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RESEARCH

Lactate dehydrogenase as promising marker for prognosis of brain metastasis

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Abstract

Background Lactate dehydrogenase (LDH) is a biomarker for cancer. However, the relationship between serum LDH levels and the survival of patients with brain metastasis has been fully revealed. We aimed to evaluate the serum LDH levels and assess its prognostic value in patients with BM.

Methods The serum LDH levels were collected from 2507 patients with BM. Patients were categorized into four groups according to the quartile of serum LDH levels. The association between serum LDH levels and overall survival (OS) was evaluated using Cox regression models and Kaplan–Meier curves. Three predictive models were used to evaluate patients.

Results The Kaplan–Meier curve for survival by the serum LDH group demonstrates clear separation between four groups ($P < 0.001$). The participants in the lower group had longer OS than those in the higher group. After adjusting in multivariate Cox regression models remained significant for patients in the Q4 compared with patients in the Q1 (Q4:Q1 OR 1.58, 95% CI 1.38–1.80). Furthermore, the GPA-LDH model generates a pooled area under the curve of 0.630 (95% CI 0.600, 0.660).

Conclusions Serum LDH levels and OS in patients with brain metastasis is an inverse association. Moreover, Serum LDH levels can improve the prognosis of the GPA model.

Keywords Brain metastasis · Lactate dehydrogenase · Prognosis · Retrospective analysis

Introduction

Cancer is a significant cause of death globally [1]. Furthermore, cancer metastasis carries a substantial mortality burden, and brain metastasis (BM) poses distinct clinical challenges [2]. The judgment of the prognosis of BM is a complex challenge due to the heterogeneity of the patient population: BM may come from a variety of primary tumors, patients have received several different treatment schemes, drug resistance to various treatment methods has emerged, and so on [3, 4].

Aberrant energy metabolism is one of the hallmarks of cancer [5]. Under aerobic conditions, most normal cells oxidize pyruvate produced by glycolysis to carbon dioxide through the mitochondrial tricarboxylic acid (TCA) cycle. This reaction produces nicotinamide adenine dinucleotide (NADH) and promotes oxidative phosphorylation to maximize the synthesis of adenosine triphosphate (ATP) and produce the least lactic acid. Tumor cells tend to convert glucose to lactate compared with most normal tissues, even if oxygen supports mitochondrial oxidative phosphorylation. This phenomenon is known as the "Warburg effect" [6–8].

Lactate dehydrogenase (LDH) is tetrameric NAD^+-specific dehydrogenase, which converts pyruvate to lactate, and is a critical enzyme involved in glycolysis [9, 10]. Two genes, LDH-A and LDH-B, are differentially

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expressed in somatic cells to form five combinations of tetramers [11]. It is well known that LDH is an essential biomarker for inflammation, tissue damage and ischemia [12]. Multiple studies have revealed that an abnormally high serum LDH is related to the proliferation of cancer-initiating cells, distant metastasis, and poor prognosis [10, 13–16].

The Graded Prognostic Assessment (GPA) is an objective prognostic score system to predict the survival of BM patients [17, 18]. It includes Karnofsky performance score (KPS), age, presence of extracranial metastases, and the number of brain metastases. Because the GPA is the least subjective, quantitative, and data more accessible, it is widely used in clinical practice.

Therefore, we conducted a retrospective study of 2507 patients with brain metastasis to investigate the prognostic significance of changes in serum LDH levels and update the GPA model.

Methods

Study design and data source

The database encompassed patients diagnosed and treated for brain metastasis in West China Hospital of Sichuan University between December 2013 and August 2021. This was a retrospective study utilizing the International Classification of Diseases, 10th revision (ICD-10 codes: C79.3) to identify brain metastasis patients. The clinical data, including medical history, imaging examination, and laboratory examination, were retrieved by the electronic medical record system to identify death records from the Household Registration Administration System.

The institutional review committee of West China Hospital has approved the database and approved the exemption of patients' informed consent.

Patient eligibility

Inclusion criteria for the study were as follows: (1) The primary solid tumor was diagnosed. (2) BM present either at initial diagnosis or at relapse by computed tomography (CT), contrast-enhanced computed tomography (CECT), magnetic resonance imaging (MRI), or positron emission tomography/computed tomography (PET-CT) scanning with or without histologic confirmation.

Exclusive criteria: (1) Their registry number of patients in the medical record system was wrong. (2) The data on survival is missing. (3) The patient's serum LDH levels are missing.

There were 4150 patients with brain metastasis records, and 2507 of them had information on serum LDH levels.

Risk and main outcomes

The risk factor was assessed in serum LDH level, with blood samples of serum LDH collected for the first time from patients with BM after admission.

Eleven pretreatment factors (sex, age, body mass index, KPS, primary lesion, number of metastases, presence of extracranial metastases, history of hypertension, history of diabetes, drinking status, smoking status), four treatment-related factors (targeted therapy, immunotherapy, chemotherapy, radiotherapy), and five laboratory examination data (leukocyte count, erythrocyte count, platelet count, neutrophil count) were reviewed and analyzed. Age, KPS, number of brain metastases, and extracranial systemic metastases were used to evaluate patients according to the GPA model developed by RTOG [17]. A novel model (including age, KPS, number of brain metastases, extracranial systemic metastases, and serum LDH level) is also developed to predict patients` survival. We applied both GPA and the GPA-LDH model based on clinical information in the medical records.

The primary endpoint for the prognostic factor was overall survival (OS), which was defined as the time between the patient's first admission after diagnosis of BM and the patient's death. If a patient was not dead, survival was censored on August 15, 2021.

Statistical analyses

Depending on the normality of distribution, as determined by the Kolmogorov–Smirnov test. Continuous variables are expressed as the mean ± standard deviation (SD) or medians with interquartile ranges. Categorical variables are represented by numbers and proportions (%). We interpolated directly using the median for data missing completely at random.

Univariate and multivariate Cox regression models were used to identify the notable correlation between clinically relevant baseline factors and OS. Given that variables identified as affecting outcomes by univariable analysis might be covariates ($P < 0.05$), we implemented multivariable Cox proportional regression analysis to identify independent factors related to OS. When these factors were still statistically significant in multivariate analysis, they were considered related to OS's independence. Multivariable analysis in which age, KPS, primary lesion, the number of brain metastases, presence of extracranial metastases, smoking status, drinking status, laboratory examinations, and therapy were adjusted as covariates.

Subgroup analyses were performed according to sex, age, Body Mass Index (BMI), primary lesion, Karnofsky

Performance Status(KPS), medical history, personal history, history of treatment, presence of extracranial metastases, and number of metastases.

To evaluate each predictive model, we measured it from the following three aspects: discrimination ability, calibration degree, and clinical utility. The predicted performance of the same predictive factors of the full GPA model, LDH, and the GPA-LDH model was compared with Harrell's C index, a continuous version of the net reclassification improvement (NRI), integrated discrimination improvement (IDI), the decision curve analysis (DCA) [19–21]. Additionally, we did a time-dependent AUROC analysis to test the predictive ability of different survival models on patients` overall survival [22]. The AUROC measures the discrimination of a predictive test and coincides with the C-statistic.

All tests of significance were 2-sided, and a P value less than 0.05 was considered significant. All statistical analyses were performed in R software. (version 4.1.2, R Foundation for Statistical Computing).

Results

Patients

In total, this study included 2507 patients with BM (Table 1). The demographic, clinical, and laboratory baseline characteristics of patients are presented in Table 1. Patients were categorized into four groups (Q1: serum LDH level ≤ 152, Q2:152 < serum LDH level ≤ 181, Q3:181 < serum LDH level ≤ 239, Q4: serum LDH level > 239) according to the quartile of serum LDH level. The majority of patients (56.8%) who were less than 60 years of age had no extracranial metastases (80.7%). The number of metastases in patients was > = 2, accounting for 68.3%. Those with Karnofsky performance scores of 70–80 accounted for 84.9%.

Survival analysis

Figure 1 shows the Kaplan–Meier curve for one-year survival by serum LDH group, demonstrating clear separation between four groups (P < 0.001). The participants in the lower group had longer OS than those in the higher group. We can also notice the dose–response relationship between serum LDH level and one-year survival, which indicated the survival benefit of patients increased gradually with the increase of serum LDH level.

Cox regression analysis of OS

In univariate regression (Table 2), mortality at one year was significantly higher in patients in the Q4 of serum LDH level in patients in the Q1 (Q4:Q1 HR 1.86, 95% CI 1.64–2.11). After adjusting all covariates in the multivariate Cox regression models, the association remained significant for patients in the Q4 compared with patients in the Q1 (Q4:Q1 OR 1.58, 95% CI 1.38–1.80).

Univariate Cox regression and multivariate Cox regression between Logarithm of serum LDH level as a continuous variable and OS were also performed. (HR 2.95, 95% CI 1.583–5.499 P < 0.001, univariate Cox regression; HR 2.840, 95% CI 1.503–5.366 P < 0.001, P < 0.001, multivariate Cox regression).

In efigure 1, we used the restricted cubic splines (RCS) model fitted for Cox proportional hazards models to flexibly model and visualize the relation between serum LDH and 1-year death in patients. The risk of mortality was relatively flat until around 2.18 of the logarithm of serum LDH and then increased gradually with the increase of serum LDH (P for non-linearity = 0.089).

Subgroup analyses demonstrated that the association between serum LDH levels and overall survival was quartered by Baseline LDH Levels (P for interaction < 0.001, Table 3). And one-year survival rates of different subgroups corresponding to different baseline LDH levels(eTable 1).

Comparison of different predictive models

In predicting one-year mortality, the addition of serum LDH levels into the same predictive factors of the full GPA model generates a pooled AUC of 0.628 (95% CI 0.599, 0.658). However, the AUC of the original GPA model and that of serum LDH level alone were 0.590 (95% CI 0.560, 0.620) and 0.591 (95% CI 0.561, 0.621), respectively(Fig. 2a). The pooled AUC for the novel model was significantly higher than the other two models considered independently (P < 0.001, Fig. 2b). We calculated NRI and IDI further to add serum LDH levels to the GPA model. NRI and IDI were significant in the modified GPA model (P < 0.001). The DCA of four predictors (age, KPS, number of brain metastases, and extracranial systemic metastases), five predictors (age, KPS, number of brain metastases, extracranial systemic metastases, and serum LDH level), and serum LDH level were shown in Fig. 3. For predicting cumulative one-year probabilities of primary outcomes, when threshold probabilities were within, respectively, the net benefit of the novel model was higher than the four predictors and serum LDH level alone.

Discussion

We reported a systematic analysis and research on the association of serum LDH with overall survival among patients with BM and achieved several significant findings. First, we found that serum LDH levels were correlated

Table 1 Baseline demographics stratified by baseline LDH levels

	Overall	LDH ≤ 152	152 < LDH ≤ 181	181 < LDH ≤ 239	239 < LDH	P
n	2,507	635	619	658	595	
sex (Female, N, %)	1049 (41.8)	230 (36.2)	288 (46.5)	286 (43.5)	245 (41.2)	0.002
Age (N, %)						
< 50	690 (27.5)	211 (33.2)	161 (26.0)	164 (24.9)	154 (25.9)	0.014
50–60	734 (29.3)	178 (28.0)	174 (28.1)	198 (30.1)	184 (30.9)	
> 60	1083 (43.2)	246 (38.7)	284 (45.9)	296 (45.0)	257 (43.2)	
Body Mass Index (mean, (SD))	22.32 (2.63)	22.19 (2.55)	284 (45.9)	296 (45.0)	257 (43.2)	
Karnofsky performance score (N, %)						
< 70	369 (14.7)	96 (15.1)	93 (15.0)	85 (12.9)	95 (16.0)	0.137
70–80	2128 (84.9)	534 (84.1)	526 (85.0)	572 (86.9)	496 (83.4)	
90–100	10 (0.4)	5 (0.8)	0 (0.0)	1 (0.2)	4 (0.7)	
Primary lesion (Lung, N, %)	1802 (71.9)	426 (67.1)	442 (71.4)	488 (74.2)	446 (75.0)	0.008
Number of metastases (N, %)						
1	793 (31.6)	231 (36.4)	208 (33.6)	190 (28.9)	164 (27.6)	0.001
2–3	806 (32.1)	200 (31.5)	204 (33.0)	225 (34.2)	177 (29.7)	
> 3	908 (36.2)	204 (32.1)	207 (33.4)	243 (36.9)	254 (42.7)	
Presence of extracranial metastases (Yes, N, %)	1706 (68.0)	411 (66.4)	465 (70.7)	468 (78.7)	362 (57.0)	< 0.001
History of past illness & personal history						
History of hypertension (Yes, N, %)	402 (16.0)	77 (12.1)	103 (16.6)	108 (16.4)	114 (19.2)	0.008
History of diabetes (Yes, N, %)	219 (8.7)	47 (7.4)	55 (8.9)	60 (9.1)	57 (9.6)	0.554
Drinking status (Yes, N, %)	643 (25.6)	174 (27.4)	131 (21.2)	174 (26.4)	164 (27.6)	0.030
Smoking status (N, %)						
Current	349 (13.9)	78 (12.3)	87 (14.1)	95 (14.4)	89 (15.0)	0.099
Ever	699 (27.9)	178 (28.0)	149 (24.1)	188 (28.6)	184 (30.9)	
Never	1459 (58.2)	379 (59.7)	383 (61.9)	375 (57.0)	322 (54.1)	
Therapy						
Targeted therapy (N, %)	782 (31.2)	189 (29.8)	205 (33.1)	208 (31.6)	180 (30.3)	0.578
Immunotherapy (N, %)	48 (1.9)	13 (2.0)	12 (1.9)	10 (1.5)	13 (2.2)	0.84
Chemotherapy (N, %)	1658 (66.1)	418 (65.8)	396 (64.0)	443 (67.3)	401 (67.4)	0.541
Radiotherapy (N, %)	1186 (47.3)	327 (51.5)	282 (45.6)	297 (45.1)	280 (47.1)	0.09
Biomarker						
Leukocyte count ($*10^9$/L, median [IQR])	6.6 [5.2, 8.2]	6.3 [5.0, 7.6]	6.4 [5.0, 7.7]	6.6 [5.2, 8.3]	7.2 [5.7, 9.2]	< 0.001
Erythrocyte count ($*10^{12}$/L, median [IQR])	4.3 [3.9, 4.7]	4.3 [4.0, 4.8]	4.3 [4.0, 4.6]	4.3 [3.9, 4.7]	4.2 [3.8, 4.6]	< 0.001
Platelet count ($*10^9$/L, median [IQR])	203.0 [153.0, 252.0]	195.0[149.0, 233.5]	202.0 [152.5, 256.5]	200.0[150.3, 251.0]	211.1[161.0, 270.0]	0.001
Neutrophil count ($*10^9$/L, median [IQR])	4.5 [3.3, 5.8]	4.2 [3.1, 5.2]	4.1 [3.1, 5.3]	4.5 [3.3, 6.0]	5.0 [3.9, 6.8]	< 0.001

Table 1 (continued)

	Overall	LDH ≤ 152	152 < LDH ≤ 181	181 < LDH ≤ 239	239 < LDH	P
Lymphocyte count (*10^9/L, median [IQR])	1.4 [1.0, 1.7]	1.4 [1.1, 1.7]	1.4 [1.0, 1.8]	1.3 [1.0, 1.7]	1.3 [1.0, 1.6]	0.002

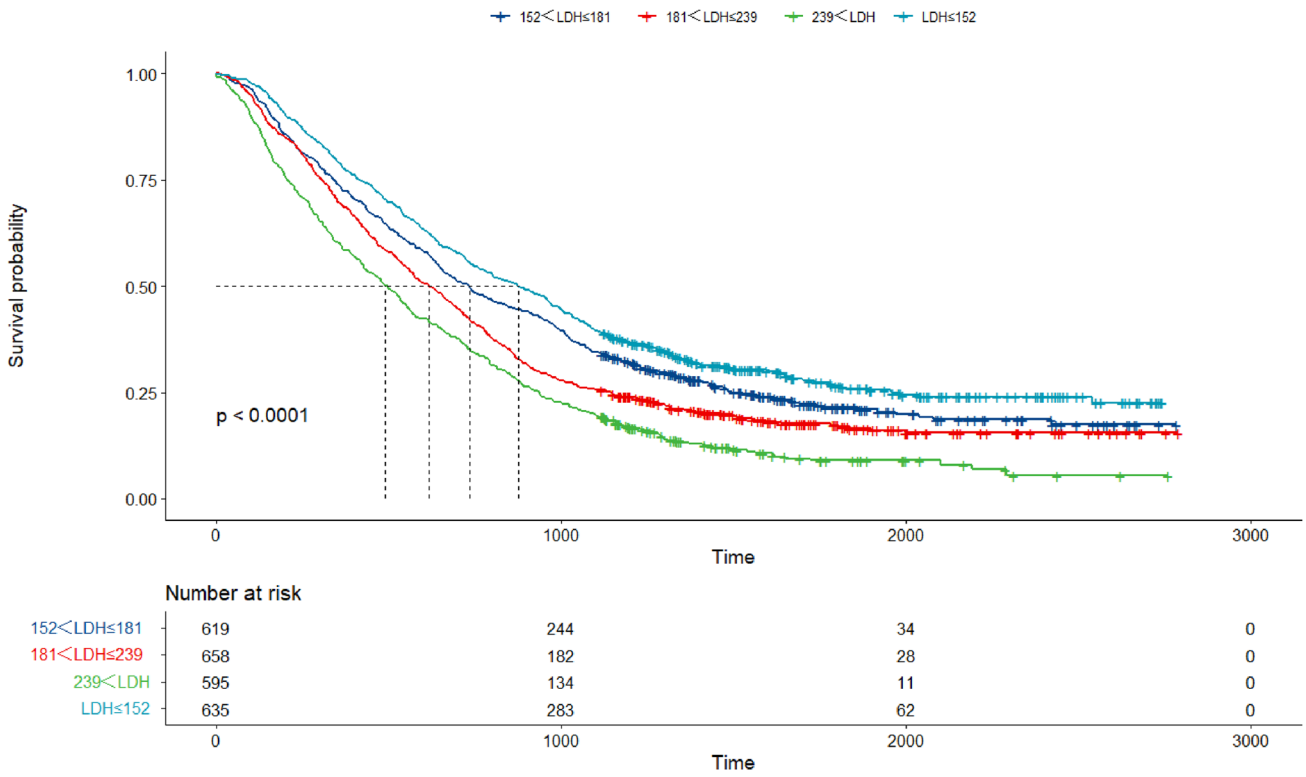


Fig. 1 Kaplan–Meier overall survival analysis of 2507 patients with brain metastases regarding the serum LDH groups. LDH, Lactate dehydrogenase

with OS of patients with BM. Moreover, the performance of the GPA model was significantly improved with the addition of serum LDH levels.

Unsurprisingly, the lactates play an essential role in tumor cells, and serum lactates can represent the metabolic activities of tumor cells and reflect the uptake of glucose [7]. When the tissue is hypoxic, the transcription factor hypoxia-inducible factor -1 (HIF-1) is expressed, and a range of activities, including angiogenesis and various prosurvival mechanisms, were initiated [23, 24].

Several studies have shown that serum LDH is a biomarker and associated with an unfavorable outcome in cancer [15, 25]. Indeed, serum LDH level is included in several prognostic scores and staging systems for cutaneous melanoma, renal cell cancer, and colorectal cancer, a primary predictor of outcome in patients with adverse prognosis and distant metastases [26, 27].

Our study has several strengths. Our study is the most extensive retrospective study on the relationship between serum LDH and the prognosis of BM. We collected the serum data of patients admitted for the first time when diagnosed with brain metastasis. Furthermore, compared with previous studies, more covariates(medical history, treatments, and biomarkers) were collected. Furthermore, we

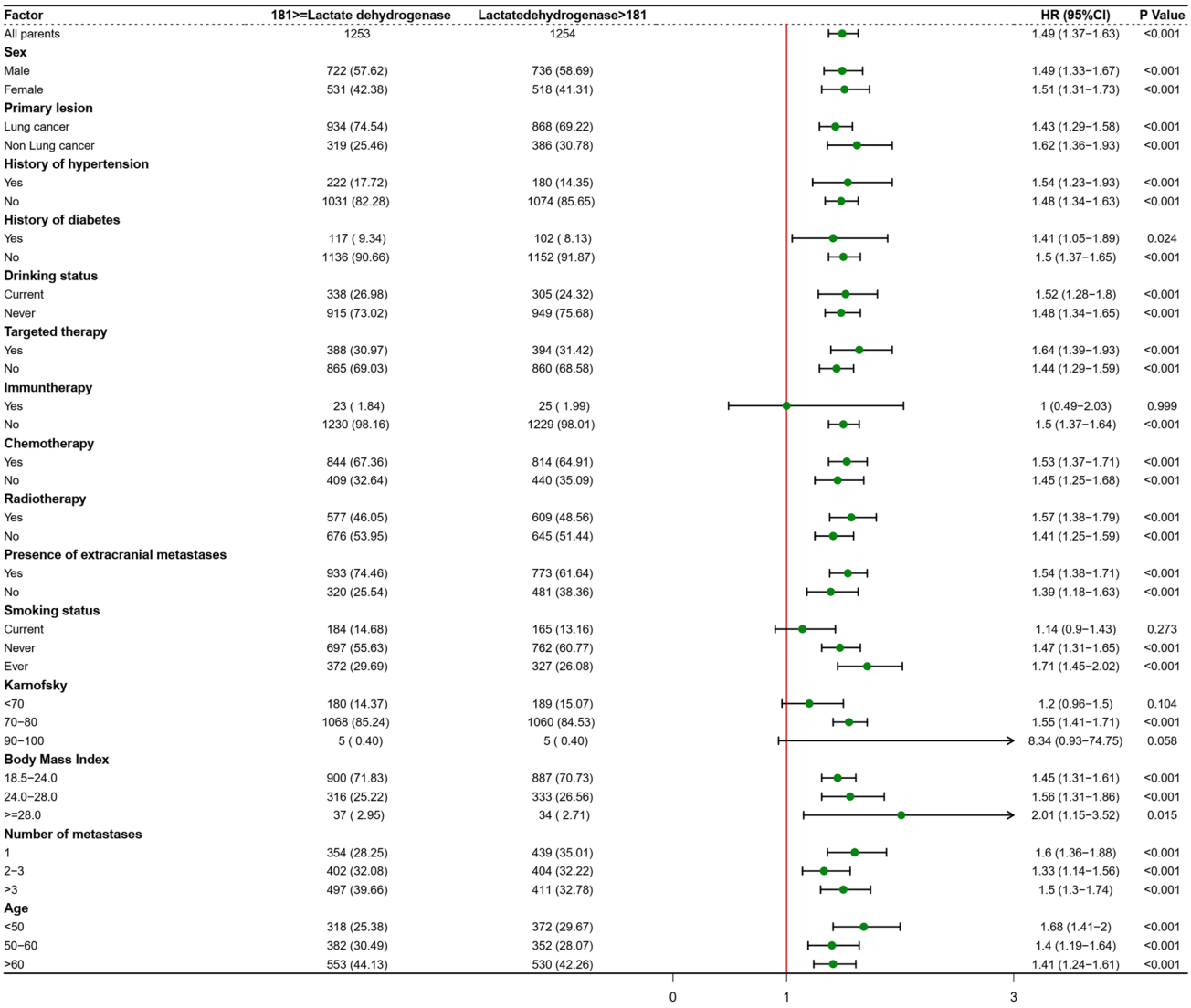
Table 2 Univariate and multivariate models for overall survival in patients with brain metastases

Factor	Univariate		Full multivariate	
	HR (95% CI)	P	HR (95% CI)	P
Male	1.21 (1.11–1.33)	**< 0.001**	1.10 (0.94–1.29)	0.217
Age				
< 50	Reference		Reference	
50–60	1.15 (1.02–1.29)	**0.021**	1.07(0.94–1.22)	0.295
> 60	1.27 (1.14–1.41)	**< 0.001**	0.96 (0.84–1.10)	0.548
Karnofsky performance score				
< 70	Reference		Reference	
70–80	0.7 (0.62–0.79)	**< 0.001**	0.85 (0.73–0.99)	**0.042**
90–100	0.91 (0.45–1.84)	0.796	0.78 (0.66–0.93)	0.006
Body Mass Index	0.97 (0.96–0.99)	**< 0.001**	0.98 (0.96–1.00)	**0.071**
Primary lesion: Lung	1.23 (1.11–1.36)	**< 0.001**	1.19 (1.04–1.36)	**0.009**
Number of metastases				
1	Reference		Reference	
2–3	1.1 (0.98–1.23)	0.097	1.14 (0.97–1.34)	0.111
> 3	1.28 (1.15–1.47)	**< 0.001**	1.21 (1.08–1.35)	**0.001**
Presence of extracranial metastases Yes	1.10 (1.00–1.21)	0.061		
History of past illness & personal history				
History of hypertension Yes	1.04 (0.93–1.18)	0.471		
History of diabetes Yes	1.07(0.92–1.25)	0.39		
Drinking status				
Never	Reference		Reference	
Current	1.16 (1.05–1.28)	**0.003**	1.03 (0.91–1.18)	0.625
Smoking status				
Never	Reference		Reference	
Current	1.26 (1.11–1.43)	**< 0.001**	1.16 (0.96–1.40)	0.113
Ever	1.23 (1.11–1.36)	**< 0.001**	1.14 (0.97–1.34)	0.119
Therapy				
Targeted therapy	0.71 (0.65–0.79)	**< 0.001**	0.75 (0.40–0.87)	**< 0.001**
Immunotherapy	0.69 (0.49–0.99)	**0.043**	0.59 (0.40–0.87)	**0.008**
Chemotherapy	0.78 (0.71–0.85)	**< 0.001**	0.85 (0.75–0.96)	**0.009**
Radiotherapy	0.84 (0.77–0.92)	**< 0.001**	0.94 (0.84–1.05)	0.289
Biomarker				
Erythrocyte count	0.81 (0.75–0.87)	**< 0.001**	0.84 (0.77–0.92)	**< 0.001**
Leukocyte count	1.02 (1.02–1.03)	**< 0.001**	1.07 (0.96–1.20)	**0.223**
Platelet count	1 (1.00–1.00)	**0.034**	1 (1.00–1.00)	0.744
Neutrophil count	1.07 (1.06–1.09)	**< 0.001**	0.98 (0.87–1.10)	0.698
Lymphocyte count	0.79 (0.73–0.86)	**< 0.001**	0.77 (0.66–0.92)	**0.003**
Lactate dehydrogenase				
≤ 152	Reference		Reference	
152 < LDH ≤ 181	1.18 (1.04–1.34)	**0.013**	1.16 (1.00–1.34)	**0.056**
181 < LDH ≤ 239	1.43 (1.26–1.62)	**< 0.001**	1.41 (1.22–1.63)	**< 0.001**
239 < LDH	1.86 (1.64–2.11)	**< 0.001**	1.52 (1.31–1.77)	**< 0.001**

When P is less than 0.05, there is a significant difference, so we use bold text to express it

Table 3 Subgroup analysis of the baseline LDH Levels on overall survival

Factor	181>=Lactate dehydrogenase	Lactatedehydrogenase>181	HR (95%CI)	P Value
All parents	1253	1254	1.49 (1.37–1.63)	<0.001
Sex				
Male	722 (57.62)	736 (58.69)	1.49 (1.33–1.67)	<0.001
Female	531 (42.38)	518 (41.31)	1.51 (1.31–1.73)	<0.001
Primary lesion				
Lung cancer	934 (74.54)	868 (69.22)	1.43 (1.29–1.58)	<0.001
Non Lung cancer	319 (25.46)	386 (30.78)	1.62 (1.36–1.93)	<0.001
History of hypertension				
Yes	222 (17.72)	180 (14.35)	1.54 (1.23–1.93)	<0.001
No	1031 (82.28)	1074 (85.65)	1.48 (1.34–1.63)	<0.001
History of diabetes				
Yes	117 (9.34)	102 (8.13)	1.41 (1.05–1.89)	0.024
No	1136 (90.66)	1152 (91.87)	1.5 (1.37–1.65)	<0.001
Drinking status				
Current	338 (26.98)	305 (24.32)	1.52 (1.28–1.8)	<0.001
Never	915 (73.02)	949 (75.68)	1.48 (1.34–1.65)	<0.001
Targeted therapy				
Yes	388 (30.97)	394 (31.42)	1.64 (1.39–1.93)	<0.001
No	865 (69.03)	860 (68.58)	1.44 (1.29–1.59)	<0.001
Immuntherapy				
Yes	23 (1.84)	25 (1.99)	1 (0.49–2.03)	0.999
No	1230 (98.16)	1229 (98.01)	1.5 (1.37–1.64)	<0.001
Chemotherapy				
Yes	844 (67.36)	814 (64.91)	1.53 (1.37–1.71)	<0.001
No	409 (32.64)	440 (35.09)	1.45 (1.25–1.68)	<0.001
Radiotherapy				
Yes	577 (46.05)	609 (48.56)	1.57 (1.38–1.79)	<0.001
No	676 (53.95)	645 (51.44)	1.41 (1.25–1.59)	<0.001
Presence of extracranial metastases				
Yes	933 (74.46)	773 (61.64)	1.54 (1.38–1.71)	<0.001
No	320 (25.54)	481 (38.36)	1.39 (1.18–1.63)	<0.001
Smoking status				
Current	184 (14.68)	165 (13.16)	1.14 (0.9–1.43)	0.273
Never	697 (55.63)	762 (60.77)	1.47 (1.31–1.65)	<0.001
Ever	372 (29.69)	327 (26.08)	1.71 (1.45–2.02)	<0.001
Karnofsky				
<70	180 (14.37)	189 (15.07)	1.2 (0.96–1.5)	0.104
70–80	1068 (85.24)	1060 (84.53)	1.55 (1.41–1.71)	<0.001
90–100	5 (0.40)	5 (0.40)	8.34 (0.93–74.75)	0.058
Body Mass Index				
18.5–24.0	900 (71.83)	887 (70.73)	1.45 (1.31–1.61)	<0.001
24.0–28.0	316 (25.22)	333 (26.56)	1.56 (1.31–1.86)	<0.001
>=28.0	37 (2.95)	34 (2.71)	2.01 (1.15–3.52)	0.015
Number of metastases				
1	354 (28.25)	439 (35.01)	1.6 (1.36–1.88)	<0.001
2–3	402 (32.08)	404 (32.22)	1.33 (1.14–1.56)	<0.001
>3	497 (39.66)	411 (32.78)	1.5 (1.3–1.74)	<0.001
Age				
<50	318 (25.38)	372 (29.67)	1.68 (1.41–2)	<0.001
50–60	382 (30.49)	352 (28.07)	1.4 (1.19–1.64)	<0.001
>60	553 (44.13)	530 (42.26)	1.41 (1.24–1.61)	<0.001



performed multivariable Cox regressions to minimize bias from confounders. Patients' death data were collected accurately and entirely by reducing loss of follow-up. Moreover, we also propose to improve the GPA model of patients with BM by adding the variable of serum LDH to the original GPA model.

Nevertheless, our study had several limitations. First, the data set evaluated was a heterogeneous cohort of patients with BM. We collected the survival time of patients with brain metastasis from different primary tumors and did not study the survival time of patients with different primary tumors separately. Second, most of the subjects we studied are lung cancer, and there will be selection bias in the final results. Third, The effect of different treatment methods on serum lactate dehydrogenase.

Conclusions

Based on serum LDH collected retrospectively, our study demonstrated an inverse association between serum LDH levels and OS in patients with BM. Moreover, serum LDH levels can improve the prognosis of the GPA model. Therefore, future mechanistic studies are necessary to determine whether serum LDH is a proxy of tumor brain metastasis and severity, which explains its association with cancer survival.

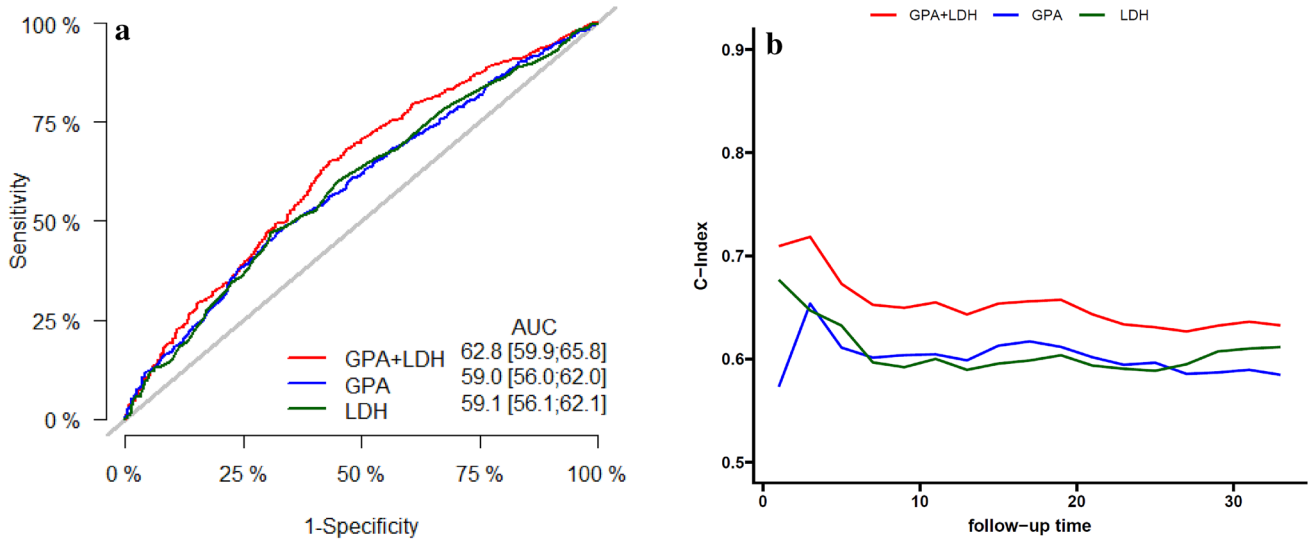


Fig. 2 **a** The ROC curve analysis for predicting the one-year mortality in 2507 patients with brain metastases. **b** AUROC curve for GPA, LDH, and GPA and LDH. *ROC* receiver operating characteristics; *AUROC* area under the time-dependent receiver operating characteristic curve; *GPA* Graded Prognostic Assessment; *LDH* serum Lactate dehydrogenase

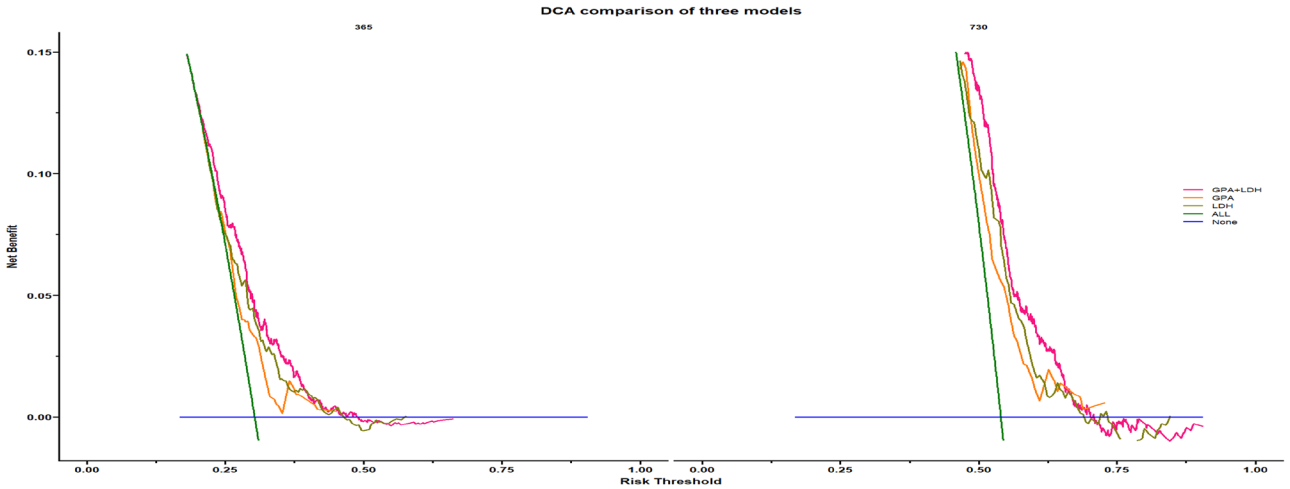


Fig. 3 DCA comparison of three models. DCA for evaluating the accuracy of three models in predicting the overall survival. *DCA* decision curve analysis; *GPA* Graded Prognostic Assessment; *LDH* serum lactate dehydrogenase

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Author contributions FF and XCP conceived the study and designed the protocol. YYP, YH, and JYY collected data and cleaned data. YYP, YZ and ZRL analyzed and interpret data. YYP and YZ wrote the first draft of the paper. FF, XCP, YYP, YZ, ZRL, YH, JYY, RJZ, and JJW critically revised successive drafts of the paper and approved the final version. FF and XCP are the guarantors of the review.

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Data availability Yes.

Declarations

Competing interests The author declare that they have no competing interest.

Ethical approval The study was approved by Ethics Committee on Biomedical Research West China Hospital of Sichuan University. The study was performed in accordance with the Declaration of Helsinki.

Consent for publication Yes.

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