explore the prognostic significance of LDH in this disease.

Methods and materials: Two hundred forty-four patients diagnosed with primary duodenum adenocarcinoma who were treated at the Sun Yat-sen Cancer Center from February 1996 to January 2016 were retrospectively analysed. We collected routine clinical data, including baseline LDH. Patients were classified into a normal LDH group (≤ 245 U/L) and higher LDH group (>245 U/L). Correlations of the LDH level and other clinicopathological characteristics were explored using the Chi-square test. Prognostic factors for overall survival were identified using univariate and multivariate analyses.

Results: Two hundred seven patients (84.9%) had normal LDH levels, while 37 patients (15.1%) had abnormally high LDH levels. Higher LDH levels were significantly associated with more distant metastasis, node metastasis, poor differentiation and TNM stage III-IV ($P<0.05$). Consistently, patients with node metastasis, poor differentiation and TNM stage III-IV had a significantly higher median LDH level ($P<0.05$). The median survival of patients in the higher LDH group was significantly shorter than that of the patients in the normal LDH group (16.3 m vs. 42.5 m, $P=0.02$). Using multivariate analysis, LDH, age and radical surgery were independent prognostic factors associated with overall survival (OS) (HR=1.571, $P=0.036$ for LDH; HR=1.514, $P=0.013$ for age; HR=0.248, $P<0.0001$ for radical surgery, respectively).

Conclusions: For the first time, our research suggests that baseline serum LDH is an independent prognostic factor in primary duodenum adenocarcinoma patients and elevated baseline serum LDH indicates a poor prognosis.

Key words: lactate dehydrogenase; primary duodenum adenocarcinoma; prognosis; serum biomarker

Background

Primary duodenum adenocarcinoma is a rare tumour with a very low estimated incidence rate ($<0.5/100,000$) [1-2]. It makes up approximately half

of small bowel cancers and approximately 1% of all gastrointestinal cancers [3]. Due to a lack of specific duodenal adenocarcinoma symptoms, a portion of

patients are diagnosed at the metastatic stage [4]. The median overall survival (OS) of metastatic duodenum adenocarcinoma, ranging from 2 to 8 months, is much worse than advanced colorectal cancer [4]. Various studies have attempted to evaluate different prognostic factors for primary duodenum adenocarcinoma, and some studies have identified the T stage, nodal metastasis, pathologic grade, lymphovascular invasion, age, weight loss and perineural invasion as prognostic factors [5-12]. Due to the rare incidence, the number of patients in previous studies was relatively small, with a range from 17 to 178 patients [5-12]. However, none of these studies identified any prognostic serum biomarker.

The metabolism of tumour cells has its own characteristics. To coincide with the rapid development of the tumour, tumour cells produce energy through glycolysis. We call this the Warburg effect. This alternation of cancer cell metabolism is believed to be a main change in neoplastic transformation [13]. The hypoxic microenvironment is another feature of malignant tumours. In conditions of hypoxia, lactate dehydrogenase (LDH) can convert pyruvate to lactate to support tumour cells. Hypoxia inducible factor 1 α (HIF-1 α) can transcriptionally upregulate LDH in tumour cells to ensure anaerobic glycolysis and produce enough lactate [14]. High levels of lactate can in turn promote higher expression of HIF-1 α . Thus, HIF-1 α and LDH interact and strengthen each other [14]. Furthermore, higher LDH is significantly correlated with increased vascular density and decreased infiltration of lymphocytes within the tumours. Therefore, the increased LDH level reflects these alterations and suggests more severe tumour burden, tumour angiogenesis and tumour progression conditions, all of which lead to the poor prognosis of malignant tumours [15].

Elevated serum LDH has been confirmed as a poor prognostic factor in many types of malignancies, such as renal cell cancer, nasopharyngeal carcinoma, pancreatic cancer, lymphoma, breast cancer, prostate cancer, colorectal cancer, lung cancer and oesophageal squamous cell carcinoma [16-24]. Some researchers even incorporated LDH into the prognostic scores [19, 24]. The serum LDH level is routinely tested in daily clinical practice, which is economical and convenient to perform. It is worthwhile for us to explore the prognostic significance of the serum LDH level in patients with primary duodenum adenocarcinoma.

For the first time, this research investigates the prognostic significance of serum LDH level in a large cohort of 244 patients with primary duodenum adenocarcinoma. The relationship between LDH and other clinical factors was also explored in the current study.

Methods

Patient selection and evaluation

We studied electronic medical records of primary duodenum adenocarcinoma patients hospitalized in Sun Yat-sen Cancer Center from February 1996 to January 2016. Written informed consent was provided by all patients included in our study. The ethics committees of Sun Yat-sen Cancer Center approved our study. We conducted this study and observed the Helsinki declaration.

We included patients who were diagnosed as having primary duodenum adenocarcinoma by pathology. The exclusion criteria is as follows: (1) pathologically diagnosed with other types of tumours, such as gastrointestinal stromal tumour, neuroendocrine carcinoma and lymphoma; (2) patients with tumours of the distal common bile duct, pancreas or the ampulla of Vater; and (3) patients with incomplete clinicopathological factor information, with synchronous malignant tumours or patients who were lost to follow-up within three months. In total, 244 patients were enrolled in our study.

Data collection

At first diagnosis, we collected clinical data, including gender, age, abdominal pain, smoking history, family history of cancer, white blood cells (WBC), neutrophil, lymphocyte, monocyte, haemoglobin, platelet, albumin, LDH, TNM stage, pathological differentiation, endoscopy examination and imaging results. TNM stages were classified according to the 7th edition of the TNM staging system by the American Joint Committee on Cancer standards (AJCC). We measured the serum LDH after 2 months of therapy. We also included other prognostic factors, such as the platelet-lymphocyte ratio (PLR), lymphocyte-monocyte ratio (LMR), neutrophil-lymphocyte ratio (NLR), and prognostic nutritional index (PNI, $PNI = 5 \times \text{lymphocyte count} (10^9/L) + 10 \times \text{albumin} (g/dL)$). We regularly followed up patients by phone or using follow-up in the outpatient clinic. The last follow-up date was June 20th, 2017. The OS was the primary outcome and defined as the period from diagnosis to the date of death or to the date of the last follow-up.

Statistical analysis

We performed statistical analysis using SPSS (version 22.0; IBM Corp., Armonk, NY, USA), GraphPad Prism 6.0 (GraphPad Software Inc., La Jolla, CA, USA) and MedCalc software (version 11.4.20; MedCalc Software bvba, Acaciaaan, Belgium). We considered a two-tailed $P < 0.05$ as

statistical significance. Cut-off points for the LDH, WBC, haemoglobin and platelet levels were determined using the upper limit of the normal levels, while cut-off values of NLR, PLR, PNI, and LMR were established using the receiver operating characteristic (ROC) curve analysis. The optimal cut-off value had the maximum Youden index (sensitivity + specificity – 1). We compared differences in the categorical factors between the groups using the Chi-square test and Fisher's exact test. Median values between the different groups were compared using the Mann-Whitney test. In the univariate analyses, we estimated the survival difference of the distinct variables using the Kaplan–Meier method (log-rank test) and identified significant factors. We subsequently brought these factors into the Cox proportional hazards regression model in multivariate analysis to distinguish the independent prognostic factors.

Results

Patient characteristics

A total of 244 patients with primary duodenum adenocarcinoma were included in our study. Baseline demographics are shown in Table 1. The median age was 57 years old with an interquartile range (IQR) of 49-63 years old. One hundred fifty-four (63.1%) patients were male and 90 (36.9%) patients were female. Ninety-five (38.9%) patients presented with abdominal pain at the first diagnosis. Fifty-two (21.3%) patients were diagnosed with a metastatic tumour and 192 (78.7%) patients had a non-metastatic tumour. Thirty-seven (15.2%), 86 (35.2%) and 69 (28.3%) patients were diagnosed at stages I, II and III, respectively. One hundred sixty-four (67.2%) patients received radical surgery while 80 (32.8%) patients received palliative therapies, such as chemotherapy and radiotherapy. For all included patients, the 1-year, 2-year, 3-year and 5-year survival rates were 75.0%, 57.8%, 42.6% and 27.5%, respectively. For patients who received radical surgery, the 1-year, 2-year, 3-year and 5-year survival rates were 90.2%, 74.4%, 57.3% and 35.4%, respectively. Eventually, 207 (84.9%) patients were classified into the normal LDH (≤ 245 U/L) group, while 37 (15.1%) patients were in the higher LDH (>245 U/L) group.

The median baseline serum LDH levels were significantly higher in patients with node metastases than those without (188.5U/L vs. 171.5U/L, $P=0.01$). The same can be said for those with stage III-IV compared to those with stage I-II (190U/L vs. 171U/L, $P=0.009$), as well as those with poor differentiation compared to those with well & moderate differentiation (190U/L vs. 171U/L,

$P=0.018$) (Figure 1).

Table 1. Baseline demographics of 244 patients with primary duodenum adenocarcinoma.

Characteristic	No. of cases (%)
Age, years (median/IQR)	57 (49-63)
Gender	
Male	154 (63.1)
Female	90 (36.9)
Abdominal pain	
Yes	95 (38.9)
No	149 (61.1)
Smoking history	
Yes	56 (23.0)
No	188 (77.0)
Family history of cancer	
Yes	33 (13.5)
No	211 (86.5)
Laboratory parameters (median/ IQR)	
WBC ($\times 10^9/L$)	7.4 (5.6-10.4)
Neutrophil ($\times 10^9/L$)	5.1 (3.3-7.5)
Lymphocyte ($\times 10^9/L$)	1.4 (1.1-1.8)
Monocyte ($\times 10^9/L$)	0.5 (0.4-0.8)
Haemoglobin (g/L)	108 (95-123)
Platelet ($\times 10^9/L$)	259 (186-340)
Albumin (g/L)	38 (34.5-41.3)
LDH (U/L)	176 (153-216)
T category (AJCC 7th)	
T1	10 (4.1)
T2	61 (25.0)
T3	54 (22.1)
T4	119 (48.8)
N category (AJCC 7th)	
N0	128 (52.5)
N1	92 (37.7)
N2	24 (9.8)
M category (AJCC 7th)	
M0	192 (78.7)
M1	52 (21.3)
TNM (AJCC 7th)	
I	37 (15.2)
II	86 (35.2)
III	69 (28.3)
IV	52 (21.3)
Radical surgery	
Yes	164 (67.2)
No	80 (32.8)
1-year survival rate	183 (75.0)
2-year survival rate	141 (57.8)
3-year survival rate	104 (42.6)
5-year survival rate	67 (27.5)

IQR: Interquartile range; TNM: Tumour-node-metastasis; AJCC: American Joint Committee on Cancer; WBC: white blood cell; LDH: lactate dehydrogenase.

The association between LDH and clinicopathological factors

We classified all patients into a series of subgroups according to the cut-off values of the different clinicopathological factors and analysed the potential correlations between these factors and the serum LDH level. We found that higher LDH level (>245 U/L) was significantly associated with more distant metastasis, more node metastasis, poorer

differentiation, more advanced TNM stage(III-IV) and higher neutrophil to lymphocyte ratio (NLR)($P<0.05$). There was a statistical trend between the higher LDH level and older age (>57 years old) ($P=0.051$). We did not find other significant associations between the LDH and other clinicopathological factors listed in Table 2 so far.

Survival analysis

The median survival of all the patients was 31.3 months. At the end of our study, a total of 148 patients died of primary duodenum adenocarcinoma and 96 patients had survived. Median survival of the patients with a normal LDH level(≤ 245 U/L) was significantly longer than that of patients with a higher LDH level(>245 U/L) (42.5 m vs. 16.3 m, $P=0.02$). The 1-year, 2-year, 3-year and 5-year survival rates were 77.8%, 60.4%, 44.9% and 28.5%, respectively, for patients in the normal LDH group, while the rates were 59.5%, 43.2%, 29.7% and 21.6% for those in the higher LDH group, respectively. As shown in Table 3 and Figure 2, various factors, including age, node metastasis, distant metastasis, radical surgery, TNM stage, degree of differentiation, PNI and LDH were all significantly associated with OS($P<0.05$). However,

factors such as gender, T category (T1-2 vs. T3-4), NLR, PLR and LMR were not associated with survival in the current study ($P>0.05$). In the multivariate analysis, we brought all the significant variables determined by the univariate analyses into the Cox proportional hazards model. As the results showed, LDH, age and radical surgery were independent prognostic factors associated with the OS (HR=1.571, $P=0.036$ for LDH; HR=1.514, $P=0.013$ for age; HR=0.248, $P<0.0001$ for radical surgery, respectively).

Based on the serum LDH values before and after 2 months of radical or palliative treatment, we divided these patients into 4 groups: the low-low group($n=180$), low-high group($n=27$), high-low group($n=17$) and high-high group ($n=20$) (Table 4). The high-high group showed a similar OS with that of the low-high and high-low group (14.5 m vs 15.4 m vs 39.3 m, $P>0.05$), while the high-low group showed a similar OS with that of the low-low group (39.3 m vs 52.1 m, $P=0.592$). Patients with elevated LDH before or after 2 months of treatment (High-high/high-low/low-high group) showed a significantly shorter OS than that of the low-low group (15.9 m vs 52.1 m, $P=0.0003$) (Table 4 and Figure 3).

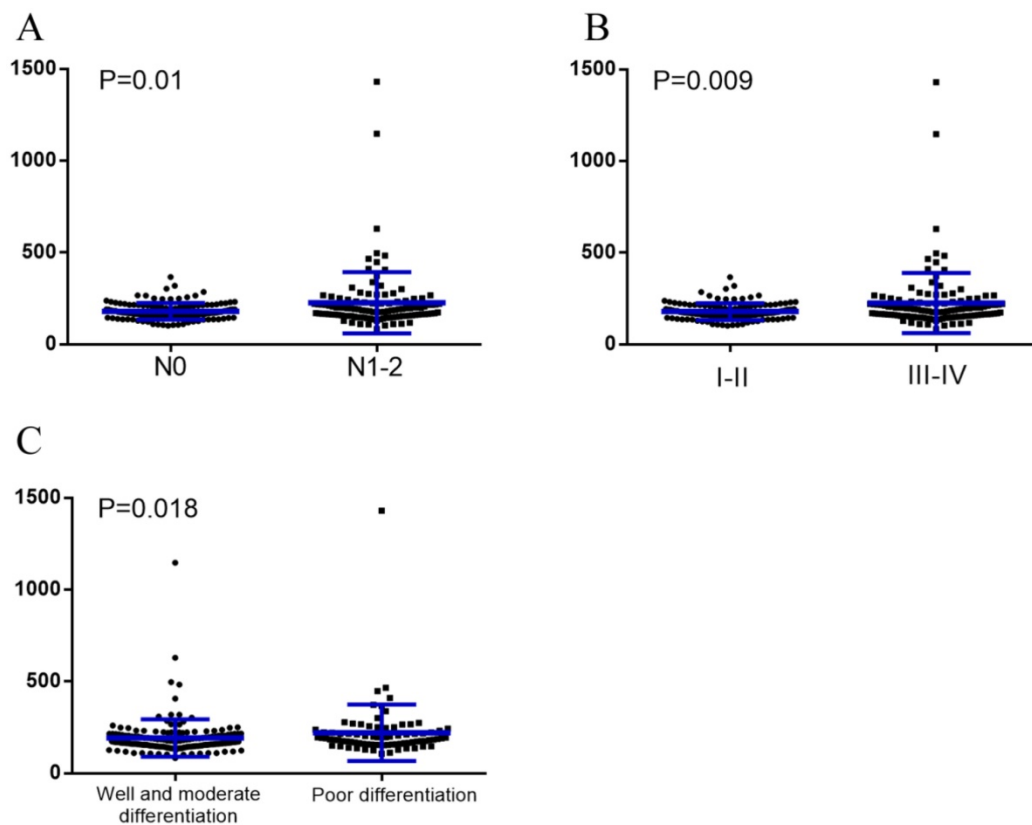


Figure 1. Baseline serum LDH levels were compared using the Mann-Whitney test in different subgroups. (A), Without node metastasis vs. with node metastasis; (B), TNM stage I - II vs. TNM stage III-IV; (C), Well and moderate differentiation vs. poor differentiation.

Table 2. Correlation analysis for clinicopathologic variables in the normal LDH group and higher LDH group among the 244 primary duodenum adenocarcinoma patients.

Variable	Normal LDH ≤ 245 U/L n (%)	High LDH > 245 U/L n (%)	P value
Total	207 (84.9)	37 (15.1)	
Age, years			0.051
> 57	92 (44.4)	23 (62.2)	
≤ 57	115 (55.6)	14 (37.8)	
Gender			0.584
male	129 (62.3)	25 (67.6)	
female	78 (37.7)	12 (32.4)	
WBC			0.315
> 10 * 10 ⁹ /L	53 (25.6)	13 (35.1)	
≤ 10 * 10 ⁹ /L	154 (74.4)	24 (64.9)	
Haemoglobin			0.695
> 120 g/L	58 (28.0)	9 (24.3)	
≤ 120 g/L	149 (72.0)	28 (75.7)	
Platelet			1
> 300 * 10 ⁹ /L	73 (35.3)	13 (35.1)	
≤ 300 * 10 ⁹ /L	134 (64.7)	24 (64.9)	
NLR			0.022
> 2.56	131 (63.3)	31 (83.8)	
≤ 2.56	76 (36.7)	6 (16.2)	
PLR			0.673
> 267.5	47 (22.7)	10 (27)	
≤ 267.5	160 (77.3)	27 (73)	
PNI			0.216
> 45.7	102 (49.3)	14 (37.8)	
≤ 45.7	105 (50.7)	23 (62.2)	
LMR			0.521
> 4.7	44 (21.3)	6 (16.2)	
≤ 4.7	163 (78.7)	31 (83.8)	
T category			0.239
1-2	57 (27.5)	14 (37.8)	
3-4	150 (72.5)	23 (62.2)	
N category			0.012
0	116 (56.0)	12 (32.4)	
1-2	91 (44.0)	25 (67.6)	
M category (M0/M1)			0.031
0	168 (81.2)	24 (64.9)	
1	39 (18.8)	13 (35.1)	
Degree of differentiation			0.037
Well and moderately differentiated	144 (69.6)	19 (51.4)	
Poorly differentiated	63 (30.4)	18 (48.6)	
TNM stage			0.007
I-II	112 (54.1)	11 (29.7)	
III-IV	95 (45.9)	26 (70.3)	

LDH: lactate dehydrogenase; TNM: Tumour-node-metastasis; WBC: white blood cell; PLR: platelet-lymphocyte ratio; LMR: lymphocyte-monocyte ratio; PNI: prognostic nutritional index; NLR: neutrophil-lymphocyte ratio.

Comparison of LA-TNM and TNM staging systems

To improve the prognostic value of the TNM staging system, we integrated age and LDH into this system. Age > 57 and LDH > 245U/L were assigned 1 point while age ≤ 57 and LDH ≤ 245U/L were assigned 0 points. Figure 4 A and B show the survival curves stratified by the TNM and LA-TNM staging system, respectively. The log-rank test showed that the P

values of these two staging systems were both less than 0.001. A staging system had a better performance when it had a higher χ^2 value and a lower Akaike information criterion(AIC) value in the likelihood ratio test (LRT). The LRT indicated that the χ^2 value of the LA-TNM system was significantly higher than that of the TNM system (38.49 vs. 29.29, $P < 0.001$). Moreover, the AIC value of the LA-TNM system was significantly lower than that of the TNM system (1437 vs. 1445.32, $P < 0.001$) (Table 5). Therefore, the LA-TNM system was superior to the TNM system in predicting the overall survival of this cohort of patients in our study.

Table 3. Univariate and multivariate analyses of the prognostic factors for the overall survival of 244 patients with primary duodenum adenocarcinoma.

Variable	Univariate		Multivariate				
	Log-rank χ^2	P value	B	SE	HR	95% CI	P value
Gender (male/female)	2.33	0.13					
Age, years (> 57/≤ 57)	12.09	0.0005*	0.415	0.167	1.514	1.093 to 2.096	0.013
T category (AJCC 7th) (T1/T2/T3/T4)	4.97	0.17					
N category (AJCC 7th)	12.06	0.0024*					
N0			NA	NA	1	Reference	NA
N1			0.230	0.540	1.258	0.4389 to 3.6083	0.670
N2			0.582	0.589	1.789	0.5671 to 5.6424	0.324
M category (AJCC 7th) (M0/M1)	61.61	< 0.0001*	0.206	0.305	1.228	0.6777 to 2.2256	0.500
Radical surgery (Yes/No)	82.54	< 0.0001*	-1.396	0.172	0.248	0.177 to 0.346	< 0.0001
TNM (AJCC 7th) (I-II/ III-IV)	14.94	0.0001*	-0.278	0.587	0.757	0.2411 to 2.3774	0.635
Degree of differentiation	7.40	0.02*					
Well differentiation			NA	NA	1	Reference	NA
Moderate differentiation			-0.168	0.263	0.846	0.5067 to 1.4114	0.523
Poor differentiation			0.142	0.284	1.153	0.6625 to 2.0070	0.616
NLR (> 2.56/≤ 2.56)	3.32	0.07					
PLR (> 267.5/≤ 267.5)	0.89	0.34					
PNI (> 45.7/≤ 45.7)	4.98	0.03*	0.023	0.179	1.023	0.7214 to 1.4505	0.899
LMR (> 4.7/≤ 4.7)	2.51	0.11					
LDH (> 245/≤ 245)	5.25	0.02*	0.452	0.216	1.571	1.032 to 2.393	0.036

*All variables have a P value less than 0.05. We entered all the variables with $P < 0.05$ into multivariate analyses. NA: not applicable; TNM: Tumour-node-metastasis; AJCC: American Joint Committee on Cancer; WBC: white blood cell; PLR: platelet-lymphocyte ratio; LMR: lymphocyte-monocyte ratio; PNI: prognostic nutritional index; LDH: lactate dehydrogenase; NLR: neutrophil-lymphocyte ratio.

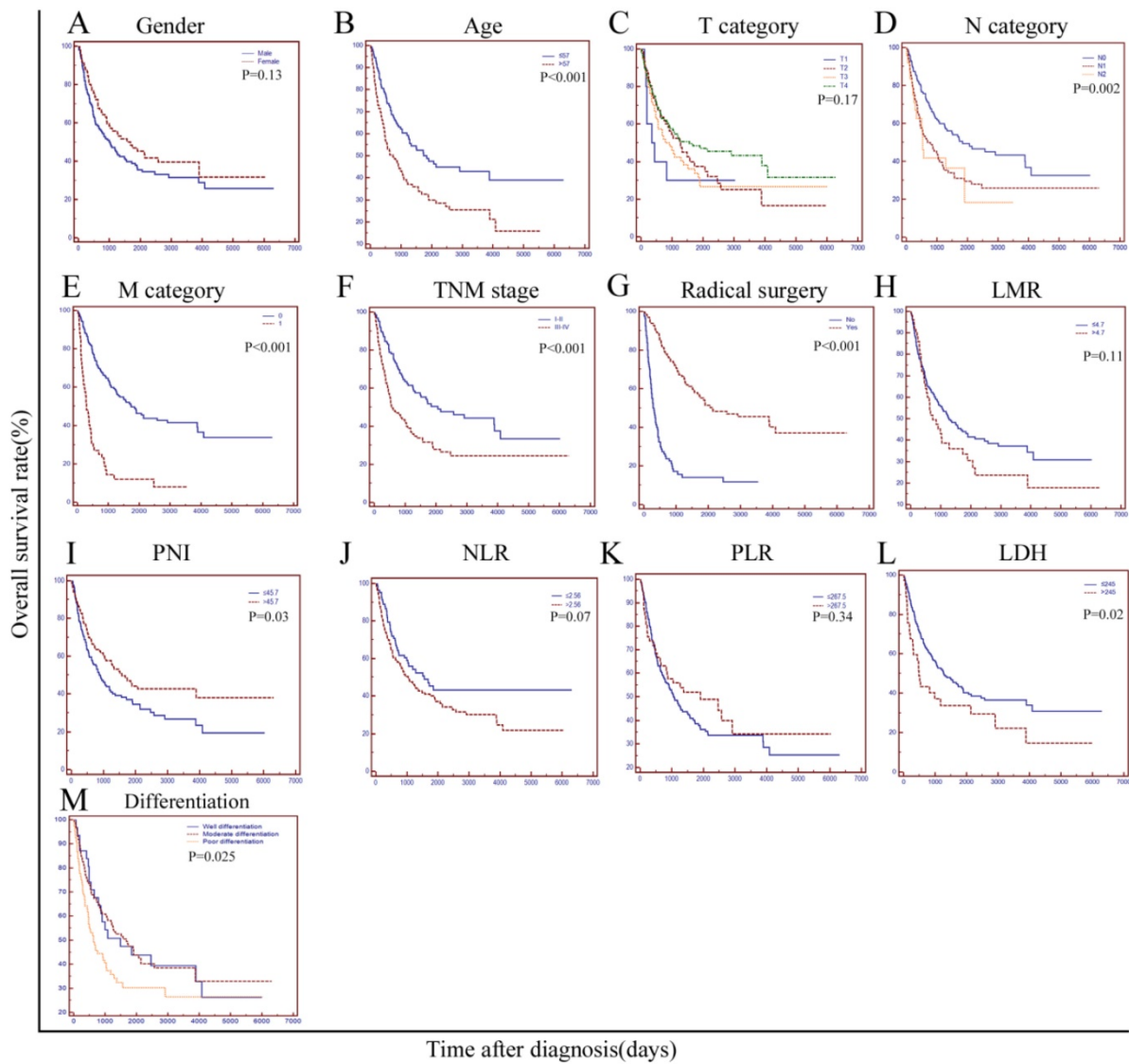


Figure 2. Kaplan-Meier curves stratified by different variables in 244 patients with duodenum adenocarcinoma. OS curves stratified by (A), gender; (B), age; (C), T category; (D), N category; (E), M category; (F), Simplified TNM stage (I - II vs. III-IV); (G), radical surgery; (H), LMR; (I), PNI; (J), NLR; (K), PLR; (L), LDH, and (M), Degree of pathological differentiation. TNM: tumour-node-metastasis; LMR: lymphocyte-monocyte ratio; PNI: the prognostic nutritional index; NLR: the neutrophil-lymphocyte ratio; PLR: the platelet-lymphocyte ratio; LDH: lactate dehydrogenase.

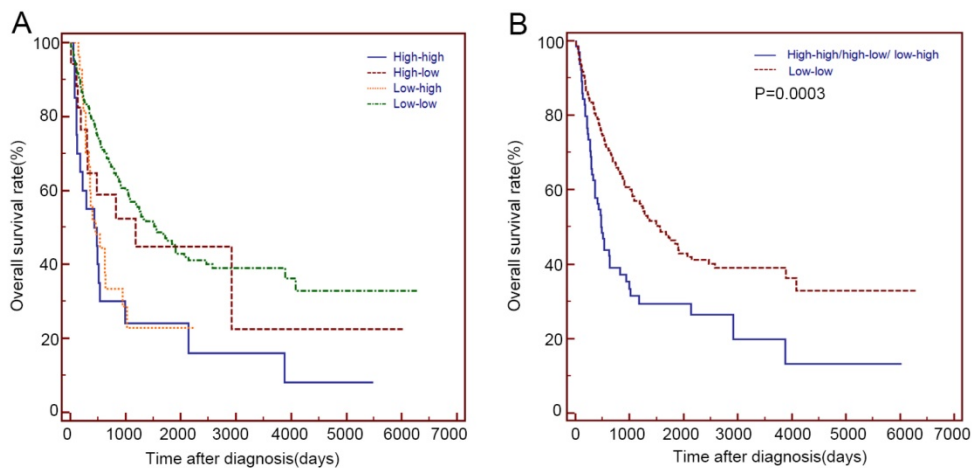


Figure 3. Kaplan-Meier curves for the OS of 244 patients with primary duodenum adenocarcinoma, which were stratified by the values of serum LDH before and after 2 months of radical or palliative treatments. (A) low-low group, low-high group, high-low group and high-high group (B) low-low group and High-high/high-low/low-high group.

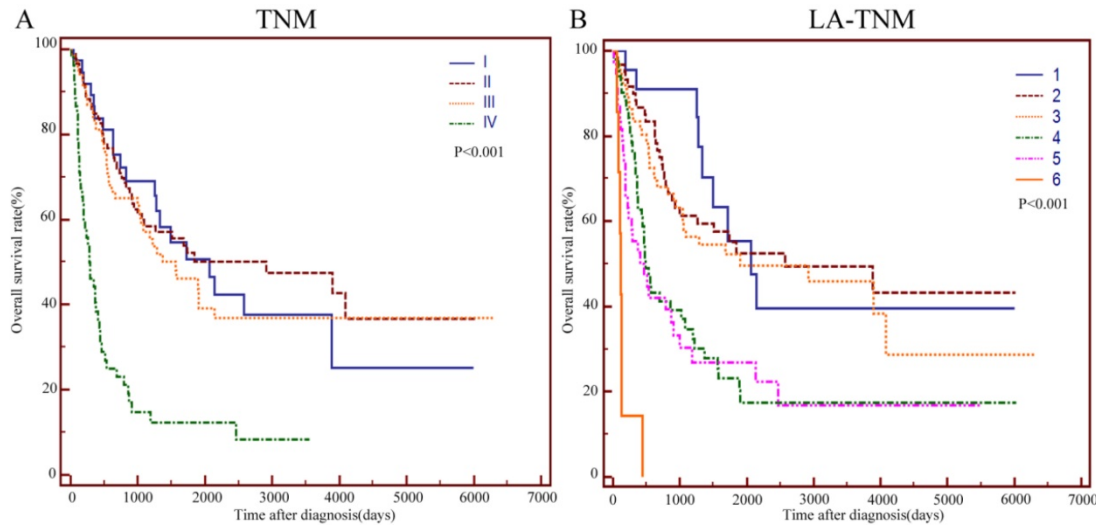


Figure 4. Kaplan-Meier curves for the OS of 244 patients with primary duodenum adenocarcinoma, which were stratified by TNM (A), and LA-TNM (B). TNM: Tumour-node-metastasis; LA: LDH-Age.

Table 4. Overall survival of the different groups based on serum LDH before and after treatment among the 244 primary duodenum adenocarcinoma patients in the present study.

Serum LDH	Median overall survival(months)	95% CI	p value
High-high(n=20)	14.5	1.1-27.9	
High-low(n=17)	39.3	0-80.6	Vs. high-high: 0.116 Vs. low-low: 0.592
Low-high(n=27)	15.4	6-24.8	Vs. high-high: 0.499
Low-low(n=180)	52.1	36.7-67.6	Vs. high-high: <0.0001
High-high/high-low/low-high(n=64)	15.9	11.7-20.1	Vs. low-low: <0.0001

LDH: lactate dehydrogenase

Table 5. Comparisons of the value of the TNM and LA-TNM systems in the predicting prognosis of the overall survival among the 244 primary duodenum adenocarcinoma patients in the present study.

Stage system	Likelihood ratio test χ^2	AIC	p value
TNM	29.29	1445.32	< 0.01
LA-TNM	38.46	1437	< 0.01

LA: LDH-Age; TNM: Tumour-node-metastasis; AIC: Akaike information criterion.

Discussion

Our team previously confirmed that the serum LDH level was an independent prognostic factor in locally advanced nasopharyngeal carcinoma and oesophageal squamous cell carcinoma [18,19]. Other researchers have also confirmed LDH as an independent prognostic factor in pancreatic cancer and colorectal cancer [21, 23]. However, the prognostic significance of LDH in primary duodenum adenocarcinoma has never been assessed hitherto. To the best of our knowledge, this is the first study exploring the prognostic value of LDH in a large

cohort of patients with primary duodenum adenocarcinoma, and we found that elevated baseline serum LDH indicated a poor prognosis.

The tumour microenvironment is frequently hypoxic due to the rapid growth of the tumour cells [13]. In hypoxic conditions, LDH can catalyse pyruvate into lactic acid and plays a key role in anaerobic glycolysis. HIF-1 α and Myc are reported to transcriptionally activate key genes in tumour cellular energy metabolism, such as *LDH*, thereby raising anaerobic glycolysis and producing high levels of lactate [14,28]. High levels of lactate will in turn enhance the expression of HIF-1 α [14-15]. By modulating metabolism and affecting the tumour microenvironment, the elevation of LDH is closely related to the tumour aggressiveness, metastasis, invasion and tumour burden [14-15]. Consistent with this, our study suggested that a higher LDH level was significantly associated with more distant metastasis, node metastasis, poor differentiation and TNM stage III - IV. On the other hand, a significantly higher median LDH level was observed in patients with a node metastasis, poor differentiation and a TNM stage of III - IV. Researchers revealed that the expression of lactate dehydrogenase-5 (LDH-5) was associated with the hypoxia-inducible factor (HIF-1 α) pathway, angiogenic factor production and poor prognosis in gastric cancer, but not in primary duodenum adenocarcinoma [15]. Further work needs to be done to clarify if these aspects have some distinctive features in primary duodenum adenocarcinoma.

In addition to hypoxia, inflammation is another essential characteristic of tumours, leading to shorter survival in cancer patients [25-27]. Systemic

inflammation is correlated with hypoxia. Our study demonstrated that the LDH level ($>245\text{U/L}$) was significantly associated with a higher NLR.

Previous studies revealed that LDH, HIF-1 α and Myc may be regulated by PI3K/Akt/TORC1/HIF pathway [28-30]. In renal cell cancer carcinoma patients with high LDH levels, temsirolimus could provide survival benefits by inhibiting TORC1[28]. Further studies need to be done to clarify whether temsirolimus will benefit primary duodenum adenocarcinoma patients with a higher level of LDH. It is worth mentioning that in colon cancer cells, researchers have found that LDH inhibitors could reduce production of lactate and reduce inflammation-induced changes [31].

An association between a high LDH level and tumour angiogenesis was determined by preclinical studies. HIF-1 α was confirmed to increase the serum LDH level and tumour angiogenesis *in vivo*. Low levels of LDH may be predictive of the effectiveness of antiangiogenetic therapies [32-33]. In a recent study, LDH was found to be capable of predicting the benefits from bevacizumab beyond progression in metastatic colorectal cancer. Patients with low serum LDH levels achieved significant PFS benefits from the bevacizumab maintenance treatment [32]. In another study, the colorectal cancer patients with high serum LDH levels did not benefit from regorafenib [33]. Moreover, a retrospective study included 21 unresectable or recurrent duodenum cancer patients to explore the value of the combination of chemotherapy with bevacizumab. The median OS of patients who received a bevacizumab-chemotherapy combination therapy was 21.9 months [34]. The predictive role of LDH in primary duodenum adenocarcinoma patients receiving antiangiogenetic therapy needs to be further validated.

The cut-off values of LDH varied in the different studies, ranging from 170 to 450U/L. A recent meta-analysis explored the prognostic value of LDH in different types of tumours and classified LDH into four groups: $<250\text{U/L}$, $250\text{-}300\text{U/L}$, $301\text{-}400\text{U/L}$ and $>400\text{U/L}$. They drew the conclusion that differences among the distinct cut-off points were not statistically significant ($P=0.99$) [20]. The ULN of LDH was 245U/L in our hospital, and was based on our classification of patients into either the normal LDH group ($\leq 245\text{U/L}$) or the high LDH group ($>245\text{U/L}$). Through analysis of 244 patients, we identified that patients in the higher LDH group had worse survival outcomes than those in the normal LDH group. Univariate analyses and multivariate analysis confirmed LDH as an independent prognostic indicator of OS. Higher LDH levels indicated more aggressive and unfavourable outcomes for primary

duodenum adenocarcinoma patients. Other independent prognostic factors of OS in the current study were radical surgery and age. It is no doubt that radical surgery is the most important curative treatment for patients with primary duodenum adenocarcinoma. Abeezer et al analysed the prognostic factors of 137 primary duodenum adenocarcinoma patients and found that age and the number of involved lymph nodes were independent prognostic factors [9]. We again confirmed age as a prognostic factor after multivariate analysis. A higher LDH level ($>245\text{U/L}$) indicates apparent hypoxia, exuberant angiogenesis and tumour aggressiveness, which might eventually lead to a worse OS.

To improve the prognostic value of the TNM staging system, we integrated age and LDH into this system to establish the LA-TNM staging system. LRT indicated that the LA-TNM system had a significantly larger χ^2 value and a significantly smaller AIC value when compared with the TNM system in predicting the OS. LA-TNM outperformed the TNM system in predicting the overall survival in our selected cohort of patients.

There are several limitations of our study. First, this is a retrospective and single centre study. Although we strictly selected patients in accordance with our inclusion and exclusion criteria, selection bias may still exist. Second, we set the cut-off value of the serum LDH level as the ULN of 245U/L. As such, external validation cohorts from other hospitals will be needed for further confirmation of higher LDH level ($>245\text{U/L}$) as an independent risk factor for primary duodenum adenocarcinoma. Third, although the theoretical result is economical and convenient to perform, the low proportion of these patients that had a higher level of LDH may lead to limited clinical application. Additionally, a combination of serum biomarkers may be worth exploring. Large scale prospective randomized controlled clinical trials are warranted to further clarify the prognostic value of LDH in primary duodenum adenocarcinoma. Basic studies should be conducted to study the mechanisms of LDH and LDH inhibitors in primary duodenum adenocarcinoma.

In conclusion, our study provided the first demonstration that LDH is an independent prognostic factor for primary duodenum adenocarcinoma and that elevated baseline serum LDH levels indicate a poor prognosis.

Abbreviations

TNM: Tumour-node-metastasis; AJCC: American Joint Committee on Cancer; OS: overall survival; ROC curve: receiver operating characteristics curve; WBC: white blood cell; PLR:

platelet-lymphocyte ratio; LMR: lymphocyte-monocyte ratio; PNI: prognostic nutritional index; LDH: lactate dehydrogenase; NLR: neutrophil-lymphocyte ratio.

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Competing Interests

The authors have declared that no competing interest exists.

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