

Survival of Patients with Lung Cancer in the Setting of Liver Cirrhosis: A Multicenter Propensity Score Matching Study

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Purpose: The survival outcome of lung cancer patients with coexisting liver cirrhosis has thus far received limited attention in the literature. In this study, we evaluated whether liver cirrhosis is an independent risk factor for the survival of patients with lung cancer.

Materials and Methods: We conducted a retrospective, multicenter, propensity-matched study of lung cancer patients with and without liver cirrhosis. To determine differences in survival, we sought to identify risk factors associated with poor outcomes using Kaplan–Meier survival analysis and Cox proportional hazards regression.

Results: There were no statistically significant differences in the baseline clinical characteristics of patients between the cirrhosis and non-cirrhosis groups. The median overall survival of patients with and without cirrhosis was 13.07 months (95% confidence interval [CI]: 10.56–16.84) and 13.67 months (95% CI: 10.42–16.91), respectively ($p=0.76$). Cox proportional hazards regression analysis revealed that liver cirrhosis was not an independent risk factor for poor outcome (hazard ratio [HR]: 1.057, 95% CI: 0.805–1.388, $p=0.690$). In patients with cirrhosis, lower serum albumin levels, higher Charlson Comorbidity Index score, advanced-stage lung cancer, and treatment modality were factors associated with poor outcome. Increase in serum albumin by 1 g was associated with a 30% reduction in the risk of mortality (HR: 0.700, 95% CI: 0.494–0.993, $p=0.045$). While every point increase in the Charlson Comorbidity Index score by 1 point was linked to a 9% higher risk of mortality (HR: 1.090, 95% CI: 1.023–1.161, $p=0.007$).

Conclusion: The survival rates of lung cancer patients with and without cirrhosis did not differ significantly. Higher serum albumin levels and lower Charlson Comorbidity Index scores were associated with improved survival.

Keywords: liver cirrhosis, lung neoplasm, outcome, survival

Introduction

Cancer, a leading cause of death worldwide, is an important public health concern. In 2020, the estimated new cases of lung cancer in men and women were 116,300 and 112,520, respectively.¹ Although lung cancer accounts for only 12.9% of newly diagnosed cancer cases, it is responsible for 23.5% of all cancer-related deaths; this percentage is higher than those associated with breast, colon, and prostate cancers combined.² Despite improvements in medical and surgical therapy, the overall 5-year survival for patients with lung cancer is only 19.4%, mainly due to the advanced stage of disease at diagnosis. Only 16.4% of lung cancer cases are localized and suitable for curative resection at the time of diagnosis.² Surgical

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treatment currently offers the best chance for long-term survival in patients with early-stage lung cancer. Unfortunately, surgical resection is not suitable in some cases owing to existing comorbidities, such as liver cirrhosis. Liver cirrhosis (ie, irreversible fibrosis of the liver) is the 13th leading cause of years of life lost, only one place behind lung cancer.³ The 1-year mortality rate associated with cirrhosis varies widely depending on clinical decompensation, ranging from 1% to 57%.⁴ Surgical stress is considered a possible decompensating event in patients with compensated liver cirrhosis.⁵ Research addressing the combination of these two conditions is limited and primarily consists of small surgical cases series.^{6–8} Since clinical investigations involving lung cancer patients with liver cirrhosis are scarce in the medical literature, we conducted a multicenter propensity score matching clinical study to evaluate outcomes in this setting.

Materials and Methods

The institutional review board of Chang Gung Memorial Hospital approved this clinical study and waived the requirement for individual informed consent due to its retrospective design. All obtained information was maintained confidential according to the ethical standards of the hospital and in compliance with the tenets of the Declaration of Helsinki.

We used the Chang Gung Memorial Hospital Cancer Registry to collect clinical data from three hospitals belonging to the Chang Gung Medical Foundation (Kaohsiung Chang Gung Hospital, Keelung Chang Gung Memorial Hospital, and Chiayi Chang Gung Memorial Hospital). In this study, we included all adult patients (aged >18 years) diagnosed with liver cirrhosis (International Classification of Diseases, 9th Revision (ICD-9), code: 571.2, 571.2, 571.9) and lung cancer (ICD-9, code: 162) from January 2007 to December 2012.

The etiology of liver cirrhosis was established according to standard criteria for infection with hepatitis B virus (positive serum test for hepatitis B surface antigen), hepatitis C virus (seropositivity for hepatitis C virus antibody), coinfection with hepatitis B and C viruses, alcoholism, or unknown. We used a combination of imaging examinations (ie, nodular, small, and shrunken liver, splenomegaly, and portosystemic collateral on ultrasonography, and/or computed tomography) in association with an abnormal serologic test, endoscopic evidence of esophageal varices, direct surgical inspection, or pathological examination.

Using propensity score matching based on age, sex, smoking status, histology, cancer stage, and treatment modality, patients with lung cancer and coexisting liver cirrhosis were matched (1:1) with lung cancer patients without liver cirrhosis. We collected the following information from the medical records: age at diagnosis of lung cancer, sex, smoking history, creatinine level, albumin level, Model for End-Stage Liver Disease (MELD) score,⁹ Child–Pugh Score,¹⁰ Charlson Comorbidity Index (CCI),¹¹ lung cancer histology and stage at diagnosis, primary treatment (all treatment modalities administered within 3 months post diagnosis), and overall survival. For the Child–Pugh Score, the total score was used rather than the patients being divided into subgroups: class A (5–6 points); class B (7–9 points); and class C (10–15 points). For the CCI, we used the total scores from each morbidity score to determine potential associations with mortality. Lung cancer staging was performed according to the 7th edition of the TNM staging system.¹² Overall survival was calculated from the day of pathological confirmation until the last follow-up or 31st December 2015. Typically, the case manager of the cancer center contacted the patients by telephone to follow up regarding their condition. Those not reachable by telephone and withdrawn from the National Health Insurance scheme were presumed dead. The National Health Insurance scheme of Taiwan offers universal coverage to >99% of the population. Individuals are excluded from the National Health Insurance scheme only because of death, outstanding premium payments for >6 months, emigration, or change of nationality. For status update, the Health Promotion Administration, Ministry of Health and Welfare, Taiwan, releases an annual death report concerning all patients with cancer registered in each cancer center.

We collected all laboratory examination data from 3 months before diagnosis to the day of treatment initiation. In the final analysis, we used the data obtained at the closest date to that of diagnosis. Some patients had missing data for albumin levels (n=23, 7.77%), international normalized ratio (n=22, 7.43%), sodium levels (n=7, 2.36%), and total bilirubin levels (n=21, 7.09%). We analyzed the pattern of these missing data and classified them as missing at random; the multiple imputation technique (number of imputations: 5) was used to replace the missing values.¹³

Statistical Analysis

We simultaneously calculated the propensity score using logistic regression, with cirrhosis as the dependent

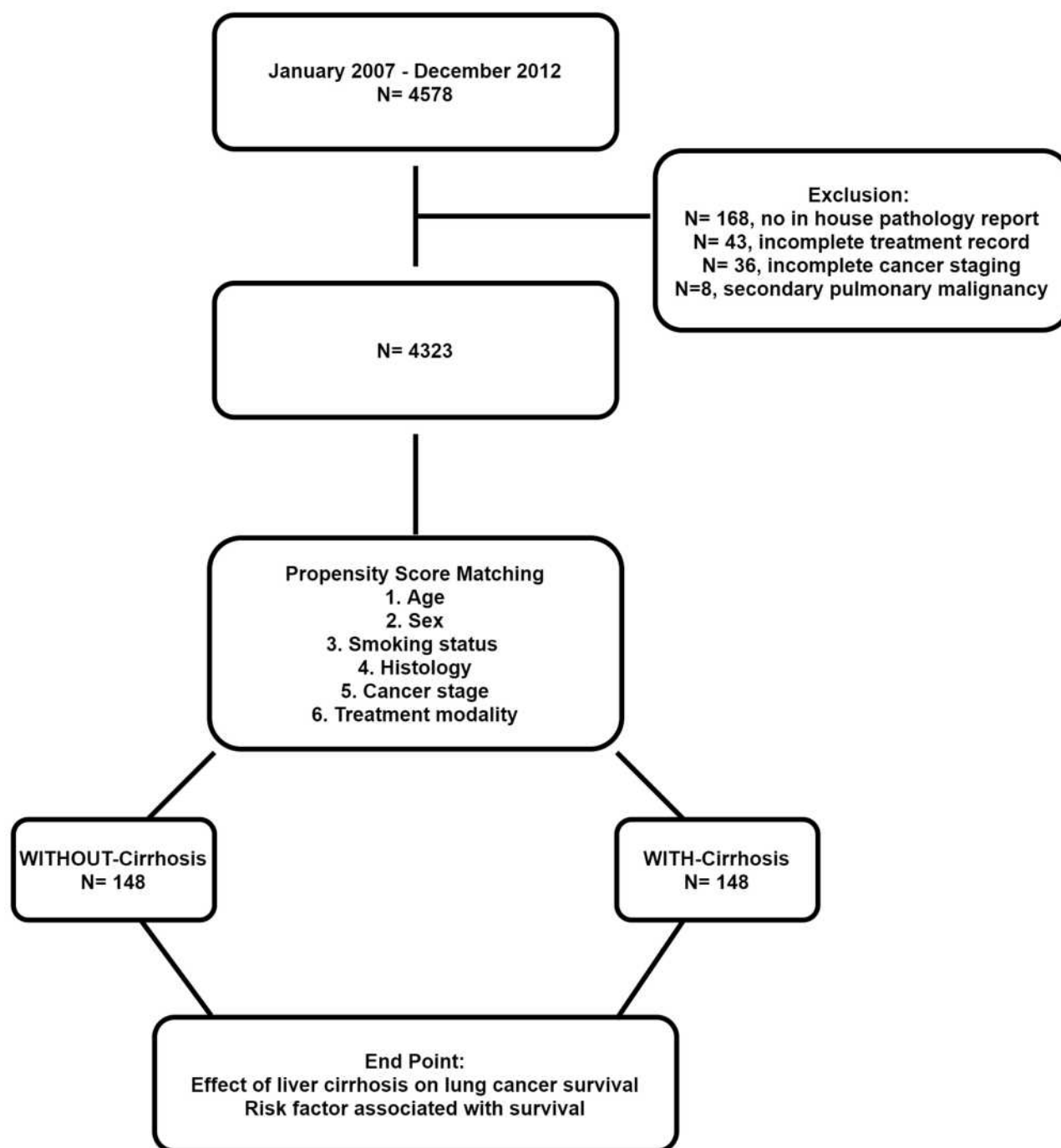


Figure 1 Patient selection and matching process.

variable, and propensity score matching to select control patients (ie, patients without cirrhosis) based on several confounders.¹⁴ We used a caliper width 0.2-fold greater than the standard deviation of the propensity score without replacement to match patients with and without cirrhosis.¹⁵ Because of no normal distribution, continuous data are presented as the median \pm standard deviation and

categorical data are presented as percentages. We used the chi-square or Fisher's exact test to analyze categorical variables (depending on the cell size) and analysis of variance for continuous variables. Clinical stages were classified into stages I–IIIA versus stages IIIB–IV. Treatment modalities were grouped into supportive treatment, surgical treatment (excluding diagnostic/staging

Table 1 Demographic Characteristics of Lung Cancer Patients with and without Liver Cirrhosis

Characteristic	Total (%)	Non-Cirrhosis Group	Cirrhosis Group	p-value
Number of patients	296 (100)	148 (50)	148 (50)	
Age, years (median±SD)	68 ± 11.28	68 ± 10.91	68 ± 11.67	0.75
Sex				0.88
Female	58 (19.5)	30 (10.1)	28 (9.4)	
Male	240 (80.5)	120 (40.3)	120 (40.3)	
Smoking history				0.91
No	118 (39.6)	60 (20.1)	58 (19.5)	
Yes	180 (60.4)	90 (30.2)	90 (30.2)	
Creatinine, in mg/dl (median±SD)	0.95 ± 1.06	0.91 ± 0.48	0.98 ± 1.42	0.12
Albumin	3.30 ± 0.69	3.40 ± 0.66	3.24 ± 0.71	0.006
Total bilirubin	0.83 ± 1.45	0.75 ± 1.41	0.90 ± 1.50	0.23
INR	1.05 ± 0.23	1.01 ± 0.21	1.07 ± 0.25	0.057
Ascites (yes)	13 (4.4)	1 (0.3)	12 (4.1)	0.003
Encephalopathy (yes)	28 (9.5)	1 (0.3)	27 (9.1)	<0.001
MELD score	8 ± 3.52	7 ± 3.43	9 ± 3.54	0.006
Child–Pugh Score	6 ± 1.09	6 ± 1.03	6 ± 1.10	0.001
Charlson Comorbidity Index score (median±SD)	7 ± 2.63	7 ± 2.61	7 ± 2.65	0.117
Lung cancer stage				0.68
IA–IIIA	87 (28.2)	36 (12.1)	48 (16.1)	
IA	18 (6)	9 (3)	9 (3)	
IB	26 (8.7)	11 (3.7)	15 (5)	
IIA	6 (2.0)	2 (0.7)	4 (1.3)	
IIB	4 (1.3)	2 (0.7)	2 (0.7)	
IIIA	30 (10.1)	12 (4)	18 (6)	
IIIB–IV	214 (71.8)	114 (38.3)	100 (33.6)	
IIIB	32 (10.7)	15 (5)	17 (5.7)	
IV	182 (61.1)	99 (33.2)	83 (27.9)	
Histology				1.00
NSCLC	263 (88.3)	132 (44.3)	131 (44)	
SCLC	35 (11.7)	18 (6)	17 (5.7)	
Treatment				0.58
No treatment/supportive care	51 (17.1)	24 (8.1)	27 (9.1)	
Surgical treatment	67 (22.5)	31 (10.4)	36 (12.1)	
OP	35 (11.7)	16 (5.4)	19 (6.4)	
OP+CT	23 (7.7)	7 (2.3)	16 (5.4)	
OP+CT+RT	4 (1.3)	3 (1)	1 (0.3)	
OP+Target	5 (1.7)	5 (1.7)	0 (0)	
Medical treatment	180 (60.4)	95 (31.9)	85 (28.5)	
CT	92 (30.9)	51 (17.1)	41 (13.8)	
CT+RT	37 (12.4)	16 (5.4)	21 (7)	
CT+Target	6 (2)	5 (1.7)	1 (0.3)	
RT	10 (3.4)	5 (1.7)	5 (1.7)	
RT+Target	4 (1.3)	2 (0.7)	2 (0.7)	
Target	30 (10.1)	15 (5)	15 (5)	
Cryotherapy	1 (0.3)	1 (0.3)	0 (0)	

Notes: The Charlson Comorbidity Index score was calculated with the exclusion of liver cirrhosis.

Abbreviations: CT, chemotherapy; INR, international normalized ratio; MELD, Model for End-Stage Liver Disease; NSCLC, non-small cell lung cancer; OP, surgical resection; RT, radiotherapy; SCLC, small cell lung cancer; SD, standard deviation; Target, target therapy.

Table 2 Etiology of Liver Cirrhosis

	N (%)
Alcoholism	38 (25.67%)
Hepatitis B virus	42 (28.38%)
Hepatitis C virus	41 (27.70%)
Hepatitis B and C viruses	9 (6.08%)
Non-alcoholic fatty liver disease	4 (2.70%)
Unknown	14 (9.46%)

procedure), and medical treatment. For survival analysis, we used the Kaplan–Meier method and the Log rank test to calculate differences in survival. Cox proportional hazards regression analysis was performed to estimate the level of significance and relative risk with a 95% confidence interval (CI). A p-value <0.05 denoted statistically significant difference. The clinical data were analyzed using the SPSS 21.0 software (IBM Corporation, Armonk, NY, USA).

Results

Patient Selection

During the study period, 4323 patients with lung cancer were included in the analysis and matched as described in the Methods section. Figure 1 shows the patient selection and matching process.

Patient Characteristics

Following the matching process, there was no statistically significant difference in the baseline clinical characteristics of patients. Table 1 presents the clinical characteristics of the cohort. Significant differences between patients with and without cirrhosis were observed in MELD score (9

± 3.54 vs 7 ± 3.43 , respectively, $p=0.006$), Child–Pugh score (6.00 ± 1.10 vs 6.00 ± 1.03 , respectively, $p=0.001$), and serum albumin levels (3.24 ± 0.71 vs 3.40 ± 0.66 , respectively, $p=0.006$). Patients with cirrhosis were more likely to present with ascites and encephalopathy versus those without cirrhosis (Table 1). The etiologies of liver cirrhosis were alcoholism ($n=38$, 25.67%), infection with hepatitis B virus ($n=42$, 28.38%), infection with hepatitis C virus ($n=41$, 27.70%), coinfection with hepatitis B and C ($n=9$, 6.08%), non-alcoholic fatty liver disease ($n=4$, 2.70%), and unknown ($n=14$, 9.46%) (Table 2). The distribution of histological types according to the stages of lung cancer for patients with and without cirrhosis is displayed in Table 3. The most common histological type was adenocarcinoma, followed by squamous cell carcinoma.

Survival Outcome of Lung Cancer Patients with and without Cirrhosis

Kaplan–Meier survival analysis did not reveal a statistically significant difference in survival between patients with and without cirrhosis (Figure 2). The median overall survival of patients with and without cirrhosis was 13.07 months (95% CI: 10.56–16.84) and 13.67 months (95% CI: 10.42–16.91), respectively ($p=0.76$) (Figure 2).

Cox proportional hazards regression analysis revealed that serum albumin levels, CCI score, advanced-stage lung cancer, and treatment modality were independent factors associated with poor outcome for patients with cirrhosis (Table 4). Increase in serum albumin by 1 g was associated with a 30% reduction in the risk of mortality (hazard ratio [HR]: 0.700, 95% CI: 0.494–0.993, $p=0.045$). Increase in the CCI score by 1 point was linked to a 9% higher risk of mortality (HR: 1.090, 95% CI: 1.023–1.161, $p=0.007$). A significant difference in survival was observed

Table 3 Distribution of Cancer Histology According to Cancer Stage

Histological Type (N, %)	Without Cirrhosis (N)		With Cirrhosis (N)	
	Stage IA–IIIA	Stage IIIB–IV	Stage IA–IIIA	Stage IIIB–IV
NSCLC (261, 88.2%)	34	96	46	85
Adenocarcinoma	22	59	27	46
Squamous cell carcinoma	8	22	10	24
Adenosquamous cell carcinoma	1	4	5	6
Large cell carcinoma	0	3	0	2
Sarcomatoid carcinoma	3	1	4	1
Non-small cell carcinoma	0	7	0	6
SCLC (35, 11.8%)	1	17	2	15

Abbreviations: NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.

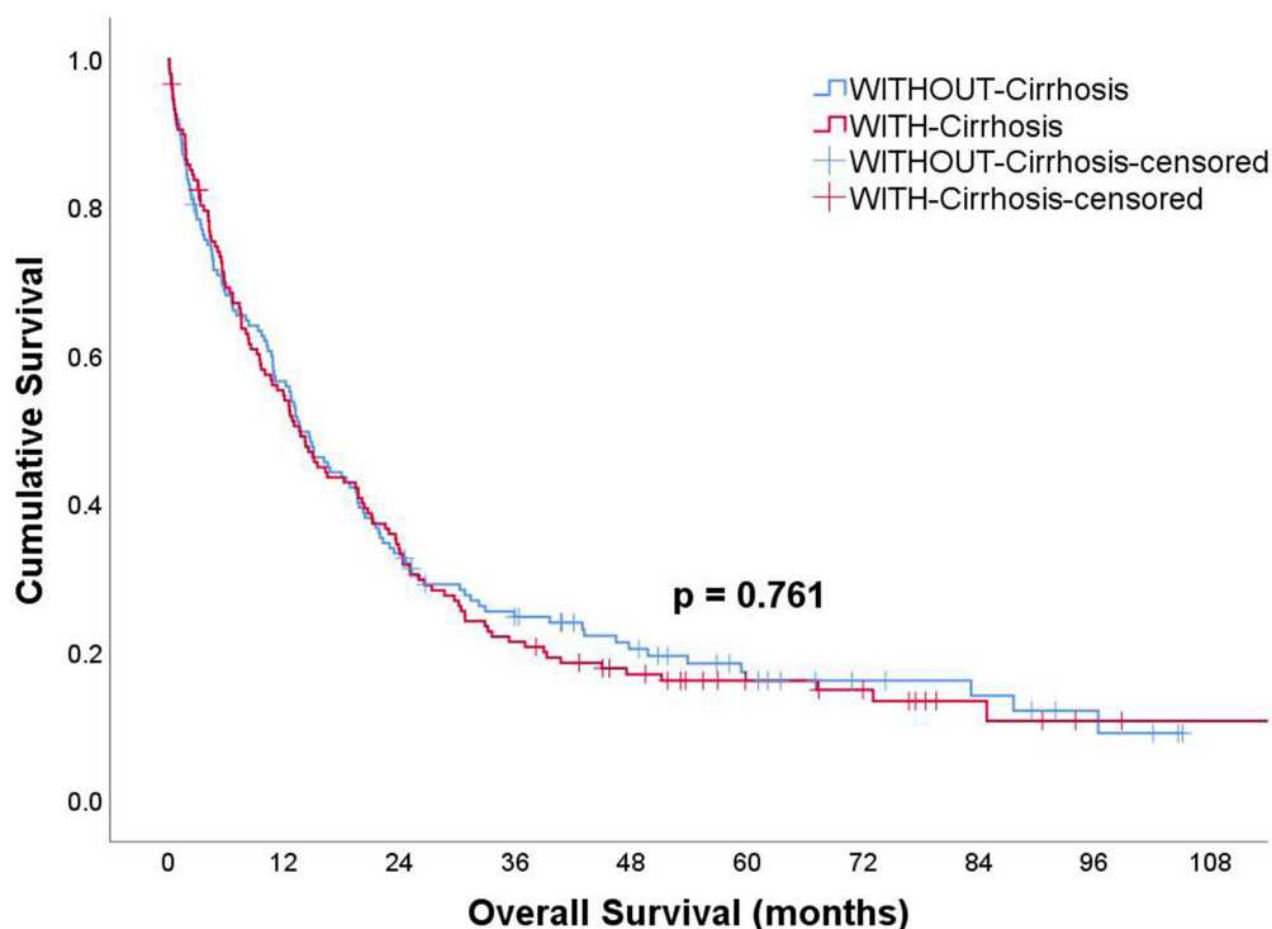


Figure 2 Survival curve for lung cancer patients with and without cirrhosis. There was no statistically significant difference in survival for WITH-Cirrhosis and WITHOUT-Cirrhosis lung cancer patients. The median overall survival for patients WITH-Cirrhosis was 13.07 months (95% CI 10.56–16.84) compared to 13.67 months (95% CI 10.42–16.91) for patients WITHOUT-Cirrhosis, $p=0.76$.

depending on the treatment modality. Using medical treatment as a reference, surgical treatment improved the chance of survival by 50% (HR: 0.502, 95% CI: 0.288–0.874, $p=0.015$).

Discussion

Cirrhosis is the consequence of damage to the liver induced by various etiologies. The most common causes are alcoholism, infection with hepatitis virus, and non-alcoholic fatty liver disease.¹⁶ Hepatitis B and C viruses are endemic in Taiwan;¹⁷ as expected, the most common cause of liver cirrhosis in Taiwan is infection with hepatitis B virus, followed by infection with hepatitis C virus.^{18–20} Consistent with previous reports, in this study, the main causes of liver cirrhosis were infections with hepatitis B and C viruses, followed by alcoholism and non-alcoholic fatty liver disease (Table 2).

Population-based studies have demonstrated that patients with liver cirrhosis are at an increased risk of developing lung cancer.^{21,22} Unfortunately, limited research has been conducted thus far to investigate this association. Only a few studies have assessed the survival outcome of these patients in detail. According to our analysis, the median overall survival of patients with and without cirrhosis was 13.67 months (95% CI: 10.42–16.91) and 13.07 months (95% CI: 10.56–16.84), respectively ($p=0.76$). The 5-year survival rate was 18.24% and 19.58%, respectively. This is consistent with the results of a study conducted by Chiang et al,²³ in which the 5-year survival rate of patients with lung cancer in Taiwan was 16.3%.

Traditionally, the Child–Pugh classification¹⁰ and MELD score⁹ are the most frequently used tools to determine the degree of liver function impairment. In this cohort, patients with cirrhosis showed higher values for

Table 4 Adjusted Cox Proportional Hazards Regression Analysis for Survival

	Adjusted Hazard Ratio	95% CI	p-value
Liver cirrhosis			
No	Ref		
Yes	1.057	0.805–1.388	0.690
Age	1.001	0.988–1.014	0.901
Sex			
Female	Ref		
Male	0.878	0.573–1.346	0.550
Smoking history			
No	Ref		
Yes	1.113	0.797–1.554	0.529
Creatinine	1.076	0.907–1.277	0.400
Albumin	0.700	0.494–0.993	0.045
Total bilirubin	0.983	0.862–1.121	0.799
INR	1.645	0.841–3.217	0.146
Ascites			
No	Ref		
Yes	0.933	0.430–2.026	0.862
Encephalopathy			
No	Ref		
Yes	0.947	0.502–1.787	0.866
MELD score	1.021	0.958–1.088	0.530
Child–Pugh Score	1.083	0.838–1.398	0.543
Charlson Comorbidity Index score	1.090	1.023–1.161	0.007
Stage			
IA–IIIA	Ref		
IIIB–IV	0.607	0.390–0.944	0.027
Histology			
NSCLC	Ref		
SCLC	0.748	0.504–1.109	0.149
Treatment			
Supportive	1.737	1.204–2.505	0.003
Medical	Ref		
Surgical	0.502	0.288–0.874	0.015

Notes: The Charlson Comorbidity Index score was calculated with the exclusion of liver cirrhosis. Serum albumin level, Charlson Comorbidity Index score, advanced-stage lung cancer, and treatment modality were independent factors associated with poor outcomes in patients for with cirrhosis. Increase in serum albumin by 1 g was associated with a 30% reduction in the risk of mortality (HR: 0.700, 95% CI: 0.494–0.993, $p=0.045$). Increase in the Charlson Comorbidity Index score by 1 point was linked to a 9% higher risk of mortality (HR: 1.090, 95% CI: 1.023–1.161, $p=0.007$). Using medical treatment as a reference, surgical treatment improved the chance of survival by 50% (HR: 0.502, 95% CI: 0.288–0.874, $p=0.015$).

Abbreviations: CI, confidence interval; HR, hazard ratio; INR, international normalized ratio; MELD, Model for End-Stage Liver Disease; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.

these two indices than those without cirrhosis: MELD (9 ± 3.54 vs 7 ± 3.43 , respectively, $p=0.006$) and Child–Pugh score (6 ± 1.10 vs 6 ± 1.03 , respectively, $p=0.001$). The Child–Pugh classification includes five variables namely grade of encephalopathy and ascites, serum albumin levels, bilirubin levels, and prothrombin time, and international normalized ratio. In the present study, Cox proportional hazards regression analysis demonstrated that the Child–Pugh and MELD scores were not associated with poor outcome. However, independent examination of the components of the Child–Pugh classification revealed that higher serum albumin levels were associated with improved survival. As expected, patients with cirrhosis had lower serum albumin levels than those without cirrhosis (3.24 ± 0.71 vs 3.40 ± 0.66 , respectively, $p=0.006$). The multivariate analysis showed that an increase in serum albumin by 1 g reduced the risk of mortality by 30% (HR: 0.700, 95% CI: 0.494–0.993, $p=0.045$). This effect may be related to the functions of serum albumin beyond its vascular expander property. These include solubilization, transport, and metabolism of several substances, endothelial stabilization, homeostatic effect, antioxidant effect, and immunomodulation.²⁴ Long-term administration of albumin in patients with cirrhosis was associated with improved management of ascites, spontaneous bacterial peritonitis, renal dysfunction, and severe hepatic encephalopathy.²⁵ The therapeutic benefit of long-term administration of albumin in lung cancer patients with cirrhosis deserves further evaluation.

Lung cancer is a condition that typically affects elderly patients. The presence of multiple and severe comorbidities in elderly patients negatively affects overall survival. In this report, the CCI score in lung cancer patients with and without cirrhosis was 7 ± 2.61 and 7 ± 2.65 , respectively (after excluding the 3 points for cirrhosis) ($p=0.117$). Morishima et al²⁶ reported that increase in the CCI score by 1 point was linked to a higher risk (14%) of all-cause mortality (HR: 1.14, 95% CI: 1.04–1.24). In the Liverpool Lung Project,²⁷ the severity of comorbidities increased the risk of lung cancer-specific mortality. In this study, the CCI score (used to assess the comorbidities) was an independent risk factor for poor outcome. In line with previous reports, increase in the CCI score by 1 point was associated with a 9% higher risk of mortality (HR: 1.090, 95% CI: 1.023–1.161, $p=0.007$).^{26,27}

Despite the expansion in the armamentarium for the treatment of lung cancer, surgical resection remains the best treatment option for long-term survival. In this study, the resection rate in lung cancer patients with cirrhosis was 24.32%. This is consistent with the results of a study performed by Wang et al,²⁸ which reported a surgical resection rate of 31.78% in Taiwan. Several small clinical series assessing the surgical outcome of lung resection for patients with cirrhosis demonstrated acceptable surgical risk and long-term outcome.^{6–8} In a series of 17 patients from Japan⁶ (pneumonectomies: 3; lobectomies: 11; and wedge resection: 3), the 5-year survival rate was 45.6%. In the present cohort, the median overall survival of patients with and without cirrhosis who underwent surgery was 45.01 months (95% CI: 10.55–79.47) and 87.65 months (95% CI: 53.20–122.11), respectively ($p=0.15$); the 5-year survival rate was 47.2% and 64.5%, respectively.

The retrospective design of this study, the lack of histological grading, genetic examination, treatment summary (eg, possible reduction in the dose of chemotherapeutic drugs, toxicity), and the completion rate of the treatment are just examples of the existing limitations. Furthermore, all patients included in this analysis were Chinese; hence, caution should be exercised when generalizing the present findings to other ethnic groups.

Conclusion

Based on the present investigation, there is no significant difference in the survival of lung cancer patients with and without liver cirrhosis. For patients with adequate physical performance, surgical resection continues to be the preferred treatment option with regard to long-term survival.

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Disclosure

The authors have no conflicts of interest to report in this work.

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