中文題目：治療前低白蛋白血症可預測合併肝硬化的非轉移性食道鱗狀細胞癌病人接受放射治療為基礎的治療的九十天死亡率以及預後

英文題目：Pre-treatment hypoalbuminemia predicts higher 90-day mortality and poor prognosis in patients with non-metastatic esophageal squamous cell carcinoma and liver cirrhosis receiving radiotherapy-based therapy

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Background: Liver cirrhosis is not infrequently encountered among patients with esophageal squamous cell carcinoma (ESCC) because they share the same etiologic factor, alcohol. For patients with non-metastatic ESCC and liver cirrhosis, surgery is often contraindicated or associated with high morbidity, and radiotherapy-based therapy was commonly applied. The aim of this study was to investigate the prognosticators for overall survival in patients with non-metastatic ESCC and liver cirrhosis receiving radiotherapy-based therapy. Furthermore, we will also evaluate the predictors for the 90-day mortality rate, which is a proposed measure to reduce avoidable treatment-related toxic effects, and prevent medical waste and excessive or invalid treatment administration.

Method: Between January 2001 and December 2021, we retrospectively reviewed medical records of 1298 patients with ESCC. Among 1298 patients with ESCC, 103 patients with diagnosis of liver cirrhosis were identified. The diagnosis of liver cirrhosis was based on abdominal ultrasonography and/or computerized tomography, and/or liver biopsy results, when applicable. Among these 103 patients, 78 patients with non-metastatic ESCC and liver cirrhosis were enrolled for our analysis. The clinicopathologic parameters were collected and correlated with overall survival 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 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 overall survival. In multivariate analyses, albumin≦3.5g/dl (P=0.001, odds ratio: 2.500) and total bilirubin≧1.5mg/dl (P=0.019, odds ratio: 2.012) represented the independent adverse prognosticators for inferior overall survival. 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 patients, and others in 3 patients. Clinical 8th AJCC 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. The logistic model showed that albumin≦3.5g/dl (P=0.015, odds ratio: 16.129) and clinical 8th AJCC stage IVA (P=0.012, odds ratio: 17.544) were independently correlated with higher 90-day mortality.

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

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
$50 \leqq$ Age <60	30
$60 \leqq$ Age <70	22
$70 \leqq$ 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
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

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%	
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%	

*Statistically significant.

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*

OR, odds ratio; 95% CI, 95% confidence interval; *Statistically significant

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	
Total bilirubin	<2	57	6	0.646
	≧2	13	2	
Total bilirubin	≦1.5	55	4	0.081

	>1.5	14	4	
Esophageal varices	Absent	52	4	0.212
	Present	18	4	

*Statistically significant. x^2 test or Fisher's exact test was used for statistical analysis.

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*

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

Figure 1.
(A) Overall survival according to serum albumin. (B) Overall survival according to serum total bilirubin level.(C) Overall survival according to prolongation of prothrombin time(PT). (D) Overall survival according to ascites status. (E) Overall survival according to Child Pugh classification. (F) Overall survival according to treatment modality, concurrent chemoradiotherapy(CCRT) or radiotherapy(RT) alone.