Research Article

LDH and GGT/ALT Ratio as Novel Prognostic Biomarkers in Hepatocellular Carcinoma Patients after Liver Transplantation

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Background. Liver inflammation indices reflect its inflammatory microenvironment, which may play a role in the proliferation, invasion, and migration of carcinoma. This study is aimed at exploring the prognostic significance of serum lactate dehydrogenase (LDH) levels and gamma-glutamyl transferase (GGT)/alanine aminotransferase (ALT) ratio in hepatocellular carcinoma after liver transplant (LT).

Methods. We retrospectively analyzed data from 155 patients with a pathologically confirmed diagnosis of hepatocellular carcinoma who received LT between January 2013 and September 2017. We used receiver operating characteristics (ROC) curves to determine the optimal LDH and GGT/ALT ratio cut-off values. The Kaplan–Meier method and the logarithmic rank test were used to compare the survival curves without recurrence (RFS) and overall survival (OS). Univariate and multivariate analyses were used to identify factors associated with survival.

Results. Serum LDH levels were significantly associated with the Child-Pugh score \( (P = 0.037) \), largest tumor size \( (<50 \text{ vs. } \geq 50 \text{ mm}) \) \( (P = 0.017) \), tumor count \( (<3 \text{ vs. } \geq 3) \) \( (P = 0.009) \), microvascular invasion \( (P = 0.006) \), and the Milan criteria \( (P \leq 0.001) \). The serum GGT/ALT ratio was significantly correlated with alpha-fetoprotein (AFP) levels \( (of <400 \text{ vs. } \geq 400 \text{ ng/ml}) \) \( (P \leq 0.001) \), largest tumor size \( (of <50 \text{ vs. } \geq 50 \text{ mm}) \) \( (P \leq 0.001) \), the Edmondson grade \( (I-II \text{ vs. } III-IV) \) \( (P = 0.028) \), microvascular invasion \( (P \leq 0.001) \), and the Milan \( (P = 0.002) \) and Hangzhou criteria \( (P = 0.018) \). The survival curves showed that the patients with high LDH and the GGT/ALT ratio were associated with poor RFS and OS \( (P < 0.05) \). Univariate and multivariate analyses showed that AFP levels of \( \geq 400 \text{ ng/ml} \), largest tumor size of \( \geq 50 \text{ mm} \), microvascular invasion, LDH levels of \( \geq 213.5 \text{ U/l} \), and the GGT/ALT ratio of \( \geq 3.1338 \) were factors independently associated with RFS. Conclusion. Elevated LDH levels and the GGT/ALT ratio before LT were associated with poor OS and RFS in the present study. These factors could be used in the prognostication of patients with hepatocellular carcinoma undergoing LT.

1. Introduction

Hepatocellular carcinoma (HCC) is the most common form of primary liver tumor and is one of the leading causes of cancer-related deaths worldwide [1, 2]. Its incidence and associated mortality continue to increase and attract attention. HCC is associated with several risk factors, such as hepatitis B virus and hepatitis C virus (HCV) infections, which account for most HCC cases, in particular those diagnosed in East Asia [3]. Furthermore, HCC has also been associated with aflatoxin exposure, heavy alcohol intake, obesity, smoking, and type 2 diabetes [4, 5].

Current treatments for HCC include surgical resection, liver transplant (LT), transcatheter arterial chemoembolization (TACE), and radiofrequency ablation (RFA) [6]. LT is currently considered the most definitive treatment option for HCC, as it removes the tumor as well as the unhealthy organ, which, when retained, remains at risk of HCC recurrence due to the presence of cirrhotic tissue [7]. Patient prognosis following LT is associated with the risk of HCC recurrence; thus, several selection criteria have been established to help select patients most likely to benefit from an LT, including the Milan criteria (the diameter of a single tumor was less than 5 cm, and the maximum diameter of
multiple tumors was less than 3 cm) and the Hangzhou criteria (tumor diameter < 8 cm or tumor diameter > 8 cm, and preoperative AFP < 400 ng/ml and tumor histological grade were high and medium differentiation). Although we can apply these strict criteria to clinical trials, 5-year recurrence-free survival (RFS) of HCC after LT is only 75% [8].

In the clinical setting, abdominal ultrasound, computed tomography, magnetic resonance imaging, and alpha-fetoprotein (AFP) level assessments are commonly used to estimate the risk of HCC recurrence after surgery. These results sometimes can only work when there is a definite recurrence of HCC, so we want to seek some indices which can predict the survival of HCC after LT easily. Recent studies have shown that tumor inflammatory microenvironments can contribute to the risk of proliferation, invasion, and migration of carcinoma [9], suggesting the role of preoperative peripheral blood inflammation markers, such as C-reactive protein levels [10], platelet-to-lymphocyte ratio [11], and neutrophil-to-lymphocyte ratio [12, 13] in the postoperative period. In addition, liver inflammation indices such as gamma-glutamyl transferase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase, and lactate dehydrogenase (LDH) levels have been associated with the risk of HCC recurrence after hepatectomy [14, 15]. Notwithstanding, there have been few studies on the relationship between liver inflammation indices and HCC prognosis after LT. The present study is aimed at examining the prognostic value of LDH levels and the GGT/ALT ratio in patients with HCC who underwent LT while adjusting for clinicopathological characteristics.

2. Methods

2.1. Ethics. This study was performed according to the principles of the Declaration of Helsinki and approved by the Ethics Committee of the First Affiliated Hospital of Sun Yat-sen University. All transplanted organs came from legal donors. Before the LT, each recipient provided informed consent to their data being used for research purposes.

2.2. Patients. We retrospectively analyzed the clinical records of 155 patients that were diagnosed with HCC and received an LT at the First Affiliated Hospital of Sun Yat-sen University between January 2013 and September 2017; these patients were followed up until October 2020. Data were extracted from the China Liver Transplantation Register (http://www.cltr.org/) and patient medical records; the variables of interest included recipient age, sex, height and weight, liver encephalopathy status, ascites, pretransplant treatments, and preoperative laboratory findings, including total bilirubin and albumin levels, prothrombin time, international normalized ratio value, and GGT, ALT, LDH, creatinine, and AFP levels. We determined the number and size of tumors and the macrovascular invasion status based on imaging findings. The Edmondson tumor grade (the main methods of pathological classification of HCC at present) and microvascular invasion status were determined based on pathological findings. We also calculated body mass index, model for end-stage liver disease (MELD) score, and the Child-Pugh class and GGT/ALT ratio. All patients survived for at least 45 days postoperatively; there was no case of surgery-related death in this cohort.

2.3. Inclusion and Exclusion Criteria. Patients were eligible for this study if they met the following criteria: (1) histologically confirmed HCC, (2) absence of distant metastases, and (3) age 18-75 years. Patients were excluded from this study if

| Characteristics | Median (25th-75th percentile) or no. (%) |
|-----------------|-----------------------------------------|
| Sex             | Male 142 (91.6)                           |
|                 | Female 13 (8.3)                           |
| Age (years)     | 50 (42-58)                               |
| Child-Pugh class| A 47 (30.3)                               |
|                 | B 87 (56.1)                               |
|                 | C 21 (13.5)                               |
| MELD score      | 11 (8-18)                                |
| Tumor number    | <3 82 (32.9)                              |
|                 | ≥3 73 (47.1)                              |
| Largest tumor size (mm) | 44 (25-80)                        |
| Edmondson grading| I-II 111 (71.6)                            |
|                 | III-IV 44 (28.4)                          |
| AFP (ng/ml)     | 117.24 (10.12-2614.33)                    |
| BMI (kg/m²)     | 22.15 (20.42-24.09)                       |
| Macrovascular invasion | Yes 121 (78.1)                           |
|                 | No 34 (21.9)                              |
| Microvascular invasion | Yes 115 (74.2)                           |
|                 | No 40 (25.8)                              |
| Pre-LT treatment| Surgical resection 30 (19.3)              |
|                 | TACE 174 (47.7)                           |
|                 | RFA 29 (18.7)                             |
| Milan criteria  | Yes 49 (31.6)                             |
|                 | No 106 (68.4)                             |
| Hangzhou criteria| Yes 110 (71.0)                            |
|                 | No 45 (29.0)                              |
| HCC recurrence  | 65 (41.9)                                |
| Follow-up (months) | 40 (22-54)                          |
| GGT (U/l)       | 111 (51-201)                             |
| ALT (U/l)       | 38 (25-58)                               |
| LDH (U/l)       | 208 (181-268)                            |
they met any of the following criteria: (1) perioperative death within 45 days, (2) incomplete clinical and follow-up information, (3) combined with other cancers, (4) diagnosis of comorbidities, (5) need for repeat transplantation, or (6) multiple organ transplantation.

2.4. Treatment and Follow-Up. Some patients received several treatments prior to LT, for example, surgical resection, TACE, and RFA. In such cases, we assessed imaging findings to confirm that indications for LT were present. For all patients, survival status was determined after a minimum of 3 years of follow-up. Patients were contacted by phone or in person. The follow-up data included the date of HCC recurrence or death as well as the cause of death. All recipients were followed up regularly; peripheral blood and imaging findings were used to assess HCC recurrence; patients that required hospitalization were admitted for further treatment.

2.5. Statistical Analysis. All data were presented as counts (%) or medians (IQR). Continuous variables were compared using the t-test; categorical variables were compared using the chi-square test. Receiver operating characteristic curve (ROC) analysis and the highest Youden index value (sensitivity + specificity − 1) were used to determine the optimal cut-off value of LDH levels and the GGT/ALT ratio. The Kaplan–Meier method and the log-rank test were used to compare RFS and OS curves. Multivariate and univariate Cox regression analyses were performed to obtain a risk model. All statistical analyses were performed using SPSS version 23.0 (SPSS, Chicago, IL, USA). The P values of <0.05 were considered indicative of a statistically significant finding.

3. Results

3.1. Clinical Characteristics of Patients. The patient’s clinical characteristics are presented in Table 1. A total of 155 patients were enrolled in this study, including 142 (91.6%) and 13 (8.3%) men and women, respectively, with an overall median age of 50 (range, 42-58) years. According to the Child-Pugh class system, 47 (30.3%), 87 (56.1%), and 21 (13.5%) patients were classified as Classes A, B, and C, respectively. The median MELD score of these patients was 11 (8-18) points. Before LT, 30 (19.3%), 74 (47.7%), and 29 (18.7%) patients received surgical resection, TACE, and RFA, respectively. Some patients received multiple pre-LT treatments. The Edmondson pathological grades of I-II and III-IV were observed in 111 (71.6%) and 44 (28.4%) patients, respectively. A total of 121 (78.1%) and 115 (74.2%) patients had macrovascular and microvascular invasion, respectively. The median largest tumor size was 11 mm (range, 8-18). A total of 110 (71.0%) and 49 (31.6%) patients met the Hangzhou and Milan criteria, respectively. HCC recurrence was observed in 65 (41.9%) patients.

3.2. Cutoff Values for LDH Levels and the GGT/ALT Relationship. The analysis of the ROC curve and the Youden index revealed that the optimal cutoff values of LDH levels and the GGT/ALT ratio to predict the recurrence of HCC after surgery were 80.5 U/l (AUC = 0.647, P = 0.002) and 3.1338 (AUC = 0.744, P = 0.001), respectively (Figure 1 and Table 2).

3.3. LDH Levels, the GGT/ALT Ratio, and Other Clinicopathological Features. Serum LDH levels were significantly associated with the Child-Pugh class (P = 0.057), largest tumor size (<50 vs. ≥50 mm) (P = 0.017), tumor
number (3 vs. 3) \((P = 0.009)\), microvascular invasion \((P = 0.006)\), and Milan criteria \((P = 0.001)\). Serum ratio of GGT/ALT was significantly associated with AFP levels \(<400 \text{ vs.} \geq 400 \text{ ng/ml} \) \((P \leq 0.001)\), largest tumor size \(<50 \text{ vs.} \geq 50 \text{ mm} \) \((P = 0.001)\), Edmondson grade \((\text{I-II vs. III-IV}) \) \((P = 0.028)\), microvascular invasion status \((P = 0.001)\), and the Milan \((P = 0.002)\) and Hangzhou criteria \((P = 0.018)\) (Table 3).

### Table 3: Relationship between LDH and GGT/ALT with clinicopathologic parameters.

| Patient-related factors | LDH (U/l) | GGT/ALT |
|-------------------------|-----------|---------|
|                         | \(<213.5\) | \(\geq 213.5\) | \(<3.1338\) | \(\geq 3.1338\) |
| Sex                     | \(n = 83\) | \(n = 72\) | \(n = 85\) | \(n = 70\) |
| Male                    | 75        | 67      | 76        | 66        |
| Female                  | 8         | 5       | 9         | 4         |
| Age (years)             |           |         |           |           |
| <60                     | 65        | 60      | 72        | 53        |
| \(\geq 60\)             | 18        | 12      | 13        | 17        |
| Child-Pugh class        |           |         |           |           |
| A                       | 27        | 20      | 24        | 23        |
| B                       | 40        | 47      | 50        | 37        |
| C                       | 16        | 5       | 11        | 10        |
| Pre-LT treatment        |           |         |           |           |
| Yes                     | 51        | 40      | 51        | 40        |
| No                      | 32        | 32      | 34        | 30        |
| AFP (ng/ml)             |           |         |           |           |
| <400                    | 56        | 38      | 63        | 31        |
| \(\geq 400\)            | 27        | 34      | 22        | 39        |
| Largest tumor size (mm) |           |         |           |           |
| <50                     | 56        | 35      | 63        | 28        |
| \(\geq 50\)             | 27        | 37      | 22        | 42        |
| Tumor number            |           |         |           |           |
| <3                      | 52        | 30      | 51        | 31        |
| \(\geq 3\)              | 31        | 42      | 34        | 39        |
| Edmondson grading       |           |         |           |           |
| I-II                    | 60        | 51      | 67        | 44        |
| III-IV                  | 23        | 21      | 18        | 26        |
| Macro-vascular invasion |           |         |           |           |
| Yes                     | 18        | 16      | 17        | 17        |
| No                      | 65        | 56      | 68        | 53        |
| Micro-vascular invasion |           |         |           |           |
| Yes                     | 14        | 26      | 13        | 27        |
| No                      | 69        | 46      | 72        | 43        |
| Milan criteria          |           |         |           |           |
| Yes                     | 36        | 13      | 36        | 13        |
| No                      | 47        | 59      | 49        | 57        |
| Hangzhou criteria       |           |         |           |           |
| Yes                     | 59        | 51      | 67        | 43        |
| No                      | 24        | 21      | 18        | 27        |

### 3.4. Kaplan–Meier Survival Curves of each Patient Group.

The RFS and OS curves for patients in the high and low LDH level groups and in the high and low GGT/ALT ratio groups are presented in Figures 2(a)–2(d), respectively. The high level of LDH and the GGT/ALT ratio was significantly associated with poor RFS \((P = 0.001 \text{ and } P = 0.001)\) and poor OS \((P = 0.008 \text{ and } P = 0.001)\), respectively.

### 3.5. Risk Factors Associated with the Prognosis of HCC.

RFS was used as the outcome representative of patient prognosis, as OS may be affected by a wider range of factors. Univariate analyses revealed that AFP levels of \(\geq 400 \text{ ng/ml}\), largest tumor size of \(50 \text{ mm}\), Edmondson grade \((\text{I-II vs. III-IV})\), and the Milan \((P = 0.002)\) and Hangzhou criteria \((P = 0.018)\) (Table 3).
microvascular invasion, LDH levels of $\geq 213.5$ U/L, and the GGT/ALT ratio of 3.1338 were significantly associated with poor RFS (Table 4). Multivariate analysis revealed that AFP levels of $\geq 400$ ng/ml, largest tumor size of $\geq 50$ mm, microvascular invasion, LDH levels of $\geq 213.5$ U/L, and the GGT/ALT ratio of $\geq 3.1338$ were independent risk factors for RFS (Table 4).

4. Discussion

The prognosis of HCC remains a major focus of research. Currently, LT is considered the most effective treatment for HCC worldwide. Any type of treatment is aimed at reducing the risk of HCC recurrence. The Milan criteria are the LT eligibility criteria associated with excellent long-
GGT is a membrane-bound enzyme that plays a crucial role in glutathione (GSH) metabolism, specifically in the degradation of extracellular GSH by cleaving its gamma-glutamyl bond [20] and promoting the recovery of amino acids for intracellular glutathione synthesis [21]. GSH is the main water-soluble antioxidant within the cell, while GGT is involved in a defense mechanism against oxidative stress within cells, which, in turn, can participate in tumorigenesis [23]. A growing body of evidence suggests that abnormal LDH levels are associated with increased rates of tumor metastasis and recurrence, as well as poor treatment outcomes in several cancer types [27, 28], including HCC [29]. In the present study, elevated LDH levels (≥213.5 U/l) were significantly associated with a higher Child-Pugh class (P = 0.037), largest tumor size of ≥50 mm (P = 0.017), tumor count of ≥3 (P = 0.009), and microvascular invasion (P = 0.006); these findings are consistent with those of previous studies. Furthermore, LDH levels were associated with post-LT RFS in patients with HCC.

LDH levels are assessed during routine preoperative checks. LDH is a critical metabolic enzyme that converts pyruvate to lactate under anaerobic conditions. A growing body of evidence suggests that abnormal LDH levels are associated with increased rates of tumor metastasis and recurrence, as well as poor treatment outcomes in several cancer types [27, 28], including HCC [29]. In the present study, elevated LDH levels (≥213.5 U/l) were significantly associated with a higher Child-Pugh class (P = 0.037), largest tumor size of ≥50 mm (P = 0.017), tumor count of ≥3 (P = 0.009), and microvascular invasion (P = 0.006); these findings are consistent with those of previous studies. Furthermore, LDH levels were associated with post-LT RFS in patients with HCC.

Previous studies have examined the contribution of LDH to tumor progression. Low oxygen levels (hypoxia) characterize cancer cells and influence their function. In addition, hypoxia is an important component of the tumor microenvironment (TME) as it alters the extracellular matrix, modulates the immune response of the tumor, and increases the rate of angiogenesis [30]. Under these conditions, LDH can play a significant role in the energy supply of carcinoma cells. Even in the presence of oxygen, a phenomenon called the Warburg effect refers to carcinoma cells that preferentially convert glucose to lactate in aerobic glycolysis [31]. Changes in metabolic pathways can contribute to tumor proliferation and growth by ensuring energy and substrate supply. These alterations could create advantageous reducing conditions in the TME that are optimal for cancer metabolism.

Table 4: Univariate and multivariate analyses of factors for prediction of recurrence-free survival.

| Characteristics                          | Univariate analysis | Multivariate analysis |
|-----------------------------------------|---------------------|-----------------------|
|                                         | HR                  | 95% CI                | Value      | HR                  | 95% CI                | Value      |
| Sex (male/female)                       | 1.224               | 0.491-3.051           | 0.664      |                     |                      |            |
| Age (<60/≥60) (years)                   | 0.904               | 0.483-1.693           | 0.753      |                     |                      |            |
| Child-Pugh stage (A/B/C)                | 1.118               | 0.757-1.652           | 0.574      |                     |                      |            |
| MELD score                              | 1.017               | 0.993-1.041           | 0.179      |                     |                      |            |
| BMI (kg/m²)                             | 0.970               | 0.896-1.051           | 0.459      |                     |                      |            |
| Tumor number (<3/≥3)                    | 1.437               | 0.882-2.341           | 0.146      |                     |                      |            |
| Largest tumor size (<50/≥50) (mm)       | 2.795               | 1.701-4.593           | 0.000      | 1.841               | 1.096-3.091          | 0.021      |
| Edmondson grading (I-II/III-IV)         | 1.805               | 1.081-3.015           | 0.024      | 2.120               | 1.260-3.568          | 0.005      |
| Pre-LT treatment (yes/no)               | 1.077               | 0.653-1.776           | 0.770      |                     |                      |            |
| AFP (<400/≥400) (ng/ml)                 | 3.320               | 2.017-5.466           | 0.000      | 2.120               | 1.260-3.568          | 0.005      |
| Macrovascular invasion (yes/no)         | 1.639               | 0.929-2.892           | 0.088      |                     |                      |            |
| Microvascular invasion (yes/no)         | 2.863               | 1.729-4.742           | 0.000      | 1.771               | 1.043-3.010          | 0.035      |
| GGT/ALT (<3.1338/≥3.1338)               | 3.361               | 1.998-5.654           | 0.000      | 2.008               | 1.208-3.609          | 0.008      |
| LDH (<213.5/≥213.5) (U/l)               | 2.408               | 1.459-3.974           | 0.001      | 1.791               | 1.075-2.985          | 0.025      |
survival [32]. Elevated LDH levels are common in the malignant progression of carcinoma, including HCC.

Finally, multivariate analysis demonstrated that AFP levels (400 ng/ml), the largest tumor size (50 mm), and microvascular invasion were independently associated with RFS. These factors were recognized in the development of HCC, so we would not discuss them here.

This study has several limitations. Since this study was retrospective and single-centered, the sample size was small and may have yielded biased estimates. Future multicenter and prospective studies with large sample sizes are required to confirm our findings.

5. Conclusions

Elevated pre-LT LDH levels and GGT/ALT ratio are associated with poor OS and RFS and may be clinically useful in the prognostication of patients with HCC undergoing LT.

Data Availability

The data used to support this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare no competing interests.

Authors’ Contributions

All authors contributed to the conception and design of the study; Q.Z. contributed to the clinical data collection and statistical analysis and wrote the first draft of this manuscript; X-Y.J. designed this study and modified the final manuscript. All authors have read and approved the final manuscript.

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