Original Article

Prognostic value of lactate dehydrogenase in non-small cell lung cancer patients with brain metastases: a retrospective cohort study

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Background: At present, although there are some known molecular markers for the prognosis of non-small cell lung cancer (NSCLC) brain metastases, but there are still shortcomings in sensitivity and specificity. Lactate dehydrogenase (LDH) is one of the key enzymes involved in malignancy vital glycolytic pathway. Elevated serum LDH levels are reported significantly associated with a poor prognosis in various malignancies. However, there is currently no consensus regarding the prognostic value of LDH in NSCLC patients with brain metastases.

Methods: We retrospectively analyzed 224 patients diagnosed with lung cancer brain metastases between January 2006 and June 2020 after excluding patients meeting combined with other malignancies and inaccurate clinical information. The LDH cutoff values were obtained using a restricted cubic spline (RCS) model, and the patients were divided into two groups according to the optimal cut-off value (180 U/L). 107 patients with LDH ≤180 (47.77%) and 117 patients with LDH >180 (52.23%) were identified. Univariate and multivariate logistic regression analyses were performed to identify the risk factors. The overall survival (OS) time was defined as the time from the first diagnosis of brain metastases to the last follow-up or death. Of the included patients, 147 survived and 77 died. The Kaplan-Meier method was used to illustrate the OS difference between the two groups. Finally, sensitivity analysis was employed to evaluate the robustness of the results.

Results: The OS rate was significantly lower in the high LDH group versus the low LDH group (P=0.009). The median survival times of the high and low LDH groups were approximately 16 and 33 months, respectively. Multivariate analysis showed that high LDH was associated with a significantly worse OS [adjusted hazard ratio (aHR), 1.567; 95% confidence interval (CI): 1.058 to 2.32, P=0.025] with adjustment for covariables that P<0.05 in univariate analysis. Sensitivity analysis indicated that the results of this study are robust, despite potential unmeasured confounders.

Conclusions: High level of serum LDH indicates poor prognosis for patients with NSCLC brain metastases. This finding may provide useful prognostic information for patients and clinicians to choose more aggressive treatment strategies.

Keywords: Lactate dehydrogenase (LDH); non-small cell lung cancer (NSCLC); brain metastases

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Introduction

Lung cancer is the leading cause of malignancy-related death worldwide, accounting for approximately 18% of all cancer-related deaths (1). Non-small cell lung cancer (NSCLC) accounts for 80–85% of all lung cancers. The prognosis of NSCLC is poor, but with continued advances in treatment modalities, the 5-year survival rate for patients with NSCLC has improved to 19.8% (2). The brain is the most common metastatic site, which can lead to disease progression and a poor prognosis (3), seriously affecting the survival and quality of life of patients. There are a variety of known molecular markers for the prognosis of brain metastases from NSCLC. Carcinoembryonic antigen (CEA) is a tumor associated glycoprotein. It was found that CEA levels were significantly higher in patients with NSCLC brain metastases and related to worse prognosis (4,5). As a tumor carbohydrate antigen, the level of CA125 was closely related to the stage and degree of invasion of lung cancer. It had certain value in predicting and evaluating the development and prognosis of brain metastases. NSE is a key enzyme in glycolysis (6). The serum NSE level was higher in lung cancer patients with brain metastases which may be related to the damage of brain tissue caused by tumor brain metastasis. The reduction of NSE expression level also indicated better therapeutic effect. Thus serum NSE could be used as a prognosis marker for lung cancer patients with brain metastases (7). Biomarkers mentioned above have some advantages in the prognosis of brain metastasis of NSCLC, but their sensitivity and specificity are still insufficient, thus a single tumor marker has certain limitations. At present, the generally accepted prognostic scoring system for NSCLC brain metastasis is the diagnosis-specific graded prognostic assessment (DS-GPA), which includes four prognostic indicators: age, Karnofsky Performance Status (KPS) score, extracranial metastatic lesions, and the number of brain metastatic lesions (8,9). Nevertheless, DS-GPA score is not perfect in evaluating survival. Even in the two most favorable groups, occasional patients survive for less than 3 months. Moreover, in the unfavorable group, survival beyond 12 months has been recorded as well. In other words, marked heterogeneity in outcomes for patients with brain metastases exists (10). Therefore, the development of new markers is urgently needed.

Some serum tumor markers are associated with the prognosis of lung cancer patients (11). The detection of serum markers has many advantages, including its non-invasive nature and ability to obtain rapid and easily repeatable measurements. Lactate dehydrogenase (LDH) is a key enzyme in glycolysis metabolism, which acts as a catalyst for the conversion of pyruvate to lactic acid (12). Tumor cells require 30 times more glucose and produce 40 times more lactate through glycolysis than normal cells (13), and this feature is more prominent in patients with brain metastases. In addition, LDH can also promote tumor angiogenesis as well as cell migration and metastasis by promoting the expression of vascular endothelial growth factor (VEGF) (14). This may ultimately lead to a poor prognosis and shorter survival times in patients. Several previous studies have shown that LDH is associated with the prognosis of several cancers, including breast (15), cervical (16), lung (17), and gastric (18) cancers. However, there are currently few studies on NSCLC patients with brain metastases. Therefore, the present study aimed to evaluate whether LDH is a prognostic factor in NSCLC patients with brain metastases. We present the following article in accordance with the STARD reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1502/rc).

Methods

Patients

This study is a retrospective analysis of NSCLC patients diagnosed with brain metastases at Tumor Hospital of Yunnan Province between January 2006 and June 2020. The survival data of patients, serum LDH level and other confounding factors that may affect the prognosis of patients were collected to explore the effect of LDH level on the prognosis of patients. The patients were divided into two groups using a restricted cubic spline (RCS) model according to the level of LDH level. Univariate, multivariate, subgroup and sensitivity analyses were used to analyze the risk factors affecting the prognosis of patients.

The following variables were collected for analysis: age, sex, extracranial metastases (lung/chest/liver/bone/adrenal), KPS score, number of brain metastases, smoking status, American Joint Committee on Cancer (AJCC) T stage, AJCC N stage, AJCC M stage, treatment (i.e., whether the primary tumor was treated with surgery/chemotherapy/targeted therapy), and pathological type. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the ethics committee of Tumor Hospital of Yunnan Province (No. KYLX2022130). The requirement for individual consent for this retrospective analysis was waived.

We selected patients based on the following inclusion criteria: (I) age >18 years; (II) pathological diagnosis of NSCLC; (III) presence of brain metastases diagnosed by surgical pathology or imaging; (IV) currently undergoing chemotherapy, targeted therapy, and primary surgery; and (V) survival time (defined as the time interval between the date of diagnosis and the date of death) of more than 30 days. The exclusion criteria were as follows: (I) presence of other malignant tumors; (II) inaccurate information on primary tumor surgery, chemotherapy, and targeted therapy; and (III) absence of important data. For Cox regression analysis of survival data, outcome events should be at least 5–10 times the number of independent variables. Finally, 224 patients were selected for further analysis considering the included variables according to the above-mentioned inclusion and exclusion criteria.

Patients were followed up for survival status every 3 months after the diagnosis of NSCLC brain metastasis, then every 6 months for 3 years, and once a year for 5 years. Follow-up was carried out by outpatient and inpatient re-examination and telephone inquiry.

Clinical characteristics

The overall survival (OS) time was defined as the time from the first diagnosis of lung cancer brain metastases (rather than the first diagnosis of lung cancer) to the last follow-up or death. Definition of outcome indicators: surviving patients were marked as 1, and non-surviving patients were marked as 0. The survival time and status were also collected. The 8th version of the AJCC TNM staging system was used for staging. Patients who had smoked no more than 100 cigarettes in their lifetime were defined as non-smokers. Smokers were defined as current smokers or individuals who had quit smoking within 1 year before diagnosis. The LDH cutoff values were obtained using a RCS model, and the patients were divided into two groups according to the optimal cut-off value (180 U/L). Based on the baseline LDH levels in selected patients, 107 patients with LDH ≤180 (47.77%) and 117 patients with LDH >180 (52.23%) were identified.

Statistical analysis

A combined RCS model was established using the rms package of R software (R Core Group, Vienna, Austria) to explore the dose-response relationship between continuous changes in LDH and patient prognosis, and the continuous variable LDH was converted into a binary variable. Kaplan-Meier survival curves were drawn using the survival package, and the log-rank test was used to compare survival differences between the two groups.

Univariate and multivariate analyses of the predictors were performed using the Cox proportional hazards (PHs) regression model with the forestplot package. The prognostic value of LDH was explored through Kaplan-Meier curves and Cox regression.

Our study may be affected by many other unknown confounding factors. Even if we have collected enough known confounding factors based on previous research, there may still be unknown confounding factors that affect the reliability of our results. From the perspective of epidemiology, we need to know how stable or reliable our results are, that is, if there are one or several unknown confounding factors, how much "power" these confounding factors need to fully explain the results of our study. The sensitivity analysis of the EValue package developed by Ding and VanderWeele (19-21) was used to further evaluate the robustness of the main analysis results. Sensitivity analysis method E-value takes relative risk (RR) as the main research indicator and constructs a statistical model for RR sensitivity analysis, so as to predict the minimum strength of association between unknown confounding factors and exposure factors i.e., serum LDH level or outcomes i.e., prognosis that can be explained by the RR value.

Results

Correlation between the LDH level and prognosis of NSCLC patients with brain metastasis

To verify the relationship between LDH levels and the prognosis of NSCLC patients with brain metastases, we constructed an RCS model and found that LDH levels were

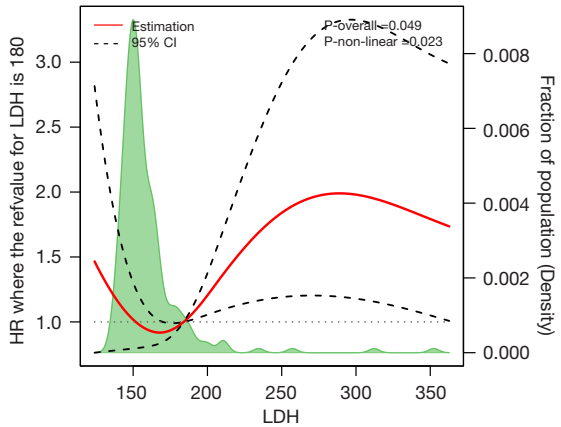

Figure 1 Restricted cubic splines for the association of NSCLC brain metastasis prognosis with LDH level. The left ordinate represents the HR, and the right ordinate represents the population density. The dotted line indicates to the 95% confidence interval. HR, hazard ratio; LDH, lactate dehydrogenase; CI, confidence interval; NSCLC, non-small cell lung cancer.

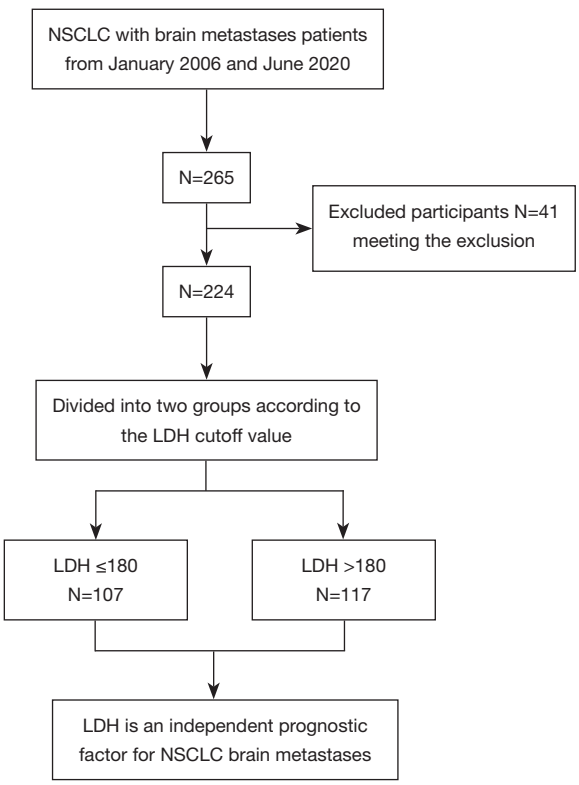

Figure 2 Flow diagram of the patient selection process. NSCLC, non-small cell lung cancer; LDH, lactate dehydrogenase.

linearly associated with the prognosis of NSCLC patients with brain metastases (overall association test: P=0.049; non-linear association test: P=0.023). The RCS model showed that for LDH ≤180, the risk of death changed slowly with increasing LDH; for LDH =180, the cutoff point/inflection point was hazard ratio (HR) ≈1; and for LDH >180, the risk of death increased significantly with increasing LDH. After removing two extreme LDH values, it was found that the LDH level of NSCLC patients with brain metastases exhibited a skewed distribution (*Figure 1*).

Baseline characteristics of the participants

Figure 2 displays the patient selection flow diagram. After applying the inclusion and exclusion criteria, we finally selected 224 participants for analysis. Of the included patients, 147 survived and 77 died. We constructed two baseline data tables based on the outcome indicators and LDH levels. Among the included variables, the proportion of patients who underwent primary tumor surgery was significantly different between the surviving and non-surviving patients (P<0.05) (Table S1). Based on the baseline LDH levels in selected patients, 107 patients with LDH ≤180 (47.77%) and 117 patients with LDH >180 (52.23%) were identified. There were significant differences between the low and high LDH groups in terms of the clinical stage (including N and M stages, P=0.034 and 0.006), primary tumor operation (P<0.001), and extracranial metastasis (lung, liver, bone, and adrenal gland, P=0.011, 0.044, 0.002 and 0.018). There were no statistically significant differences in age, sex, body mass index (BMI), KPS score, total number of metastases, smoking status, AJCC T stage, chemotherapy, targeted therapy, pathological type, or DS-GPA between the two groups (*Table 1*).

Kaplan-Meier survival curve analysis

We used the survival package of R language to draw the total survival time Kaplan-Meier curves of the different groups (*Figure 3*). Compared with the OS of patients in the low LDH expression group, that of patients in the high LDH expression group (HR =1.549, P=0.009) was worse. Moreover, the median survival time of patients in the high and low LDH groups was approximately 16 and 33 months, respectively. The log-rank test indicated that this difference

Table 1 Characteristics of patients grouped by LDH level

Variables	Total (n=224)	LDH ≤180 (n=107)	LDH >180 (n=117)	P
Age_cat, n (%)				0.057
~50	78 (34.82)	45 (42.06)	33 (28.21)	
51–60	73 (32.59)	34 (31.78)	39 (33.33)	
61~	73 (32.59)	28 (26.17)	45 (38.46)	
Sex, n (%)				0.138
Female	84 (37.5)	46 (42.99)	38 (32.48)	
Male	140 (62.5)	61 (57.01)	79 (67.52)	
BMI_cat, n (%)				0.478
Normal	163 (72.77)	75 (70.09)	88 (75.21)	
Overweight	61 (27.23)	32 (29.91)	29 (24.79)	
KPS, n (%)				0.319
~70	13 (5.8)	4 (3.74)	9 (7.69)	
70–80	60 (26.79)	32 (29.91)	28 (23.93)	
80~	151 (67.41)	71 (66.36)	80 (68.38)	
Met_{num}, n (%)				0.189
1	108 (48.21)	54 (50.47)	54 (46.15)	
2–3	60 (26.79)	32 (29.91)	28 (23.93)	
4~	56 (25.0)	21 (19.63)	35 (29.91)	
Smoking, n (%)				0.143
No	130 (58.04)	68 (63.55)	62 (52.99)	
Yes	94 (41.96)	39 (36.45)	55 (47.01)	
AJCC.T, n (%)				0.103
T1	29 (12.95)	14 (13.08)	15 (12.82)	
T2	85 (37.95)	48 (44.86)	37 (31.62)	
T3	32 (14.29)	9 (8.41)	23 (19.66)	
T4	64 (28.57)	29 (27.1)	35 (29.91)	
Tx	14 (6.25)	7 (6.54)	7 (5.98)	
AJCC.N, n (%)				0.034
N0	33 (14.73)	21 (19.63)	12 (10.26)	
N1	25 (11.16)	16 (14.95)	9 (7.69)	
N2	86 (38.39)	41 (38.32)	45 (38.46)	
N3	67 (29.91)	25 (23.36)	42 (35.9)	
Nx	13 (5.8)	4 (3.74)	9 (7.69)	

Table 1 (*continued*)

Table 1 (*continued*)

Variables	Total (n=224)	LDH ≤180 (n=107)	LDH >180 (n=117)	P
AJCC.M, n (%)				0.006
M1	17 (7.59)	6 (5.61)	11 (9.4)	
M1a–M1b	73 (32.59)	46 (42.99)	27 (23.08)	
M1c	134 (59.82)	55 (51.4)	79 (67.52)	
Surgery, n (%)				<0.001
No	145 (64.73)	56 (52.34)	89 (76.07)	
Yes	79 (35.27)	51 (47.66)	28 (23.93)	
Chemotherapy, n (%)				0.12
No	71 (31.7)	28 (26.17)	43 (36.75)	
Yes	153 (68.3)	79 (73.83)	74 (63.25)	
Targeted, n (%)				0.944
No	169 (75.45)	80 (74.77)	89 (76.07)	
Yes	55 (24.55)	27 (25.23)	28 (23.93)	
Histologic, n (%)				0.947
LAC	194 (86.61)	92 (85.98)	102 (87.18)	
Others	30 (13.39)	15 (14.02)	15 (12.82)	
Met_{Lung}, n (%)				0.011
No	111 (49.55)	63 (58.88)	48 (41.03)	
Yes	113 (50.45)	44 (41.12)	69 (58.97)	
Met_{Chest}, n (%)				0.227
No	84 (37.5)	45 (42.06)	39 (33.33)	
Yes	140 (62.5)	62 (57.94)	78 (66.67)	
Met_{Liver}, n (%)				0.044
No	206 (91.96)	103 (96.26)	103 (88.03)	
Yes	18 (8.04)	4 (3.74)	14 (11.97)	
Met_{Bone}, n (%)				0.002
No	141 (62.95)	79 (73.83)	62 (52.99)	
Yes	83 (37.05)	28 (26.17)	55 (47.01)	
$Met_{Adrenal}$, n (%)				0.018
No	191 (85.27)	98 (91.59)	93 (79.49)	
Yes	33 (14.73)	9 (8.41)	24 (20.51)	
DS_GPA, n (%)				0.056
0	5 (2.23)	2 (1.87)	3 (2.56)	
0.5	8 (3.57)	3 (2.8)	5 (4.27)	

Table 1 (*continued*)

Table 1 (*continued*)

Variables	Total (n=224)	LDH ≤180 (n=107)	LDH >180 (n=117)	P
1	29 (12.95)	12 (11.21)	17 (14.53)	
1.5	42 (18.75)	21 (19.63)	21 (17.95)	
2	51 (22.77)	19 (17.76)	32 (27.35)	
2.5	36 (16.07)	18 (16.82)	18 (15.38)	
3	27 (12.05)	16 (14.95)	11 (9.4)	
3.5	14 (6.25)	5 (4.67)	9 (7.69)	
4	12 (5.36)	11 (10.28)	1 (0.85)	

LDH, lactate dehydrogenase; BMI, body mass index; KPS, Karnofsky Performance Status; Met_{num}, number of metastasis; AJCC, American Joint Committee on Cancer; LAC, lung adenocarcinomas; Met_{Lung}, lung metastasis; Met_{Chest}, chest metastasis; Met_{Liver}, liver metastasis; Met_{Bone}, bone metastasis; $Met_{Adrenal}$, adrenal metastasis; DS_GPA, diagnosis-specific graded prognostic assessment.

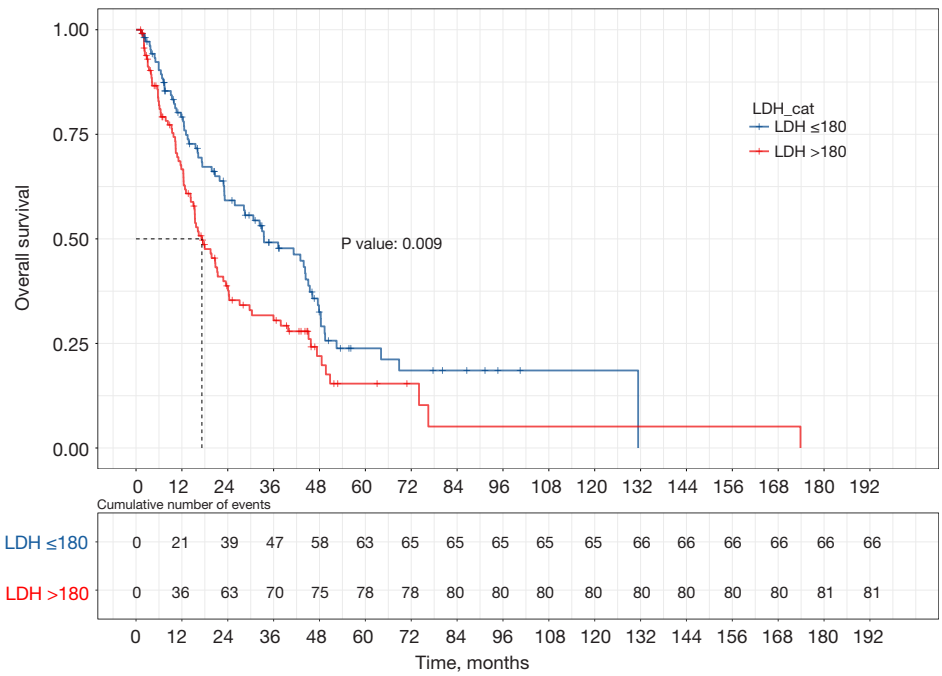

Figure 3 Kaplan-Meier analysis showing the OS in patients grouped according to LDH level. LDH, lactate dehydrogenase; OS, overall survival.

was statistically significant (P=0.009).

Univariate and multivariate Cox regression analyses

In the Schoenfeld residual diagram, the change in the visible curve with time was not obvious, so LDH satisfied the PH hypothesis (P=0.95) (Figure S1), which confirms that the Cox regression model (PHs regression model, proportional risk regression model) is meaningful.

The results showed that in univariate survival analysis, LDH >180 U/L [HR =1.549, 95% confidence interval (95% CI): 1.115–2.152, P=0.009], age (51–60 and >61 years, P=0.004 and 0.001), KPS score (70–80, >80, P=0.025 and 0.003), smoking (P=0.003), AJCC N stage (N2, N3, P=0.008 and 0.005), AJCC M1c stage (P=0.007), primary surgery (P<0.001), thoracic metastasis (P<0.001), and liver

metastasis (P=0.034) were risk factors for OS. However, patients with KPS scores ≥70 and primary surgery exhibited a lower risk of death. In the multivariate analysis, high LDH (HR =1.567, 95% CI: 1.058–2.32, P=0.025), age (51–60 and >60 years, P=0.019 and 0.002), smoking (P=0.046), AJCC M1c stage (P=0.01), and thoracic metastasis (P=0.003) were all identified as independent risk factors for OS (*Figure 4*).

Subgroup analysis

The effects of different covariables including age, sex, extracranial metastasis (lung, breast, liver, bone, and adrenal gland), KPS, number of brain metastases, smoking, AJCC T stage, AJCC N stage, AJCC M stage, BMI, and treatment (primary focus surgery/chemotherapy/targeted therapy) on the prognosis of patients grouped by serum LDH levels (high LDH group *vs.* low LDH group) were assessed. The likelihood ratio test showed that there was no significant difference between the level of serum LDH and other covariables; that is, there was no significant interaction between LDH and the above covariables (*Figure 5*).

Sensitivity analysis

In this study, there may have been unmeasured or unknown confounding factors that could lead to bias in the research results. We used sensitivity analysis to explore the robustness of the research results (*Figure 6*). The E value of LDH was 2.07 (95% CI: 1.055–2.65) and the RR was 1.36, indicating that the findings were still reliable, despite the possible presence of unmeasured confounding factors.

Discussion

This study evaluated the prognostic value of serum LDH in NSCLC patients with brain metastases. The survival time of patients with brain metastases from NSCLC is limited, and strategies for the detection of representative markers are worthy of further research, as the application of such strategies could prolong the survival time of patients. Our findings suggest that LDH is an independent prognostic factor for OS in NSCLC patients with brain metastases. The findings of this study remained reliable despite the possible presence of unmeasured confounders.

Brain metastasis is a serious complication of NSCLC. Tumor cells use 30 times more glucose and produce 40 times more lactate through glycolysis than normal cells (13), and this feature is more prominent in patients with brain metastases. One of the key enzymes in the glycolytic pathway is LDH, and five isoenzymes are widely present in human tissues. On the one hand, LDH participates in glycolysis during the process of cancer cell proliferation, provides energy for cancer cells, and promotes their growth (22). On the other hand, LDH promotes the immune escape of cancer cells by inhibiting the function of cluster of differentiation 8+ (CD8+) cells and natural kill (NK) cells (23,24). In addition, it can also promote tumor angiogenesis as well as cell migration and metastasis by promoting the expression of VEGF (14). This ultimately leads to a poor prognosis and shorter survival times in patients.

High serum LDH levels are associated with resistance to various chemotherapy regimens, such as bevacizumab 20, platinum-based agents, and programmed cell death protein 1 (PD-1), in advanced NSCLC (25). Resistance is the result of the conversion of lactate to pyruvate by stromal cells, which promotes cancer cell progression and increases their resistance to chemotherapeutic agents (26), thereby reducing patient survival. Patients with advanced NSCLC are usually treated with targeted therapy and chemotherapy. In patients with advanced NSCLC treated with immune checkpoint inhibitors (ICIs), elevated pretreatment LDH is an independent marker of poor prognosis. Moreover, the continuous increase in LDH during treatment is associated with poor OS (27). In advanced NSCLC patients receiving platinum-based chemotherapy, increased LDH (≥20%) and high LDH before treatment are associated with lower OS (28).

In this study, we enrolled patients undergoing chemotherapy, targeted therapy, and primary surgery. Their LDH values before imaging diagnosis or surgical pathology were determined, and NSCLC patients with a baseline LDH >180 U/L were selected. NSCLC patients with brain metastases demonstrated a significantly increased risk of death, which is consistent with previous findings. This study also found through univariate analysis that age (51–60 and >61 years), KPS score (70–80, >80), smoking, AJCC N stage (N2, N3), AJCC M1c stage, primary surgery, thoracic metastases, liver metastases, and LDH >180 U/L were significantly associated with a higher risk of death, while a KPS score of ≥70 points and primary tumor surgery were related to increased survival time in patients. After multivariate adjustment, high LDH was still an independent risk factor for OS (HR =1.43, 95% CI: 1.004–2.038, P=0.048); age (51–60 and >60 years), smoking, AJCC M1c stage, and thoracic metastasis were also independent

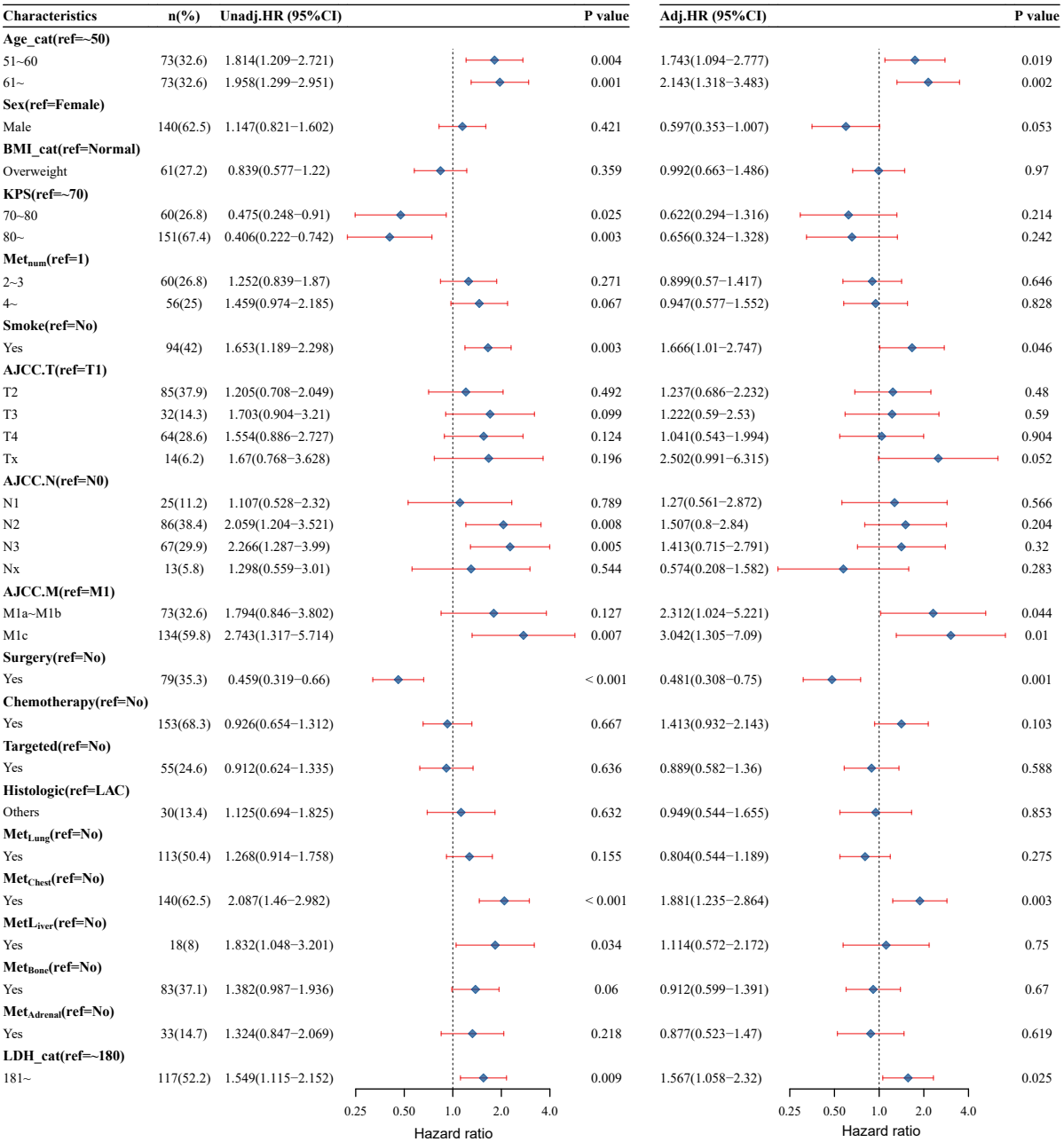

Figure 4 Forest plots of the univariate and multivariate factor analyses. Uadj.HR, unadjusted hazard ratio; CI, confidence interval; Adj.HR, adjusted hazard ratio; BMI, body mass index; KPS, Karnofsky Performance Status; Met_{num}, number of metastasis; AJCC, American Joint Committee on Cancer; LAC, lung adenocarcinomas; Met_{Lung}, lung metastasis; Met_{Chest}, chest metastasis; Met_{Liver}, liver metastasis; Met_{Bone}, bone metastasis; $Met_{Adrenal}$, adrenal metastasis; LDH, lactate dehydrogenase.

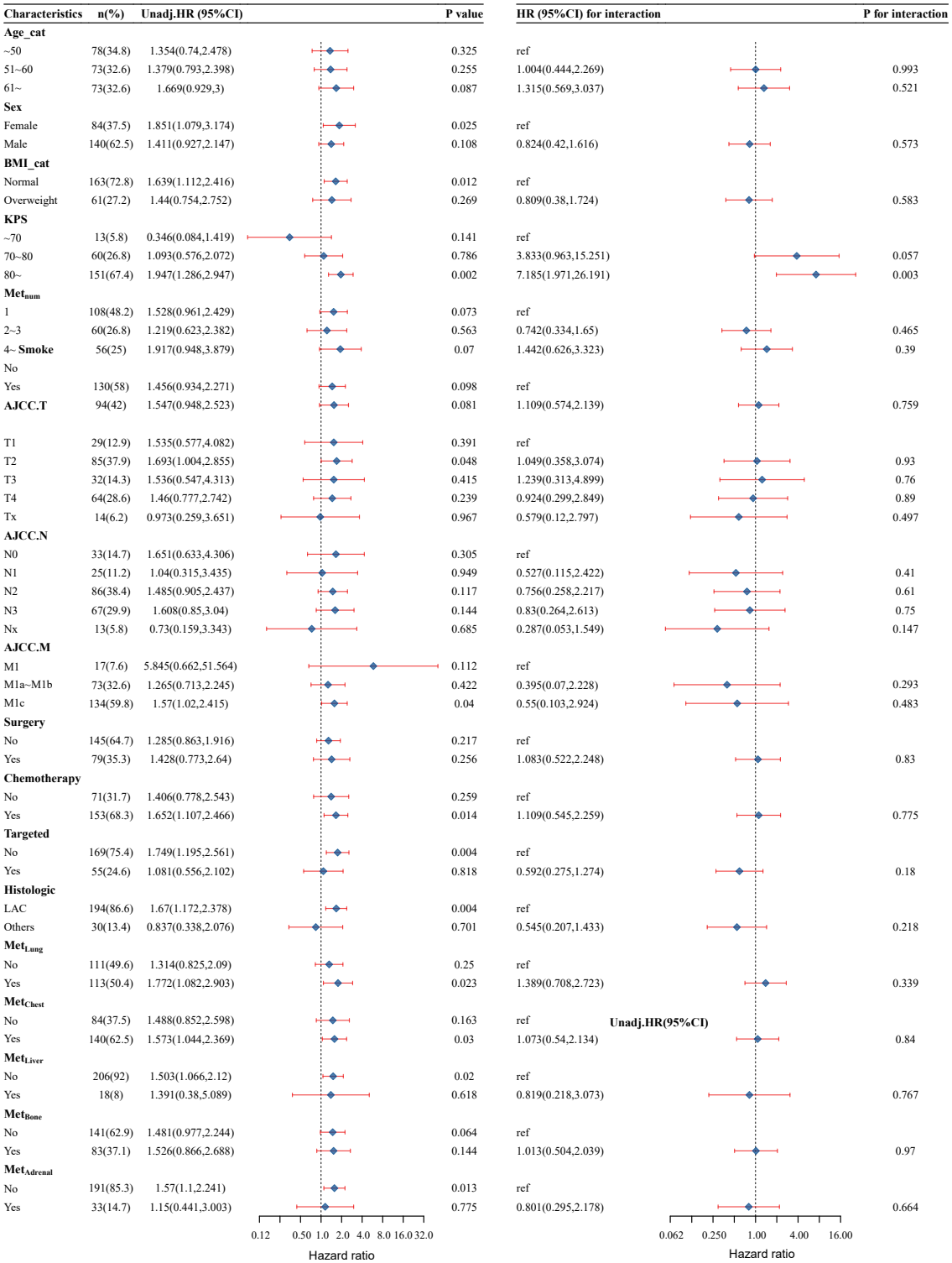

Figure 5 Subgroup analysis forest plot. Uadj.HR, unadjusted hazard ratio; CI, confidence interval; Adj.HR, adjusted hazard ratio; BMI, body mass index; KPS, Karnofsky Performance Status; Met_{num}, number of metastasis; AJCC, American Joint Committee on Cancer; LAC, lung adenocarcinomas; Met_{Lung}, lung metastasis; Met_{Chest}, chest metastasis; Met_{Liver}, liver metastasis; Met_{Bone}, bone metastasis; $Met_{Adrenal}$, adrenal metastasis.

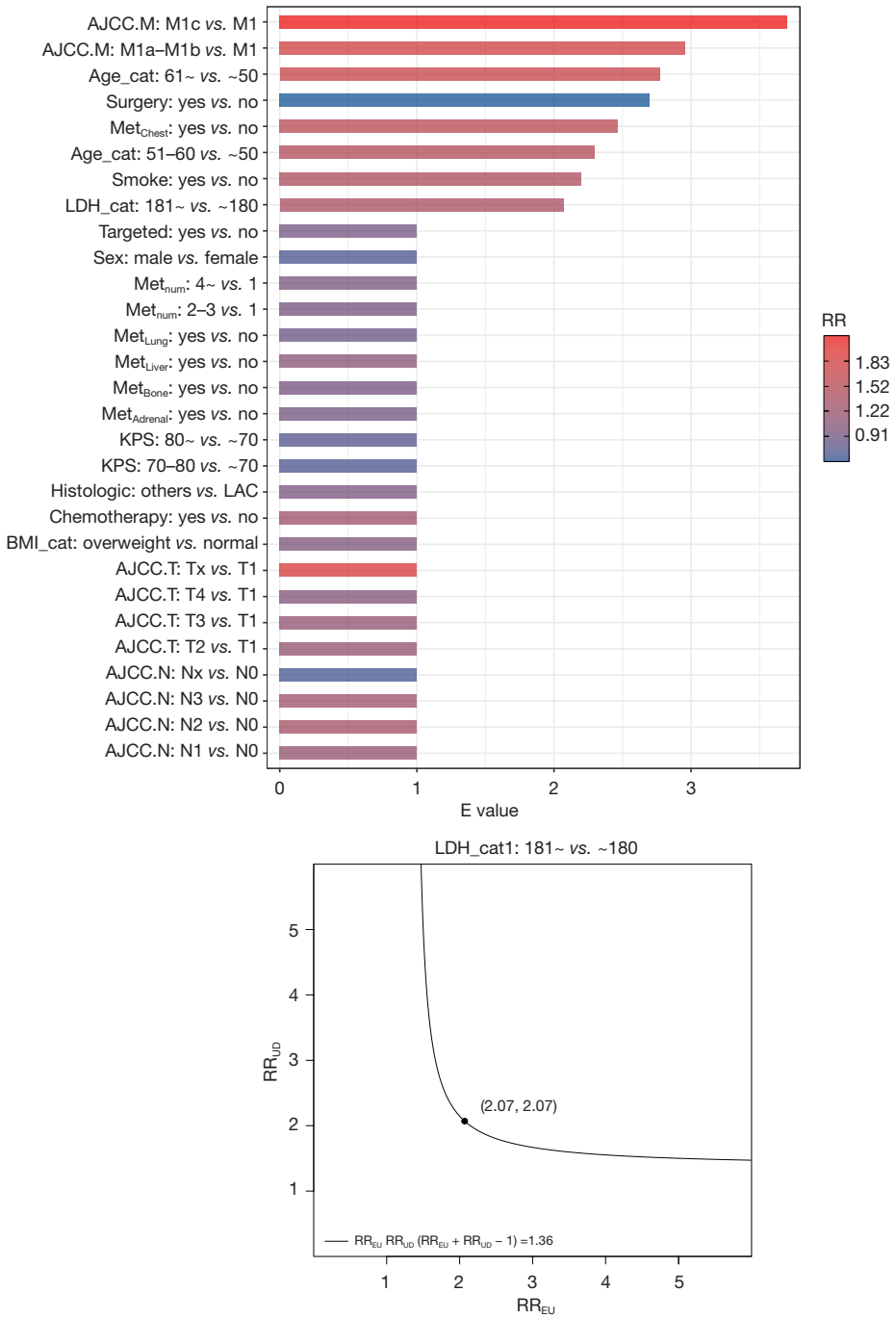

Figure 6 Calculated E-value, bar chart, and the functional relationship between RR_{EU} and RR_{UD}. AJCC, American Joint Committee on Cancer; Met_{Chest}, chest metastasis; LDH, lactate dehydrogenase; Met_{num}, number of metastasis; Met_{Lung}, lung metastasis; Met_{Liver}, liver metastasis; Met_{Bone}, bone metastasis; $Met_{Adrenal}$, adrenal metastasis; KPS, Karnofsky Performance Status; LAC, lung adenocarcinomas; BMI, body mass index; RR_{EU}, maximum relative risk (RR) for any specific level of the unmeasured confounders (U) comparing those with and without exposure (E) i.e., serum LDH level, with adjustment already made for the measured covariates; RR_{UD}, maximum relative risk (RR) for the denouement (D) i.e., prognosis comparing any 2 categories of the unmeasured confounders (U), with adjustment already made for the measured covariates.

risk factors.

Based on the above findings, patients with high LDH, AJCC M1c stage, thoracic metastases, and age ≥51 years tend to experience worse survival outcomes, and these patients may require better follow-up care. Therefore, the routine detection of LDH levels in patients with brain metastases diagnosed by imaging or by surgical pathology may provide valuable prognostic information. Moreover, for patients who require chemotherapy, the treatment of elevated LDH levels prior to cancer treatment may reduce tumor pressure and improve the efficacy of chemotherapeutic drugs, thereby prolonging the survival time of patients.

Currently, various effective LDH inhibitors have been used in clinical treatment, and the inhibition of LDH has a minimal effect on normal tissues (29). More importantly, reducing LDH activity has been shown to inhibit several other measures of cancer proliferation *in vivo* (30). Galloflavin, oxalate, and other inhibitors can be used to treat breast cancer (31), hepatocellular carcinoma (32), endometrial cancer (33), pancreatic cancer (34), nasopharyngeal cancer (35), Burkitt lymphoma (36), and other malignant tumors. In the future, more types of LDH inhibitors may be used in patients with advanced NSCLC, thereby improving the survival time of patients.

There are some limitations to this study that should be noted. Firstly, this study suffers from the limitations inherent to retrospective analyses of observational data from a single center. It also lacks LDH gene expression analysis in NSCLC patients with brain metastases, analysis of NSCLC brain metastases before and after chemotherapy, and a comparative study of LDH in patients with metastatic disease. In addition, LDH levels may be affected by other factors. Although this study has certain limitations, it still has a certain guiding significance for the treatment of patients with advanced NSCLC with brain metastases.

Conclusions

The mortality risk increases sharply in NSCLC patients with brain metastases with LDH >180 U/L. High LDH is an independent risk factor for NSCLC patients with brain metastases.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1502/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1502/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1502/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the ethics committee of Tumor Hospital of Yunnan Province (No. KYLX2022130). The requirement for individual consent for this retrospective analysis was waived.

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Supplementary

Table S1 Characteristics of patients grouped by survival

Variables	Total (n=224)	0 (n=77)	1 (n=147)	P
Age_cat, n (%)				0.092
~50	78 (34.82)	34 (44.16)	44 (29.93)	
51~60	73 (32.59)	20 (25.97)	53 (36.05)	
61~	73 (32.59)	23 (29.87)	50 (34.01)	
Sex, n (%)				0.913
Female	84 (37.5)	28 (36.36)	56 (38.1)	
Male	140 (62.5)	49 (63.64)	91 (61.9)	
BMI_cat, n (%)				0.628
Normal	163 (72.77)	54 (70.13)	109 (74.15)	
Overweight	61 (27.23)	23 (29.87)	38 (25.85)	
KPS, n (%)				0.091
~70	13 (5.8)	1 (1.3)	12 (8.16)	
70~80	60 (26.79)	20 (25.97)	40 (27.21)	
80~	151 (67.41)	56 (72.73)	95 (64.63)	
Metnum, n (%)				0.65
1	108 (48.21)	34 (44.16)	74 (50.34)	
2~3	60 (26.79)	23 (29.87)	37 (25.17)	
4~	56 (25)	20 (25.97)	36 (24.49)	
Smoke, n (%)				0.17
No	130 (58.04)	50 (64.94)	80 (54.42)	
Yes	94 (41.96)	27 (35.06)	67 (45.58)	
AJCC.T, n (%)				0.933
T1	29 (12.95)	11 (14.29)	18 (12.24)	
T2	85 (37.95)	27 (35.06)	58 (39.46)	
T3	32 (14.29)	11 (14.29)	21 (14.29)	
T4	64 (28.57)	24 (31.17)	40 (27.21)	
Tx	14 (6.25)	4 (5.19)	10 (6.8)	
AJCC.N, n (%)				0.138
N0	33 (14.73)	16 (20.78)	17 (11.56)	
N1	25 (11.16)	11 (14.29)	14 (9.52)	
N2	86 (38.39)	22 (28.57)	64 (43.54)	
N3	67 (29.91)	23 (29.87)	44 (29.93)	
Nx	13 (5.8)	5 (6.49)	8 (5.44)	
AJCC.M, n (%)				0.234
M1	17 (7.59)	9 (11.69)	8 (5.44)	
M1a~M1b	73 (32.59)	23 (29.87)	50 (34.01)	
M1c	134 (59.82)	45 (58.44)	89 (60.54)	
Surgery, n (%)				0.031
No	145 (64.73)	42 (54.55)	103 (70.07)	
Yes	79 (35.27)	35 (45.45)	44 (29.93)	
Chemotherapy, n (%)				0.784
No	71 (31.7)	23 (29.87)	48 (32.65)	
Yes	153 (68.3)	54 (70.13)	99 (67.35)	
Targeted, n (%)				0.846
No	169 (75.45)	57 (74.03)	112 (76.19)	
Yes	55 (24.55)	20 (25.97)	35 (23.81)	
Histologic, n (%)				0.938
LAC	194 (86.61)	66 (85.71)	128 (87.07)	
Others	30 (13.39)	11 (14.29)	19 (12.93)	
MetLung, n (%)				0.641
No	111 (49.55)	36 (46.75)	75 (51.02)	
Yes	113 (50.45)	41 (53.25)	72 (48.98)	
MetChest, n (%)				0.292
No	84 (37.5)	33 (42.86)	51 (34.69)	
Yes	140 (62.5)	44 (57.14)	96 (65.31)	
MetLiver, n (%)				0.383
No	206 (91.96)	73 (94.81)	133 (90.48)	
Yes	18 (8.04)	4 (5.19)	14 (9.52)	
MetBone, n (%)				0.993
No	141 (62.95)	49 (63.64)	92 (62.59)	
Yes	83 (37.05)	28 (36.36)	55 (37.41)	
MetAdrenal, n (%)				0.738
No	191 (85.27)	67 (87.01)	124 (84.35)	
Yes	33 (14.73)	10 (12.99)	23 (15.65)	
DS_PGA, n (%)				0.522
0	5 (2.23)	0 (0)	5 (3.4)	
0.5	8 (3.57)	2 (2.6)	6 (4.08)	
1	29 (12.95)	11 (14.29)	18 (12.24)	
1.5	42 (18.75)	13 (16.88)	29 (19.73)	
2	51 (22.77)	19 (24.68)	32 (21.77)	
2.5	36 (16.07)	11 (14.29)	25 (17.01)	
3	27 (12.05)	8 (10.39)	19 (12.93)	
3.5	14 (6.25)	6 (7.79)	8 (5.44)	
4	12 (5.36)	7 (9.09)	5 (3.4)	

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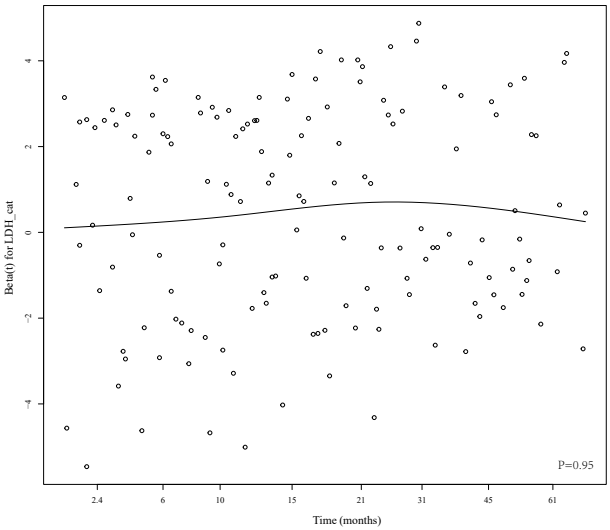

Figure S1 Schoenfeld residual diagram of LDH. LDH, lactate dehydrogenase.

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