Original Article

Increased γ-glutamyl transferase positively contributed to the poor prognosis in lung cancer patients

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Background: γ-glutamyl transferase (GGT) has a critical effect on tumor initiation, progression, and metastasis; however, the particular role of circulating GGT factor in the prognosis of lung cancer remains undetermined. The aim of this study is to identify the relationship between the circulating level of GGT and poor prognosis of lung cancer patients.

Methods: A total of 1,098 lung cancer patients whose GGT values were available were enrolled in this study and divided into positive and negative groups. SPSS 19.0 was introduced to analyze the relationship between GGT and clinical characteristics and metastasis. The relationship between survival status and GGT was completed by Kaplan-Meier method. Cox regression model was conducted to confirm whether GGT served as an independent risk factor in the prognosis of lung cancer.

Results: Elevated GGT level was positively related to liver (P<0.01), bone (P<0.01), and lymph node (P<0.05) metastasis. Kaplan-Meier analysis indicated that elevated GGT significantly contributed to poor survival of lung cancer. In the specific histological subtype analysis, we found that GGT was only positively related to the survival condition of small-cell lung cancer (P<0.01), but not adenocarcinoma (ADC) (P=0.08) or squamous carcinoma (SCC) (P=0.49). Multivariate Cox regression model indicated that GGT could act as an independent factor for prediction of poor prognosis in lung cancer.

Conclusions: Our results confirmed that GGT contributed to poor survival of lung cancer and was important in prediction of metastasis and poor prognosis.

Keywords: γ-glutamyl transferase (GGT); lung cancer; survival status; poor prognosis

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Introduction

Lung cancer has the highest mortality rates among all cancers due to its late diagnosis (1). The routine techniques for lung cancer diagnosis include low-dose computed tomography (LDCT), sputum cytology testing and chest X-ray (2). While a LDCT can detect tumors at an earlier stage and help reduce the tumor mortality rate by up to 20% (3), CT-based diagnosis of lung cancer has a significant false-positive rate (4). Meanwhile, traditional serum biomarkers, such as neuron-specific enolase (NSE) (5), carbohydrate antigen 125 (6) and carcinoembryonic antigen (CEA), play critical roles in the diagnosis and prognosis of lung cancer patients despite their low sensitivity and specificity which range between 50% and 60% (7,8). Thus, novel, economical and noninvasive biomarkers are urgently needed for early diagnosis of lung cancer (9).

The enzyme, γ-glutamyl transferase (GGT), is associated with many disease outcomes (10) and has a prognostic

value for various cancers (11). Ma *et al*. reported that elevated serum GGT levels in hepatocellular carcinoma patients treated with radiofrequency ablation may serve as a prognostic marker to predict significantly decreased overall survival (OS) and recurrence (12). A study of several serum biomarkers in metastatic colorectal cancer, including GGT, alkaline phosphatase, and CEA, showed that combination of GGT and CEA have prognostic value to predict overall and progression-free survival (13). Kunutsor and Laukkanen found that increased GGT level contributed to poor prognosis in middle-aged prostate cancer patients (14), while another study also indicated that serum GGT level is a novel independent factor for poor prognosis of renal cell carcinoma (15).

However, a systematic analysis of the association between circulating GGT and the survival status of lung cancer patients has not yet been conducted. The present study retrospectively investigated GGT serum levels in Chinese lung cancer patients to determine whether it can be feasibly used as a prognostic parameter.

Methods

Patients

Lung cancer patients treated at the Pneumology Department of West China Hospital (Chengdu, China) between January 2008 and July 2012 were enrolled in the present study. All patient medical information was obtained from a prospective database. Exclusion criteria included lack of GGT level data, pathological cancer confirmation, follow-up data, evidence of lung cancer metastasis. Metastasis was determined by biopsy and whole-body CT scan. Survival time was determined as the time from disease diagnosis to the date of death or last follow-up by telephone inquiry. Tumor stages were defined according to the 7th edition of Tumor-Node-Metastasis staging (16). Subtype classification of lung cancer, especially ADC, was based on the 2015 WHO classification (17).

Clinical design

Serum GGT concentration was assessed by an immunoassay in the Medical Laboratory Department of the West China Hospital before surgery or any other treatment. Patients were classified into two groups (positive and negative) based on a serum GGT cut-off value of 40 U/L, which is widely recognized as the normal level. Patients in the positive group had a serum GGT level of ≥40 U/L, whereas patients in the negative group had a GGT level of <40 U/L. A correlation analysis of pretreatment serum GGT levels and clinical parameters (e.g., gender, age, smoking status, tumor type, tumor stage, and distant metastasis) was performed for patients classified as having lung cancer, adenocarcinoma (ADC), and squamous cell carcinoma (SCC). The relationship between serum GGT levels and survival prognosis was also investigated. A multivariate Cox regression model was used to determine whether serum GGT levels could serve as a prognostic parameter for lung cancer.

GGT measurement

Before operation initiation, as part the of routine pre-treatment, blood samples were drawn so as to evaluate the hepatic damage, and other biochemical tests. The period occurred about 24 to 48 hours before starting the specific therapy by way of a peripheral venous puncture. We examined and analyzed GGT concentrations using an enzymatic colorimetric test at 37 ℃. The identical conditions were used for L-g-glutamyl-3-carboxy-4-nitroanilide substrate (18).

Statistical analysis

SPSS version 19.0 was used to analyze all obtained data. A Chi-square test was used to evaluate the intergroup differences for discontinuous data. Survival status was analyzed by Kaplan-Meier curve and a multivariate Cox regression hazard ratio (HR) model was used to identify independent prognostic factors by analyzing clinical characteristics, and metastasis survival status. $P<0.05$ was considered statistically significant.

Results

Relationship between serum GGT levels and metastasis

A total of 1,098 patients with lung cancer were included in the present study and classified into the GGT-positive (N=320) and -negative (N=778) groups, based on a pretreatment serum GGT level cutoff of 40 U/L. Demographic and clinicopathological parameters of all enrolled patients are shown in *Table 1*. GGT stratification analysis showed very significant differences between the two groups with respect to clinicopathological features, such as gender ($P<0.001$), smoking status ($P<0.001$), and tumor

Table 1 Demographics and clinical pathological features of all enrolled lung cancer patients

Characteristics	No. of patients (%) (n=1,098)
Gender	
Male	754 (68.7)
Female	344 (31.3)
Age	
<45	93 (8.5)
45–65	643 (58.6)
>65	362 (33.0)
Histological classification	
Adenocarcinoma (ADC)	290 (26.4)
Squamous (SCC)	581 (52.9)
SCLC	195 (17.8)
Others	32 (2.9)
Stage	
I	103 (9.4)
II	106 (9.7)
III	283 (25.8)
IV	606 (55.2)
Metastasis	
No	278 (25.3)
Yes	820 (74.7)
GGT	
Negative	778 (70.9)
Positive	320 (29.1)

SCLC, small cell lung cancer; GGT, γ-glutamyl transferase.

stage (P<0.01), but not histological classification (P=0.164) or age (P=0.211). Serum GGT levels were also closely related to metastasis to bone (positive: 37.9%, negative: 62.1%; P<0.01), liver (positive: 42.2%, negative: 57.8%; P<0.01), and lymph nodes (positive: 31.7%, negative: 68.3%; P<0.05) (*Table 2*).

Correlation between GGT levels and metastasis incidence in ADC and SCC

Lung cancer primarily consists of two subtypes: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). NSCLC cases were mainly composed of ADC and squamous carcinoma (SCC). We next analyzed the association between the serum GGT levels, clinical characteristics, and metastasis in ADC patients. The results showed a pronounced correlation with the presence of metastatic lesions in bone (negative: 56.3%, positive: 43.8, P<0.01), liver (negative: 54.2%, positive: 45.8, P<0.05), and lymph nodes (negative: 63.3%, positive: 36.7, P<0.01). However, GGT-positive levels were not related to clinical features, such as gender (P=0.952), smoking status (P=0.902), and tumor stage (P=0.183) (*Table 3*). Overall, a total of 290 patients (negative: 195, positive: 95) were diagnosed with SCC. Histological subtype analysis showed that elevated serum GGT levels were not significantly correlated with clinicopathological parameters or diverse metastasis occurrence (all P>0.05) (*Table 4*) in SCC patients.

Association between serum GGT levels, lung cancer, clinical characteristics, and survival

Kaplan-Meier survival curves played a more important role in the assessment of the mortality at 3–5 years. Five-year survival analysis, specifically follow-ups ranging from 1 to 60 months, confirmed that high concentrations of serum GGT were closely associated with survival of all lung cancer patients (P<0.01). In particular, elevated serum GGT levels were significantly associated with survival of SCLC patients (P<0.01), but not ADC (P=0.08) or SCC (P=0.49) (*Figure 1A*). With respect to clinical characteristics, serum GGT levels were significantly correlated with survival in males (P<0.01), non-smokers (P<0.01), and tumor stages III–IV (P<0.01). Serum GGT levels were not significantly associated with any other clinical features (*Figure 1B,C*).

Independent factors for predicting a poor prognosis

By multivariate Cox regression model, based on the cut-off value for GGT level, we attempted to determine whether serum GGT levels can serve as an independent factor for predicting a poor prognosis in lung cancer patients. A multivariate Cox regression model can be used to analyze associations between multiple factors and OS times of patients; and, as is shown in *Table 5*, a significant difference was found for metastasis [95% confidence interval (CI): 1.196–1.814; P<0.001]. *Table 5* provides additional information concerning the multi-variable survival analysis. Compared with the GGT-negative group, the HR of GGT-positive patients increased by 0.858, with a 95% CI (0.730–1.009) (P=0.064). The HR value of all lung cancer

Table 2 Correlation of clinical characteristics and metastasis after stratification analysis by serum GGT levels

Variables	Negative (%) (n=778)	Positive (%) (n=320)	Total (n=1,098)	P value
Basic characteristics				
Age				
<45 years	60 (64.5)	33 (35.5)	93	0.211
45–65 years	452 (70.3)	191 (29.7)	643	
>65 years	266 (73.5)	96 (26.5)	362	
Gender				
Male	509 (67.5)	245 (32.5)	754	<0.001***
Female	269 (78.2)	75 (21.8)	344	
Histological classification				
Adenocarcinoma (ADC)	429 (73.8)	152 (26.2)	581	0.164
Squamous (SCC)	195 (67.2)	95 (32.8)	290	
SCLC	132 (67.7)	63 (32.3)	195	
Others	22 (68.8)	10 (31.3)	32	
Smoke status				
No	364 (76.3)	113 (23.7)	477	<0.001***
Yes	414 (66.7)	207 (33.3)	621	
Stage				
I	76 (73.8)	27 (26.2)	103	<0.01**
II	83 (78.3)	23 (21.7)	106	
III	215 (76.0)	68 (24.0)	283	
IV	404 (66.7)	202 (33.3)	606	
Metastasis				
Brain				
No	694 (71.4)	278 (28.6)	972	0.271
Yes	84 (66.7)	42 (33.3)	126	
Bone				
No	639 (73.1)	235 (26.9)	874	<0.01**
Yes	139 (62.1)	85 (37.9)	224	
Liver				
No	719 (72.2)	277 (27.8)	996	<0.01**
Yes	59 (57.8)	43 (42.2)	102	
Adrenal gland				
No	739 (71.3)	298 (28.7)	1,037	0.221
Yes	39 (63.9)	22 (36.1)	61	

Table 2 (*continued*)

Table 2 (*continued*)

Variables	Negative (%) (n=778)	Positive (%) (n=320)	Total (n=1,098)	P value
Lymph node				
No	334 (74.6)	114 (25.4)	448	<0.05*
Yes	444 (68.3)	206 (31.7)	650	
Intrapulmonary				
No	689 (71.3)	277 (28.7)	966	0.355
Yes	89 (67.4)	43 (32.6)	132	
Pleural				
No	662 (71.0)	271 (29.0)	933	0.865
Yes	116 (70.3)	49 (29.7)	165	
Mediastinal				
No	758 (71)	309 (29.0)	1,067	0.431
Yes	20 (64.5)	11 (35.5)	31	

P values were calculated using the Chi-square test. *, P<0.05; **, P<0.01; ***, P<0.001. GGT, γ-glutamyl transferase.

patients older than 65 years increased to 0.659 (95% CI: 0.562–0.773, P<0.001). Meanwhile, smoking history (HR, 1.202, 95% CI: 1.029–1.404, P<0.05) and advanced tumor stage (III: HR, 0.492, 95% CI: 0.360–0.671; IV: HR, 0.736, 95% CI: 0.616–0.880) were identified as independent risk factors for predicting poor outcomes (*Table 5*).

Specific histological subtype analysis had revealed similar results for the ADC patients. Other factors that could be used to predict a poor outcome in ADC patients included being ≥65 years old (HR, 0.704, 95% CI: 0.560–0.886), a smoking history (HR, 1.271, 95% CI: 1.028–1.571), tumor stages II–IV (II: HR, 0.180; III: HR, 0.437; IV: HR, 0.735), and presence of metastases (HR, 1.583, 95% CI: 1.153–2.173). The HR also increased by 0.927 in the GGT-positive group (95% CI: 0.734–1.170, P=0.521). Furthermore, the results demonstrated that serum GGT levels could be employed as a crucial biomarker in ADC patients (*Table 6*). Nevertheless, only elevated GGT levels identified a poor prognosis factor for SCLC.

Discussion

Although the prognostic value of serum GGT level in several tumors has been identified, the value concerning poor prognosis for lung cancer has not yet been determined. In our study, a large-scale population was classified into negative and positive groups. Here, we found that elevated serum GGT levels were more strongly associated with clinicopathological parameters, such as gender (P<0.001), smoking status (P<0.001), and tumor stage (P<0.01). Other clinical-pathological features showed no significant difference. Moreover, serum GGT levels showed a dramatic correlation with metastasis to the liver (P<0.01), bone (P<0.01), and lymph nodes (P<0.05) (*Table 2*), and a similar relationship was even more pronounced for ADC patients. The results revealed that high serum GGT levels were positively associated with metastasis (bone: P<0.01; liver: P<0.05; lymph node: P<0.01) (*Table 3*). Elevated GGT levels also positively correlated with the patient's OS rate for all lung cancer and subtypes (P<0.01), specifically SCLC (P<0.01) but not with ADC or SCC, males (P<0.01), smoking status (P<0.01), and tumor stage (P<0.01) (*Figure 1A,B,C*). These results are mostly consistent with previous studies in sex difference. In one study of serum GGT and coronary artery calcification (CAC) (19), elevated GGT level was an independent and reliable indicator for males but not females, with the key difference being attributed to more alcohol consumption in men compared with women (20). However, there is another interesting study with contrasting results. In Kim's study, the results revealed that elevated GGT level indicated poor clinical outcomes in females (21). In addition, GGT was strongly associated with incidence of tumor. It has also been reported that GTT can mediate GSH metabolism to produce lipid peroxidation, thus

Table 3 Association of clinical characteristics and metastasis stratified by GGT levels in adenocarcinoma patients (ADC)

Variables	Negative (%) (n=378)	Positive (%) (n=177)	Total (n=555)	P value
Basic characteristics				
Gender				
Male	311 (68.1)	146 (31.9)	457	0.952
Female	67 (68.4)	31 (31.6)	98	
Smoke status				
No	128 (68.4)	59 (31.6)	187	0.902
Yes	250 (67.9)	118 (32.1)	368	
Stage				
I	23 (56.1)	18 (43.9)	41	0.183
II	35 (66.0)	18 (34.0)	53	
III	109 (64.9)	59 (35.1)	168	
IV	211 (72.0)	82 (28.0)	293	
Metastasis				
Brain				0.298
No	335 (67.4)	162 (32.6)	497	
Yes	43 (74.1)	15 (25.9)	58	
Bone				
No	324 (70.6)	135 (29.4)	459	<0.01**
Yes	54 (56.3)	42 (43.8)	96	
Liver				
No	352 (69.4)	155 (30.6)	507	<0.05*
Yes	26 (54.2)	22 (45.8)	48	
Adrenal gland				
No	357 (68.4)	165 (31.6)	522	0.57
Yes	21 (63.6)	12 (36.4)	33	
Lymph node				
No	178 (74.5)	61 (25.5)	239	<0.01**
Yes	200 (63.3)	116 (36.7)	316	
Intrapulmonary				
No	334 (68.2)	156 (31.8)	490	0.939
Yes	44 (67.7)	21 (32.3)	65	
Pleural				
No	331 (68.0)	156 (32.0)	487	0.849
Yes	47 (69.1)	21 (30.9)	68	
Mediastinal				
No	372 (68.1)	174 (31.9)	546	0.925
Yes	6 (66.7)	3 (33.3)	9	

P values were calculated using the Chi-square test. *, P<0.05; **, P<0.01. GGT, γ-glutamyl transferase.

Table 4 Association of clinical characteristics and metastasis stratified by GGT levels in squamous carcinoma patients (SCC)

Variables	Negative (%) (n=195)	Positive (%) (n=95)	Total (n=290)	P value
Basic characteristics				
Gender				
Male	173 (65.8)	90 (34.2)	263	0.098
Female	22 (81.5)	5 (18.5)	27	
Age				
<45 years	5 (55.6)	4 (44.4)	9	0.706
45–65 years	121 (68.4)	56 (31.6)	177	
>65 years	69 (66.3)	35 (33.7)	104	
Smoke status				
No	38 (71.7)	15 (28.3)	53	0.444
Yes	157 (66.2)	80 (33.8)	237	
Stage				
I	17 (65.4)	9 (34.6)	26	0.73
II	29 (70.7)	12 (29.3)	41	
III	73 (70.2)	31 (29.8)	104	
IV	76 (63.9)	43 (36.1)	119	
Metastasis				
Brain				
No	187 (67.8)	89 (32.2)	276	0.409
Yes	8 (57.1)	6 (42.9)	14	
Bone				
No	171 (68.7)	78 (31.3)	249	0.2
Yes	24 (58.5)	17 (41.5)	41	
Liver				
No	182 (68.7)	83 (31.3)	265	0.089
Yes	13 (52.0)	12 (48.0)	25	
Adrenal gland				
No	185 (66.8)	92 (33.2)	277	0.447
Yes	10 (76.9)	3 (23.1)	13	
Lymph node				
No	84 (71.2)	34 (28.8)	118	0.236
Yes	111 (64.5)	61 (35.5)	172	
Intrapulmonary				
No	178 (68.5)	82 (31.5)	260	0.192
Yes	17 (56.7)	13 (43.3)	30	
Pleural				
No	179 (68.6)	82 (31.4)	261	0.144
Yes	16 (55.2)	13 (44.8)	29	
Mediastinal				
No	190 (67.6)	91 (32.4)	281	0.448
Yes	5 (55.6)	4 (44.4)	9	

GGT, γ-glutamyl transferase.

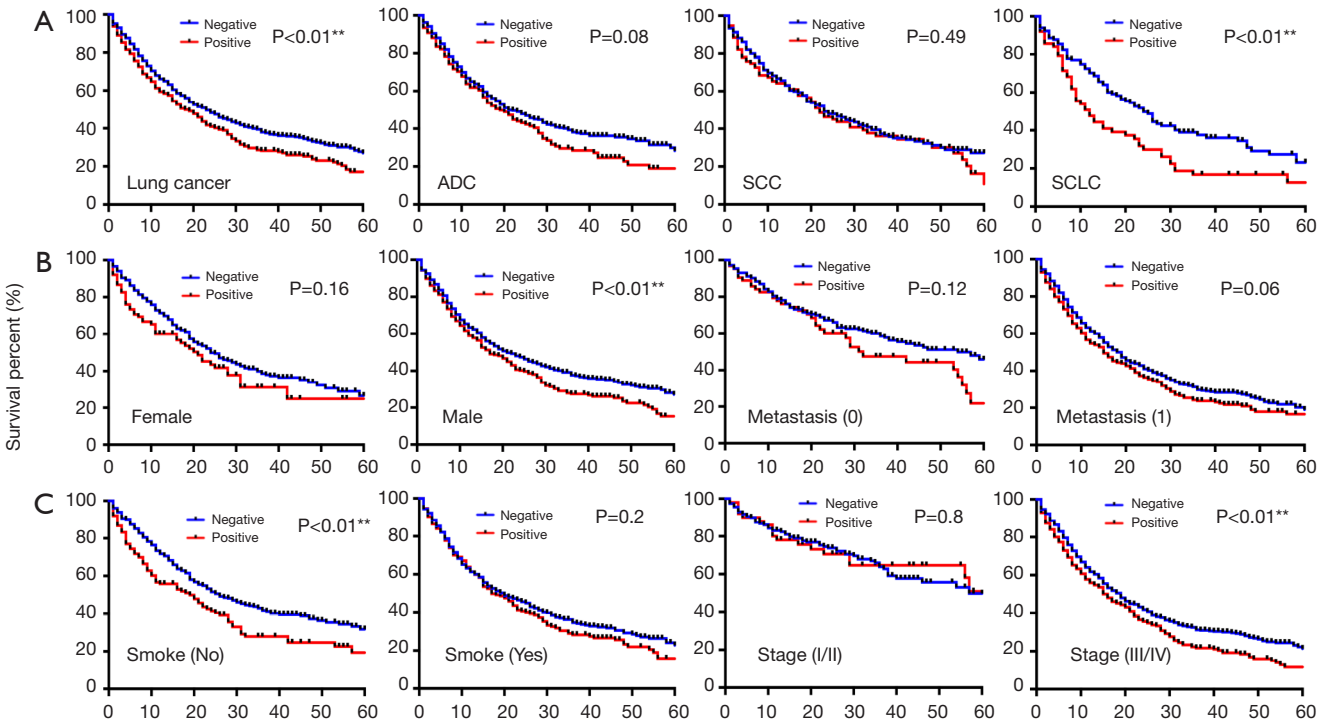

Figure 1 The survival status of lung cancer patients and clinicopathological parameters correlated with GGT. (A) All lung cancer patients, ADC patients, SCC patients, SCLC patients; (B) female/male/metastasis (0/1) patients; (C) smoke (no/yes), stage (I/II) and stage (III/IV). GGT, γ -glutamyl transferase; ADC, adenocarcinoma; SCC, squamous carcinoma; SCLC, small cell lung cancer.

Table 5 Multivariate analysis for all lung cancer

Variables	SE	Exp(B)	95% CI for Exp(B)	P value
Age				
<45				
45–65	0.149	0.645	0.482–0.863	<0.01**
>65	0.081	0.659	0.562–0.773	<0.001***
Smokes (no/yes)	0.079	1.202	1.029–1.404	<0.05
Stages				
I				
II	0.199	0.326	0.220–0.481	
III	0.159	0.492	0.360–0.671	<0.001***
IV	0.091	0.736	0.616–0.880	<0.01**
Metastasis (no/yes)	0.106	1.473	1.196–1.814	<0.001***
GGT (negative/positive)	0.083	0.858	0.730–1.009	0.064

P values were calculated using the Chi-square test. **, P<0.01; ***, P<0.001. GGT, γ-glutamyl transferase.

Table 6 Multivariate analysis for adenocarcinoma patients

Variables	SE	Exp(B)	95% CI for Exp(B)	P value
Age				
<45				
45–65	0.182	0.652	0.456–0.931	<0.05*
>65	0.117	0.704	0.560–0.886	0.01
Smokes (no/yes)	0.108	1.271	1.028–1.571	<0.05*
Stages				
I				
II	0.338	0.18	0.093–0.350	<0.001***
III	0.256	0.437	0.265–0.721	<0.01**
IV	0.141	0.735	0.557–0.970	<0.05*
Metastasis (no/yes)	0.162	1.583	1.153–2.173	<0.01**
GGT (negative/positive)	0.119	0.927	0.734–1.170	0.521

P values were calculated using the Chi-square test. *, P<0.05; **, P<0.01; ***, P<0.001. GGT, γ-glutamyl transferase.

explaining the correlation between high GGT and poor prognosis (22). Furthermore, serum GGT levels were found that is not independent poorly prognostic factor (*Table 5*).

GGT is a well-known marker of apoptosis and cellular detoxification (23) which has a remarkable relationship with metabolic syndrome, cardiovascular disease and diabetes (24). Highly active enzymes, like GGT, are secreted from organs, such as the liver, kidneys, and pancreas (25). An increasing number of clinical studies have demonstrated there to be an association between GGT and a poor survival (26) rate. Previously, Staudigl *et al*. showed that serum GGT levels could serve as a distinct prognostic parameter for breast cancer patients with metastases (18). In an analysis of 411 intrahepatic cholangiocarcinoma patients, Yin *et al*. found that high serum GGT levels could serve as a poor prognostic indicator for predicting invasive tumor behaviors (27). Yang *et al*. showed that serum GGT levels correlated with poor prognosis and the development of high-grade esophageal epithelial dysplasia in 639 patients (28). In patients with non-metastatic renal cell carcinoma with venous tumor thrombus, Luo *et al*. demonstrated that pre-operative GGT levels could act as an independent prognostic indicator (29). Elevated GGT levels have been observed to be crucial risk factor in a study of endometrial cancer survival biomarker which related with lifestyle (30). Mechanistically, in terms of tumorigenesis, the exact mechanism for correlating the elevated GGT levels and a vascular invasion with a lymph node involvement (31) remains unknown. It has been suggested that metastatic activity might be promoted by overexpression of GGT in melanoma, which regulates extracellular and intracellular GSH metabolism (32). It is possible that elevated GGT levels promote tumor growth by this method. While a large number of reports have confirmed the link between elevated serum GGT levels and tumor initiation, progression, recurrence, and metastasis, there is still an urgent need to further clarify the complete role of GGT in carcinogenesis (33). There were several potential limitations in this study. A portion of the patients were excluded due to incomplete data acquisition and the retrospective study design, and others were excluded due to alcohol abuse and hepatobiliary-diseases, which affected their serum GGT levels. Nevertheless, our results have significant clinical relevance.

To our knowledge, this study is the first to report the prognostic value of elevated circulating GGT levels in a large-scale population of lung cancer patients. Our findings confirmed that serum GGT levels play a crucial role in lung cancer susceptibility and can serve as a valuable prognostic indicator, especially in SCLC patients.

Conclusions

In conclusion, we designed this study to ascertain whether or not the GGT levels positively correlate with the occurrence of metastasis and risk survival. Our results demonstrated that GGT contributed to poor survival of

lung cancer and was crucially informative in the prediction of metastasis and poor prognosis. Further research is needed to determine if an understanding of the mechanistic pathways of GGT might have potential value in lung cancer prevention.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2018.11.11). 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). This study was approved by the Biomedical Ethics Committee Subcommittee in West China Hospital of Sichuan University. Informed consent was waived.

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