Cancer Management and Research

Elevate Series

Open Access Full Text Article

ORIGINAL RESEARCH

Hypoalbuminemia is Associated with Higher 90-Day Mortality and Poor Prognosis in Patients with Esophageal Squamous Cell Carcinoma and Liver Cirrhosis Receiving Radiotherapy-Based Therapy

Yu-Yang Hua[1], Ming-Chun Kuo[1], Yen-Hao Chen[1], Hung-I Lu[2], Chien-Ming Lo[2], Yu Chen[2], Yu-Ming Wang[3], Yun-Hsuan Lin[3], Shau-Hsuan Li[1], Shih-Yu Huang[1]

[1]Department of Hematology-Oncology, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan; [2]Department of Thoracic & Cardiovascular Surgery, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan; [3]Department of Radiation Oncology & Proton and Radiation Therapy Center, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan

Correspondence: Shau-Hsuan Li; Shih-Yu Huang, Department of Hematology-Oncology, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, No. 123, Dapi Road, Niaosong Dist, Kaohsiung City, 833, Taiwan, Tel +886-7-7317123 ext. 8303, Email lee0624@cgmh.org.tw; a724057@cgmh.org.tw

Background: Liver cirrhosis (LC) is common among patients with esophageal squamous cell carcinoma (ESCC) due to shared etiologic factor, alcohol. For non-metastatic ESCC (nmESCC) patients with cirrhosis, surgery is often contraindicated or associated with high morbidity, therefore radiotherapy-based therapy was commonly applied. This study aims to investigate prognosticators for overall survival (OS) in nmESCC and cirrhotic patients receiving radiotherapy-based therapy. Furthermore, we will also evaluate the predictors for the 90-day mortality rate to reduce avoidable treatment-related toxic effects, and prevent medical waste.

Methods: Between January 2001 and December 2021, we retrospectively reviewed medical records of 1298 ESCC patients. Total 78 patients with nmESCC and liver cirrhosis identified based on abdominal ultrasonography, computerized tomography, or liver biopsy were enrolled. Clinicopathologic parameters were collected and correlated with OS and 90-day mortality.

Results: Univariate analysis revealed that Child-Pugh classification B/C (P<0.001, versus A), radiotherapy alone (P=0.03, versus chemoradiotherapy), prothrombin time (PT) prolonged≧2 seconds (P=0.024), albumin≦3.5g/dl (P<0.001), controlled/refractory ascites (P=0.01, versus none of ascites), and total bilirubin≧1.5mg/dl (P=0.004) were significantly associated with inferior OS. In multivariate analyses, albumin≦3.5g/dl (P=0.001, odds ratio (OR): 2.500) and total bilirubin≧1.5mg/dl (P=0.019, OR: 2.012) were independent adverse prognosticators. The 90-day mortality in these 78 patients receiving radiotherapy-based therapy was 10.3% (n=8), including ESCC progression in 4 patients, liver failure in 1 patient, and others in 3. Clinical 8th American Joint Committee on Cancer (AJCC) stage IVA (P=0.02), clinical T classification T3/4 (P=0.049), PT prolonged≧4 seconds (P=0.009), and albumin≦3.5g/dl (P=0.027) were significantly correlated with higher 90-day mortality. Logistic model showed albumin≦3.5g/dl (P=0.015, OR: 16.129) and clinical 8th AJCC stage IVA (P=0.012, OR: 17.544) were independently correlated with higher 90-day mortality.

Conclusion: Hypoalbuminemia is associated with higher 90-day mortality and poor prognosis in nmESCC and liver cirrhosis patients receiving radiotherapy-based therapy.

Keywords: radiotherapy, esophageal cancer, liver cirrhosis, prognosis, albumin, nutrition

Introduction

Esophageal cancer (EC) stands as the eighth most commonly diagnosed cancer worldwide, showing an upward trajectory in incidence rates. Correspondingly, it ranks eighth in terms of cancer-related mortalities.[1] The disease is primarily categorized into two histologic types: esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC). ESCC predominantly afflicts individuals in southern and eastern Africa, as well as eastern Asia, whereas EAC is

Received: 4 September 2024
Accepted: 26 November 2024
Published: 3 December 2024

more prevalent in North America, Australia, and Europe.[2] Noteworthy risk factors for ESCC include smoking, alcoholism, caustic ingestions, achalasia, and Fanconi anemia, while Barrett's esophagus and gastroesophageal reflux disease are linked with EAC. Symptoms of esophageal cancer typically involve progressive difficulty swallowing solid foods, weight loss, regurgitation of saliva, hoarseness, and/or coughing. However, most patients in the early stages of the disease do not exhibit these symptoms. Consequently, a significant number of patients are diagnosed with locally advanced or metastatic disease.[3] The 5-year survival rates for esophageal cancer vary significantly, with approximately 43% for localized disease, about 23% for locally advanced cases, and less than 5% for metastatic instances. The survival rates between ESCC and EAC are comparable.[2–5]

Esophagectomy is the cornerstone of primary treatment for esophageal cancer.[6] However, when the tumor with invasion of major vessels or trachea, the surgical risks are increased and defined as unresectable or borderline-resectable disease. Previous review studies have consistently shown that patients with comorbidities experience poorer surgical outcomes, higher complication rates, and increased perioperative risks.[6] Among patients with esophageal squamous cell carcinoma, alcohol consumption is a prevalent risk factor, and it also contributes significantly to the development of liver cirrhosis. In Taiwan, hepatitis B virus (HBV) infection is an endemic disease, often leading to the development of liver cirrhosis and hepatocellular carcinoma (HCC) as long-term sequelae. Typically, liver cirrhosis (LC) and HCC manifest after 4–5 decades of HBV continuous infection.[7] It is reported that 7–14% of individuals diagnosed with esophageal carcinoma also have liver cirrhosis.[8,9] Dimitrios Schizas et al highlighted the association between cirrhosis and various postoperative complications following esophagectomy, including higher rates of pulmonary complications (odds ratio (OR): 2.60; 95% CI: 1.53–4.42), ascites (OR: 37.77; 95% CI: 10.95–130.28) and anastomotic leak/fistula within 30 days (OR: 2.81; 95% CI: 1.05–7.49). Liver cirrhosis is also linked to an increased 30-day mortality rate (OR: 3.04; 95% CI: 1.71–5.39).[6] Notably, patients classified as Child Pugh class A group showed lower 30-day mortality rates after esophagectomy compared to those in Child Pugh class B category.[6]

In cases of unresectable disease, definitive concurrent chemoradiotherapy (dCCRT) offered as an alternative treatment and becomes the standard of care.[6] According to PRODIGE5/ACCORD17 study, patients who underwent six cycles of oxaliplatin, leucovorin, and fluorouracil (FOLFOX) alongside 50 Gy radiotherapy administered in 25 fractions experienced a median overall survival of 20.4 months and a median progression-free survival of 9.7 months.[10] However, dCCRT poses similar challenges in cases of liver cirrhosis with compromised liver function. Additionally, some physicians may opt for radiotherapy alone in concerns of treatment-related toxicity during and after dCCRT. Nevertheless, there is a scarcity of clinical analysis regarding treatment toxicity and outcomes in this specific patient population.

The objective of our study is to explore prognostic factors that can predict mortality in liver cirrhotic patients undergoing radiotherapy-based therapy for non-metastatic esophageal squamous cell carcinoma.

Materials and Methods

Case Enrollment

We retrospectively reviewed medical records of 1298 patients coded by the disease code of International Classification of Disease (ICD-10) with esophageal squamous cell carcinoma at our institution between January 2001 and December 2021. After obtaining approval from the institutional review board to review the patient records for the outlined study, we reviewed medical charts to identify patients for retrospective analysis. Among these 1298 patients with ESCC, those who did not complete report of abdominal echography or computerized tomography (CT) report were excluded. Patients with synchronous or metachronous cancer are also excluded. Patients who ever received living donor liver transplantation were also excluded. Patients receiving protocols other than radiotherapy or concurrent chemoradiotherapy (CCRT), such as chemotherapy alone, endoscopic submucosal dissection, endoscopic mucosal resection, surgery or best supportive care were also excluded. One hundred and three patients had established diagnosis of liver cirrhosis. Among these 103 patients, distant metastatic ESCC and cervical ESCC were excluded. Eventually, 78 patients with non-metastatic ESCC and liver cirrhosis were enrolled for our analysis (Figure 1).

We documented parameters for each individual, including sex, age, clinical 8th American Joint Committee on Cancer (AJCC) staging, tumor, node, metastasis (TNM) staging, primary tumor location (upper/middle/lower esophagus), treatment

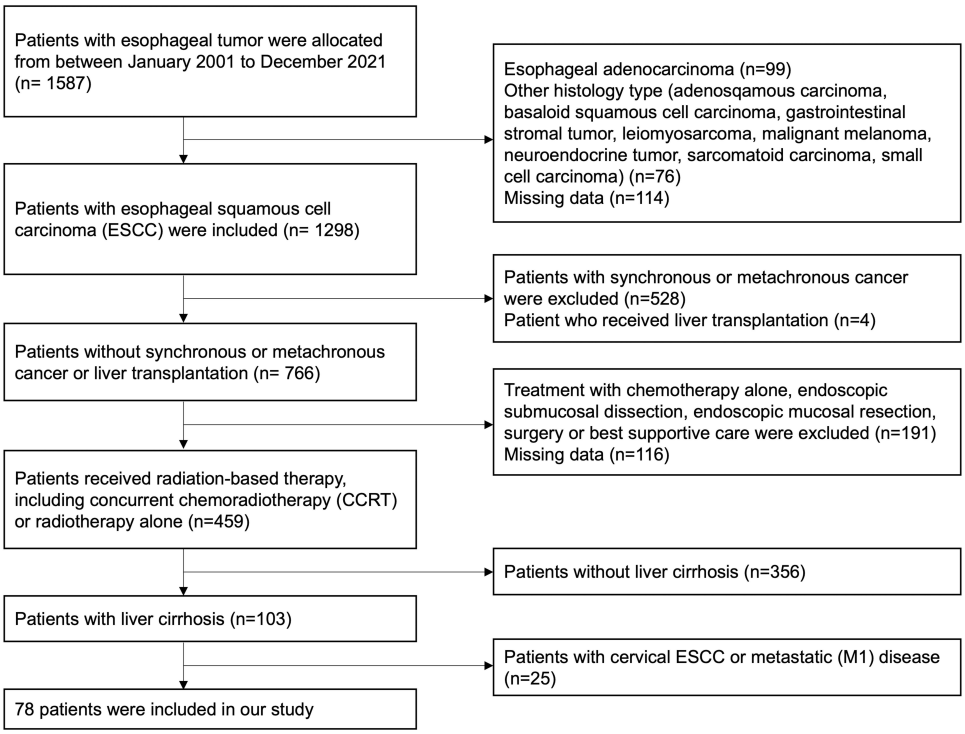

Figure 1 Enrollment flowchart.

modality, Child-Pugh score (CPS) when ESCC diagnosed, Child-Pugh classification, prothrombin time (PT), presence of ascites, albumin, total bilirubin, encephalopathy, and existence of esophageal varices detected by panendoscopy.

Liver Cirrhosis

The diagnosis of liver cirrhosis was based on abdominal ultrasonography and/or computerized tomography, and/or liver biopsy results, whichever applicable. Child-Pugh score is calculated by adding scores of parameters which reflects liver function. Each parameter scores from 1 to 3 points. Albumin level (>3.5g/dl, 2.8–3.5g/dl, <2.8g/dl), total bilirubin level (<2, 2–3, >3 mg/dl), prothrombin time prolonged (<4, 4–6, >6 seconds), encephalopathy (none, mild to moderate, severe), and ascites (none, diuretic responsive, diuretics refractory) scored as 1, 2, and 3, respectively. CPS ranges from 5 to 15 points, which is classified as Child A (CPS 5–6), Child B (CPS 7–9), and Child C(CPS10-15).

Outcome

Our primary endpoint was overall survival, defined as the time from diagnosis to death of any cause, and for cases loss of follow-up, to the time of last follow-up. Secondary endpoint was 90-day mortality, defined as mortality of any cause within 90-days when initiating treatment modality.

Statistical Analysis

Our analytic software was Statistical Product and Service Solutions (SPSS) 25th edition. We applied univariate log-rank analysis of prognostic factor for overall survival and 90-day mortality. We used multivariate Cox regression analysis for overall survival.

Results

Demographics and Clinical Characteristics of Overall Esophageal Squamous Cell Carcinoma

Of the 78 cases reviewed, 76 of them were male (97%). The age range spans from 37 to 77 years, with a mean age of 53.6 years. The majority of our cases have advanced cancer stage on the basis of AJCC 8th edition, with case number of

11, 9, 23 and 35, representing stage I, II, III, and IV, respectively. Due to no metastatic ESCC were enrolled, no patients were documented as M1 disease. Sixty-two patients received chemoradiotherapy, whereas the rest 16 patients received radiotherapy alone. There are significantly more patients classified as Child Pugh A (n=51) compared to those classified as class B (n=24) and class C (n=3). Only 2 patients were recorded with prolonged prothrombin time for more than 4 seconds. Sixty-eight percent of patients (n=53) showed no ascites in abdominal sonography document. More than half of our patients had albumin level higher than 3.5g/dl and 65 patients had total bilirubin level less than 2mg/dl. Twenty-one patients were recorded with present esophageal varices and only one patient reported hepatic encephalopathy. All of above data are shown in Table 1.

Table 1 Baseline Characteristics of 78 Patients with Non-Metastatic Esophageal Squamous Cell Carcinoma and Liver Cirrhosis Who Received Radiotherapy-Based Therapy

Parameters	No. of Cases (percentage)
Sex	
Male	76
Female	2
Age (years)(mean: 53.6, median: 52, range 37–77)	
<50	16
50≦ Age<60	30
60≦ Age<70	22
70≦ Age	10
Clinical 8th AJCC stage	
I	11
II	9
III	23
IVA	35
Clinical T classification	
T1	13
T2	12
T3	20
T4	33
Clinical N classification	
N0	16
N1	30
N2	26
N3	6
Clinical M classification	
M0	78
M1	0
Primary tumor location	
Upper	21
Middle	30
Lower	27
Treatment modality	
Radiotherapy alone	16
Chemoradiotherapy	62
Child-Pugh score	
5	32
6	19
7	13

(*Continued*)

Table 1 (Continued).

Parameters	No. of Cases (percentage)
8	6
9	5
10	2
11	0
12	1
Child-Pugh classification	
A	51
B	24
C	3
Prothrombin time: seconds prolonged	
<4	76
4–6	1
>6	1
Ascites	
None	53
Mild, controlled	24
Moderate, refractory	1
Albumin (g/dl)	
>3.5	40
3.0–3.5	28
<3.0	10
Total bilirubin (mg/dl)	
<2	65
2–3	7
>3	6
Encephalopathy	
None	77
Grade I–II	1
Grade III–IV	0
Esophageal varices	
Absent	57
Present	21

Abbreviation: AJCC, American Joint Committee on Cancer.

Prognostic Factors

Results of univariate log-rank analysis of prognostic factors for overall survival are listed in Table 2. There are no notable discrepancies in the 3-year overall survival analysis across various factors, including age, AJCC stage, T stage, N stage, primary tumor location, and the presence of esophageal varices. However, univariate analysis indicated that child-Pugh classification B/C (P<0.001, versus A), prothrombin time prolonged≧2 seconds (P=0.024), albumin≦3.5g/dl (P<0.001), controlled/refractory ascites (P=0.01, versus none of ascites), and total bilirubin≧1.5mg/dl (P=0.004) were significantly correlated with a poorer 3-year overall survival rate. Besides, chemoradiotherapy also showed better survival compared with radiotherapy alone patients (P=0.03, chemoradiotherapy versus radiotherapy alone). Kaplan–Meier curves of overall survival are shown in Figure 2. In the multivariate analyses, albumin ≦3.5g/dl (P=0.001, OR: 2.500) and total bilirubin ≧1.5mg/dl (P=0.019, OR: 2.012) emerged as independent adverse prognostic factors associated with a reduced overall survival rate in Table 3.

Among the 78 patients undergoing radiotherapy-based therapy, the 90-day mortality rate was 10.3% (n=8). The causes of mortality included disease progression in 4 patients, liver failure in one patient, and hospice care due to

Table 2 Results of Univariate Log-Rank Analysis of Prognostic Factors for Overall Survival in 78 Patients with Non-Metastatic Esophageal Squamous Cell Carcinoma and Liver Cirrhosis Who Received Radiotherapy-Based Therapy

Factors	No. of pts	Overall Survival (OS)	
		3-year OS rate (%)	P value
Age			
<58y/o	39	20%	0.338
≧58y/o	39	37%	
Clinical 8th AJCC stage			
I+II	20	30%	0.398
III+IVA	58	28%	
Clinical 8th AJCC stage			
I+II+III	43	32%	0.234
IVA	35	26%	
Clinical T classification			
T1/2	25	32%	0.215
T3/4	53	26%	
Clinical T classification			
T1/2/3	45	30%	0.418
T4	33	28%	
Clinical N classification			
N0	62	30%	0.679
N1/2/3	16	25%	
Clinical N classification			
N0/1	46	24%	0.667
N2/3	32	35%	
Primary tumor location			
Upper/Middle	51	28%	0.436
Lower	27	30%	
Primary tumor location			
Upper	21	29%	0.880
Middle/Lower	57	29%	
Treatment modality			
Chemoradiotherapy	62	33%	0.03*
Radiotherapy alone	16	13%	
Child-Pugh classification			
A	49	40%	<0.001*
B/C	29	8%	
Prothrombin time			
Seconds prolonged<1	36	35%	0.056
Seconds prolonged≧1	42	23%	
Prothrombin time			
Seconds prolonged<2	62	31%	0.024*
Seconds prolonged≧2	16	19%	
Prothrombin time			
Seconds prolonged<4	76	29%	<0.001*
Seconds prolonged≧4	2	0%	
Albumin (g/dl)			
>3.5	40	46%	<0.001*
≦3.5	38	11%	

(*Continued*)

Table 2 (Continued).

Factors	No. of pts	Overall Survival (OS)	
		3-year OS rate (%)	P value
Ascites			
None	53	34%	0.010*
Controlled/Refractory	25	17%	
Total bilirubin (mg/dl)			
<2	63	33%	0.058
≧2	15	9%	
Total bilirubin (mg/dl)			
<1.5	58	36%	0.004*
≧1.5	20	6%	
Esophageal varices			
Absent	56	32%	0.202
Present	22	20%	

Note: *Statistically significant.
Abbreviations: AJCC, American Joint Committee on Cancer; OS, Overall survival.

cachexia in 3 patients. Clinical stage IVA (P=0.02), clinical T classification T3/4 (P=0.049), prothrombin time prolonged≧4 seconds (P=0.009), and albumin≦3.5g/dl (P=0.027) were significantly correlated with higher 90-day mortality. Table 4 lists the association between clinical parameters and 90-day mortality in patients with non-metastatic esophageal squamous cell carcinoma and liver cirrhosis who received radiotherapy-based therapy. Significant findings were shown in AJCC stage I/II/III vs IVA, T1/T2 vs T3/T4, PT prolonged <1 seconds and ≧ 1 seconds, PT prolonged <4 seconds and ≧ 4 seconds, and albumin >3.5 g/dl vs ≦ 3.5g/dl. Table 5 shows that albumin≦3.5g/dl (P=0.015, OR: 16.129) and clinical stage IVA (P=0.012, OR: 17.544) were independently correlated with higher 90-day mortality.

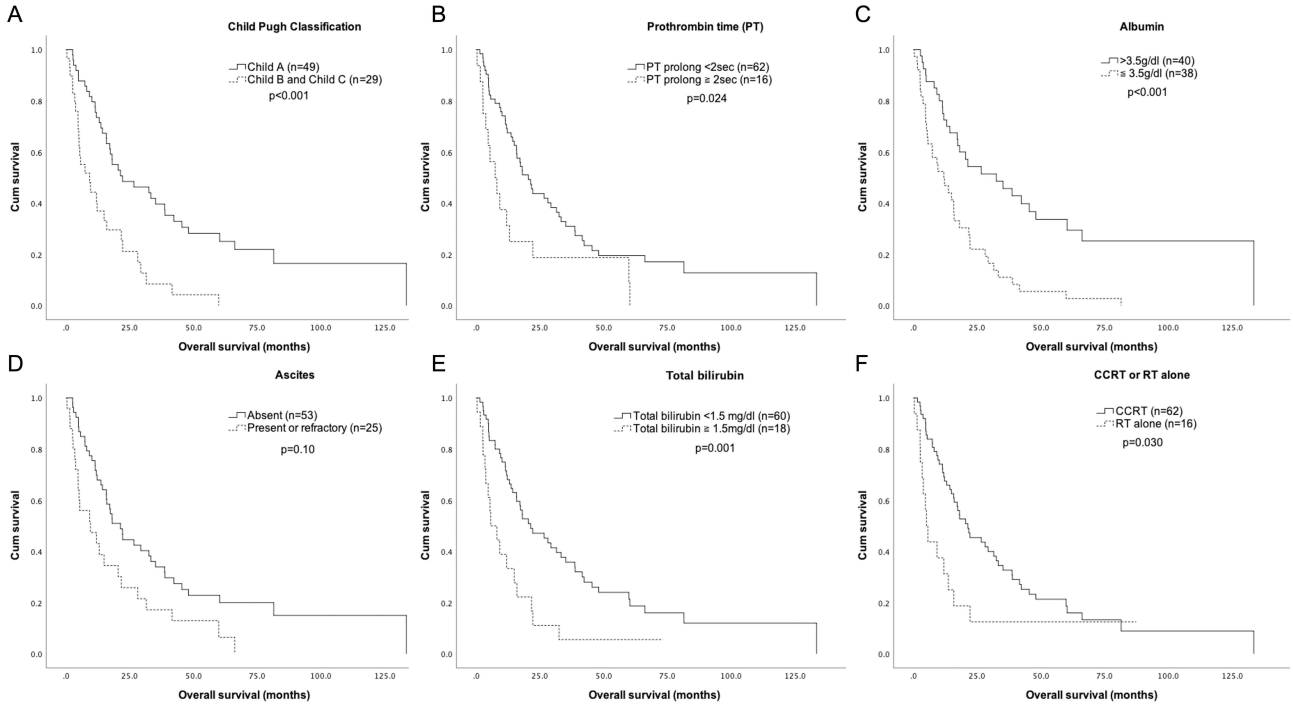

Figure 2 Kaplan Meier curve of overall survival of subgroup analyses. Kaplan-Meier estimates of overall survival of Child-Pugh classification B/C (P<0.001, versus (A) (**A**), prothrombin time prolonged≧2 seconds (P=0.024) (**B**), albumin≦3.5g/dl (P<0.001) (**C**), controlled/refractory ascites (P=0.01, versus none of ascites) (**D**), total bilirubin≧1.5mg/dl (P=0.004) (**E**) and chemoradiotherapy (P=0.03, versus radiotherapy alone) (**F**).

Table 3 Results of Multivariate Cox Regression Analysis for Overall Survival in 78 Patients with Non-Metastatic Esophageal Squamous Cell Carcinoma and Liver Cirrhosis Who Received Radiotherapy-Based Therapy

Factors	Overall survival	
	OR (95% CI)	P value
Albumin≦3.5 g/dl	2.500 (1.473~4.237)	0.001*
Total bilirubin≧1.5 mg/dl	2.012 (1.121~3.610)	0.019*

Note: *Statistically significant.
Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval.

Table 4 Associations Between Clinical Parameters and 90-Day Mortality in 78 Patients with Non-Metastatic Esophageal Squamous Cell Carcinoma and Liver Cirrhosis Who Received Radiotherapy-Based Therapy

Parameters		90-day Mortality		
		Absent	Present	P value
Age	<58y/o	35	4	1.000
	≧58y/o	35	4	
Clinical 8th AJCC stage	I+II	20	0	0.105
	III+IVA	50	8	
Clinical 8th AJCC stage	I+II+III	42	1	0.020*
	IVA	28	7	
Clinical T classification	T1/2	25	0	0.049*
	T3/4	45	8	
Clinical T classification	T1/2/3	27	6	0.065
	T4	43	2	
Clinical N classification	N0	15	1	1.000
	N1/2/3	55	7	
Clinical N classification	N0/1	41	5	1.000
	N2/3	29	3	
Primary tumor location	Upper/Middle	45	6	0.707
	Lower	25	2	
Primary tumor location	Upper	20	1	0.437
	Middle/Lower	50	7	
Treatment modality	Chemoradiotherapy	58	4	0.051
	Radiotherapy alone	12	4	
Child-Pugh classification	A	46	3	0.140
	B/C	24	5	
Prothrombin time	Prolonged<1seconds	36	0	0.006*
	Prolonged≧1seconds	34	8	
Prothrombin time	Prolonged<2seconds	58	4	0.051
	Prolonged≧2seconds	16	4	
Prothrombin time	Prolonged<4seconds	70	6	0.009*
	Prolonged≧4seconds	0	2	
Albumin (g/dl)	>3.5	39	1	0.027*
	≦3.5	31	7	
Ascites	None/Controlled	69	8	1.000
	Refractory	1	0	
Ascites	None	50	3	0.102
	Controlled/Refractory	20	5	

(*Continued*)

Table 4 (Continued).

Parameters		90-day Mortality		
		Absent	Present	P value
Total bilirubin	<2	57	6	0.646
	≧2	13	2	
Total bilirubin	<1.5	56	4	0.078
	≧1.5	14	4	
Esophageal varices	Absent	52	4	0.212
	Present	18	4	

Notes: *Statistically significant. x^2 test or Fisher's exact test was used for statistical analysis.
Abbreviation: AJCC, American Joint Committee on Cancer.

Table 5 Logistic Models for 90-Day Mortality in 78 Patients with Non-Metastatic Esophageal Squamous Cell Carcinoma and Liver Cirrhosis Who Received Radiotherapy-Based Therapy

Factors	90-day Mortality	
	OR (95% CI)	P value
Albumin ≦3.5 g/dl	16.129 (1.709~142.857)	0.015*
AJCC 8th stage IVA	17.544 (1.887~166.667)	0.012*

Note: *Statistically significant.
Abbreviations: AJCC, American Joint Committee on Cancer; OR, odds ratio; 95% CI, 95% confidence interval.

Discussion

This retrospective study aimed to analyze prognostic factors in patients with esophageal cancer and liver cirrhosis, utilizing the 8th AJCC system, who received radiotherapy-based treatment. In our database, we observed that 7.9% of patients diagnosed with esophageal cancer also had liver cirrhosis. This finding contrasts with a previous retrospective study conducted by Florence Trivin et al, where 26 (2.7%) out of 958 esophageal cancer patients were identified to have cirrhosis.[11]

In our study, univariate analysis showed significance between Child Pugh classification in B/C versus A, prothrombin time prolonged≧2 seconds, albumin≦3.5g/dl, controlled/refractory ascites, and total bilirubin≧1.5mg/dl (P=0.004) in 3-year overall survival rates. In multivariate analysis, hypoalbuminemia (≦3.5g/dl) and hyperbilirubinemia (≧1.5mg/dl) were associated with lower 3-year overall survival rates. Similar to our research, Florence Trivin et al also discovered that patients classified as Child-Pugh B had a poor prognosis and exhibited low tolerance to chemoradiotherapy.[11]

Literature reviews have extensively explored malnutrition's role as a predictor of survival in cancer. Pretreatment serum albumin levels are recognized as crucial factors with significant prognostic value in different cancer types.[12–14] Albumin levels may be a prognostic factor in advanced cancer no matter when patient treated with chemotherapy or immune checkpoint inhibitors.[15–17] Consequently, it could serve as valuable tool in clinical trials to better assess the baseline risk in cancer patients. Serum albumin serves as a valuable indicator of visceral protein function within the body.[18] The synthesis of albumin can be suppressed by malnutrition and inflammation. In cancer patients, there appears to be a correlation between body weight index and albumin synthesis, suggesting potential compensatory metabolic mechanisms.[19] In advanced stages of disease, malnutrition and inflammation further impede albumin synthesis. Tumors release proinflammatory cytokines and growth factors, such as interleukin-6 (IL-6), which stimulate the liver to produce acute-phase reaction proteins like C-reactive protein (CRP) and fibrinogen.[20] This process heightens the demand for specific amino acids, potentially leading to skeletal muscle breakdown in cases where dietary intake is inadequate. On the other hand, the presence of micrometastatic tumor cells in the liver can stimulate Kupffer cells to produce various

cytokines, including IL-1b, IL-6, and tumor necrosis factor (TNF), which may influence albumin synthesis by hepatocytes.[21] Alternatively, TNF may enhance microvascular permeability, facilitating increased transcapillary passage of albumin. In patients diagnosed with esophageal cancer and concurrent liver cirrhosis, malnutrition, insufficient daily caloric intake, and impaired synthesis function can profoundly impact the synthesis of albumin. The subsequent clinical manifestations of hypoalbuminemia may include ascites and peripheral edema, contributing to a vicious cycle of malnutrition. These patients may exhibit poorer performance status, compromised liver function, and a higher susceptibility to treatment-related toxicities. Consequently, they may experience a higher 90-day mortality rate and lower 3-year overall survival rate.

Although the management of hypoalbuminemia was not the investigation goal of our study, we thought that correcting pre-treatment hypoalbuminemia could potentially improve prognosis in esophageal cancer patients. Strategies to achieve this may involve ensuring adequate patient nutrition through methods such as oral or enteral feeding tubes. Additionally, providing aggressive supportive care to mitigate acute toxicities such as emesis, radiation esophagitis, or dysphagia is crucial to prevent interruptions in radiotherapy and the need for dose reductions. The cause–effect relationship between correcting albumin levels and clinical outcomes requires further clarification in future studies. As per current National Comprehensive Cancer Network (NCCN) guidelines and our institutional treatment protocol, the establishment of enteral feeding tubes is recommended for these patients.

Our study still has several limitations. Firstly, it is a retrospective study, which inherently limits our ability to accurately document all laboratory data. Additionally, there is the presence of selection bias in determining the treatment modality for each patient. Patients with better performance status may have been more likely to receive chemoradiotherapy, while those with poorer performance status may have been assigned to radiotherapy alone due to concerns regarding treatment-related toxicities. Furthermore, randomization was not conducted in this study. Secondly, the sample size was modest in size. Nonetheless, there is a lack of prior data exploring our objective among patients with cirrhosis in literature review. Thirdly, the diagnosis of cirrhosis relied on CT scan or abdominal sonography, rather than Fibroscan Testing, an US Food and Drug Administration (FDA)-approved non-invasive device that provides more precise and quantifiable information regarding liver scarring and fibrosis. Unfortunately, Fibroscan is not the standard diagnostic tool applied in clinical practice because of accessibility in our country. Regarding subgroups of viral hepatitis-related liver cirrhosis, some researchers utilize Fibrosis-4 (FIB-4) or AST to Platelet Ratio Index (APRI) scores to assess the extent of liver fibrosis caused by HBV or Hepatitis C virus (HCV).[22] This detailed method may be considered in future studies.

Conclusions

In conclusion, our study reveals hypoalbuminemia as a significant prognostic indicator for survival in patients with locally advanced esophageal squamous cell carcinoma and liver cirrhosis undergoing radiotherapy-based therapy. However, the potential benefit of correcting pre-radiation therapy hypoalbuminemia on clinical outcomes remains uncertain.

Abbreviations

AJCC, American Joint Committee on Cancer; APRI, AST to Platelet Ratio Index; CCRT, concurrent chemoradiotherapy; CPS, Child-Pugh score; CRP, C-reactive protein; CT, computerized tomography; dCCRT, definitive concurrent chemoradiotherapy; EAC, esophageal adenocarcinoma; EC, esophageal cancer; ESCC, esophageal squamous cell carcinoma; FDA, US Food and Drug Administration; FIB-4, Fibrosis-4 score; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ICD, International Classification of Disease; IL-6, interleukin-6; LC, Liver cirrhosis; NCCN, National Comprehensive Cancer Network; nmESCC, non-metastatic esophageal squamous cell carcinoma; OR, odds ratio; OS, overall survival; PT, prothrombin time; SPSS, Statistical Product and Service Solutions; TNF, tumor necrosis factor; TNM, tumor, node, metastasis staging.

Ethics Approval and Informed Consent

All procedures were performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. This study was approved by Chang Gung Medical Foundation Institutional Review Board (202400891B0). The requirement for individual Informed consent was waived by the Chang Gung Medical Foundation

Institutional Review Board because of the retrospective nature of the study. The study was carried out in accordance with the applicable guidelines and regulations. Every patient data was anonymized and de-identified. Confidentiality was maintained throughout the study.

Acknowledgments

The abstract of this paper, "Does liver cirrhosis affect outcomes in non-metastatic esophageal squamous cell carcinoma undergoing radiotherapy-based treatment?" was presented at the ASCO Breakthrough 2024 as a poster presentation with interim findings. The poster's abstract was published in "Poster Abstracts" in Journal of Clinical Oncology: https://ascopubs.org/doi/10.1200/JCO.2024.42.23_suppl.89

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported in part by grants from the National Science Council, Taiwan (NSTC 112-2314-B-182A-029-MY3), and Chang Gung Memorial Hospital (CMRPG8M0902 and CORPG8P0491). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Disclosure

The authors declare no competing interests.

References

1. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. *CA Cancer J Clin*. 2023;73(1):17–48. doi:10.3322/caac.21763
2. Toh Y, Oki E, Ohgaki K, et al. Alcohol drinking, cigarette smoking, and the development of squamous cell carcinoma of the esophagus: molecular mechanisms of carcinogenesis. *Int J Clin Oncol*. 2010;15(2):135–144. doi:10.1007/s10147-010-0057-6
3. DiSiena M, Perelman A, Birk J, Rezaizadeh H. Esophageal Cancer: an Updated Review. *South Med J*. 2021;114(3):161–168. doi:10.14423/SMJ.0000000000001226
4. Huang FL, Yu SJ. Esophageal cancer: risk factors, genetic association, and treatment. *Asian J Surg*. 2018;41(3):210–215. doi:10.1016/j.asjsur.2016.10.005
5. Rehm J, Taylor B, Mohapatra S, et al. Alcohol as a risk factor for liver cirrhosis: a systematic review and meta-analysis. *Drug Alcohol Rev*. 2010;29(4):437–445. doi:10.1111/j.1465-3362.2009.00153.x
6. Schizas D, Giannopoulos S, Vailas M, et al. The impact of cirrhosis on esophageal cancer surgery: an up-to-date meta-analysis. *Am J Surg*. 2020;220(4):865–872. doi:10.1016/j.amjsurg.2020.02.035
7. Liu CJ, Chen PJ. Elimination of Hepatitis B in Highly Endemic Settings: lessons Learned in Taiwan and Challenges Ahead. *Viruses*. 2020;12(8):815. doi:10.3390/v12080815
8. Dagnini G, Caldironi MW, Marin G, Buzzaccarini O, Tremolada C, Ruol A. Laparoscopy in abdominal staging of esophageal carcinoma. Report of 369 cases. *Gastrointest Endosc*. 1986;32(6):400–402. doi:10.1016/S0016-5107(86)71920-2
9. Tachibana M, Kotoh T, Kinugasa S, et al. Esophageal cancer with cirrhosis of the liver: results of esophagectomy in 18 consecutive patients. *Ann Surg Oncol*. 2000;7(10):758–763. doi:10.1007/s10434-000-0758-6
10. Conroy T, Galais MP, Raoul JL, et al. Definitive chemoradiotherapy with FOLFOX versus fluorouracil and cisplatin in patients with oesophageal cancer (PRODIGE5/ACCORD17): final results of a randomised, Phase 2/3 trial. *Lancet Oncol*. 2014;15(3):305–314. doi:10.1016/S1470-2045(14)70028-2
11. Trivin F, Boucher E, Vauleon E, et al. Management of esophageal carcinoma associated with cirrhosis: a retrospective case-control analysis. *J Oncol*. 2009;2009:173421. doi:10.1155/2009/173421
12. Chiu TJ, Huang TL, Chien CY, Huang WT, Li SH. Hypoalbuminemia and hypercalcemia are independently associated with poor treatment outcomes of anti-PD-1 immune checkpoint inhibitors in patients with recurrent or metastatic head and neck squamous cell carcinoma. *World J Surg Oncol*. 2024;22(1):242. doi:10.1186/s12957-024-03522-2
13. Ekstrom A, Brun E, Eberhard J, Segerlantz M. Second-line palliative chemotherapy, survival, and prognostic factors in patients with advanced pancreatic cancer. *Acta Oncol*. 2021;60(12):1580–1588. doi:10.1080/0284186X.2021.1973680
14. Yoshikawa N, Yoshihara M, Tamauchi S, Ikeda Y, Yokoi A, Kajiyama H. Hypoalbuminemia for the prediction of survival in patients with stage IVB cervical cancer. *PLoS One*. 2022;17(9):e0273876. doi:10.1371/journal.pone.0273876
15. Guven DC, Sahin TK, Erul E, et al. The association between albumin levels and survival in patients treated with immune checkpoint inhibitors: a systematic review and meta-analysis. *Front Mol Biosci*. 2022;9:1039121. doi:10.3389/fmolb.2022.1039121

16. McLean TW, Stewart RM, Curley TP, et al. Hypoalbuminemia in children with cancer treated with chemotherapy. *Pediatr Blood Cancer*. 2020;67(2):e28065. doi:10.1002/pbc.28065
17. Tanriverdi O, Avci N, Oktay E, et al. Pretreatment Serum Albumin Level is an Independent Prognostic Factor in Patients with Stage IIIB Non-Small Cell Lung Cancer: a Study of the Turkish Descriptive Oncological Researches Group. *Asian Pac J Cancer Prev*. 2015;16(14):5971–5976. doi:10.7314/APJCP.2015.16.14.5971
18. Yeun JY, Kaysen GA. Factors influencing serum albumin in dialysis patients. *Am J Kidney Dis*. 1998;32(6 Suppl 4):S118–25. doi:10.1016/S0272-6386(98)70174-X
19. Ballmer PE, Ochsenbein AF, Schutz-Hofmann S. Transcapillary escape rate of albumin positively correlates with plasma albumin concentration in acute but not in chronic inflammatory disease. *Metabolism*. 1994;43(6):697–705. doi:10.1016/0026-0495(94)90117-1
20. Lu CL, Lang HC, Luo JC, et al. Increasing trend of the incidence of esophageal squamous cell carcinoma, but not adenocarcinoma, in Taiwan. *Cancer Causes Control*. 2010;21(2):269–274. doi:10.1007/s10552-009-9458-0
21. McMillan DC, Watson WS, O'Gorman P, Preston T, Scott HR, McArdle CS. Albumin concentrations are primarily determined by the body cell mass and the systemic inflammatory response in cancer patients with weight loss. *Nutr Cancer*. 2001;39(2):210–213. doi:10.1207/S15327914nc392_8
22. Sonneveld MJ, Brouwer WP, Chan HL, et al. Optimisation of the use of APRI and FIB-4 to rule out cirrhosis in patients with chronic hepatitis B: results from the SONIC-B study. *Lancet Gastroenterol Hepatol*. 2019;4(7):538–544. doi:10.1016/S2468-1253(19)30087-1