


# Factors Influencing Overall Survival for Patients with Fibrolamellar Hepatocellular Carcinoma: Analysis of the Surveillance, Epidemiology, and End Results Database

Georgios Polychronidis<sup>1</sup>  
Jincheng Feng<sup>2</sup>  
Anastasia Murtha-  
Lemekhova <sup>1</sup>  
Ulrike Heger<sup>1</sup>  
Arianeb Mehrabi<sup>1</sup>  
Katrin Hoffmann<sup>1</sup>

<sup>1</sup>Department of General, Visceral and Transplant Surgery, Heidelberg University Clinic, Heidelberg, Germany;

<sup>2</sup>Department of Hepatobiliary Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, People's Republic of China

**Background:** The study aimed to develop a nomogram to predict overall survival (OS) for patients with FLC using a national database.

**Methods:** The Surveillance, Epidemiology, and End Results database of the National Cancer Institute was reviewed to identify FLC cases with histological confirmation between 2004 and 2014. Cox proportional hazards models were used to identify factors associated with OS. The validation of the nomogram was performed using concordance index (C-index) and calibration curves.

**Results:** Out of 170 cases with complete follow-up, 87 received surgery/ablation and 12 received transplantation with significantly higher OS than chemotherapy alone while transplantation combined with chemotherapy showed better survival than solely transplantation. The combination of surgery and chemotherapy showed worse OS than surgery alone. Survival was negatively influenced by T4 stadium (HR = 5.91), while young age and surgery were positive predictive factors. There was no influence of gender, ethnicity or nodal status on survival. The rate of AFP positivity was comparable with and without the presence of distal metastases.

**Conclusion:** FLC survival is greatly dependent upon appropriate surgical management irrespective of tumor stadium.

**Keywords:** fibrolamellar, hepatocellular, carcinoma, SEER

## Background

Fibrolamellar hepatocellular carcinoma (FLC) is a rare type of primary liver tumor, mostly presenting in younger patients without underlying liver disease and cirrhosis.<sup>1–3</sup> Due to its rarity, it has initially been classified as hepatocellular carcinoma (HCC), but the affected population and the underlying factors differ. National incidence also presents with marked variability, with the previously reported estimated age-adjusted incidence rate of less than 1 per 100,000 in the United States but with noticeably higher incidence in other countries such as Mexico (5.8% of liver tumors).<sup>4</sup> The most commonly reported age span for the diagnosis of FLC is under 40 years of age.<sup>5</sup> Diagnosis of FLC is mainly dependent on imaging since clinical symptoms are non-specific (abdominal pain is the most common symptom) and common biomarkers for liver disease are often negative. FLC presents most often as an enlarged single lesion with

Correspondence: Katrin Hoffmann  
Department of General, Visceral and Transplant Surgery, University of Heidelberg, Im Neuenheimer Feld 420, Heidelberg, 69120, Germany  
Email [katrin.hoffmann@med.uni-heidelberg.de](mailto:katrin.hoffmann@med.uni-heidelberg.de)



a centrally located scar in two-thirds of the cases. This makes the differentiation with other liver tumors (ie focal nodular hyperplasia) more difficult.<sup>6</sup> Other entities which resemble FLC are adenomas or metastases of neuroendocrine tumors.<sup>7</sup> The diagnosis is based on cross-imaging studies of CT and MRI, but a liver biopsy is recommended also for tumors that are deemed unresectable since there is a substantial risk of misdiagnosis.<sup>8–11</sup>

Timely resection of FLC is the main aspect of treatment; most patients are in need of extended liver resection since nodal and vascular infiltration have been reported as high as 60% and 43%, respectively.<sup>12–14</sup> The option of liver transplantation has also been used for selected cases with good prognosis; however, there is little priority for patients with non-HCC liver tumors on the waiting list.<sup>15,16</sup> A major prognosis burden is the fact that FLC presents high recurrence rates.<sup>17,18</sup> Taking into account all these factors there is a need for better prognostic tools for FLC. Our goal was to assess the survival trends of FLC and construct a nomogram for overall survival (OS).

## Methods

### Data Source

A registry-based retrospective cohort study was performed using data from the SEER database for the years 2004–2014. SEER is supported by the Surveillance Research Program (SRP) in NCI's Division of Cancer Control and Population Sciences (DCCPS). SEER Program provides information on comprehensive demographic and cancer statistics covering 28% of the US population.<sup>19</sup> The characteristics and representativeness of this database have been discussed previously.<sup>20,21</sup>

### Study Population

Between January 1, 2004, and December 31, 2014, 199 patients were diagnosed with FLC. This calendar year interval was chosen to provide a sufficient information on tumor characteristics and chemotherapy use. Cases were identified using a specific histologic code (International Classification of Diseases for Oncology [ICD-O] code 8171). Patients who had no confirmed pathology diagnosis (N=17), diagnosed at autopsy or by death certificate (N=1) and had another malignant primary tumor (N=11) were excluded. All cases were restricted to first primary FLC. A total of 170 patients were selected for further analysis.

The following variables were retrieved from the SEER database: sex, age (categorized as age <18, 18–39, 40–64, and >65 years), ethnicity (Caucasian, African-American, other (American Indian/Alaska native, Asian/Pacific islander)), year of diagnosis, insurance status, tumor multiplicity and size, tumor stage, AFP status, chemotherapy use and surgical management. Because all patient information in the SEER database is de-identified, this study was exempted from review by the Institutional Review Board.

### Statistical Analysis

We conducted a univariate analysis for surgical approach, chemotherapy, and the combination of these approaches as a categorical outcome with a list of covariates. Univariate analysis was undertaken using validated dataset macros.<sup>22</sup> The p-value was calculated by ANOVA for numerical covariates and chi-square test or Fisher's exact for categorical covariates, where appropriate. The primary end point in this study was overall survival. OS was defined as the time from diagnosis to death, date of last follow-up. Kaplan–Meier methods and the Log rank test were utilized for the survival analysis. A Cox proportional hazards model was applied for multivariate survival analysis. Candidate variables with a p value <0.01 on univariate analysis for survival were subjected to multivariable Cox regression analysis. In addition, to adjust for the potential confounding effect due to sex, the multivariable model was fit where sex was included as a covariate.

The performance of the nomogram was measured by concordance index (C-index) and assessed by comparing nomogram-predicted versus observed Kaplan–Meier estimates of survival probability rates. Bootstraps with 1000 resample were used for internal validation purposes. Bootstrapping was used to obtain a relatively unbiased estimate. Statistical analyses were carried out with SAS version 9.4 for Windows (SAS Institute Inc., Cary, NC, USA) and R version 3.5.3 (<https://www.r-project.org/>). All tests of statistical significance were 2-sided, and statistical significance was established at  $P < 0.05$ .

## Results

### Demographics

Young adults aged under 40 years had the highest incidence (70%) with the majority of patients being Caucasian males.

**Table 1** Descriptive Statistics for All Variables

Variable	Level	N (%) = 170
Age at diagnosis	Mean ± SD	33.28 ± 20.38
Age category	<18	42 (24.7)
	18–39	77 (45.3)
	40–64	32 (18.8)
	>65	19 (11.2)
Gender	Male	106 (62.4)
	Female	64 (37.6)
Year of diagnosis	2004–2007	67 (39.4)
	2008–2011	57 (33.5)
	2012–2014	46 (27.1)
Insurance Status	Uninsured	3 (1.8)
	Insured	120 (70.6)
	Unknown	47 (27.6)
Ethnicity	Caucasian	131 (77.1)
	African-American	21 (12.4)
	Other	18 (10.6)
AFP	Negative	78 (45.9)
	Positive	53 (31.2)
	Unknown	39 (22.9)
Tumor size	≤5 cm	29 (17.1)
	>5 cm	116 (68.2)
	Unknown	25 (14.7)
Number of lesions	Single lesion	102 (60.0)
	Multiple lesions	46 (27.1)
	Unknown	22 (12.9)
Distant metastasis	No	113 (66.5)
	Yes	51 (30.0)
	Unknown	6 (3.5)
Differentiation grade	G1	15 (8.8)
	G2	39 (22.9)
	G3	17 (10.0)
	Unknown	99 (58.2)
Vascular invasion	No	82 (48.2)
	Yes	67 (39.4)
	Unknown	21 (12.4)
Tumor stage	T1	71 (41.8)
	T2	22 (12.9)
	T3	47 (27.6)
	T4	14 (8.2)
	Tx	16 (9.4)
Node stage	N0	107 (62.9)
	N1	46 (27.1)
	Nx	17 (10.0)

(Continued)

**Table 1** (Continued).

Variable	Level	N (%) = 170
Chemotherapy	No	85 (50.0)
	Yes	85 (50.0)
Surgery	No surgery or ablation	71 (41.8)
	Liver resection or ablation	87 (51.2)
	Liver transplantation	12 (7.1)
Survival (months)	Mean ± SD	33.82 ± 33.61

**Note:** All data presented as N (Col %) or Mean ± SD.

The 3-year incidence of the disease showed a marked reduction of 12.3% over the three periods of study. At baseline, most tumors had surpassed the size cut-off of 5cm (68.2%) while most patients had single lesions. Vascular infiltration was present at 39.4% of tumors and most tumors did not present with positive AFP values at baseline.

More than half of the patients received surgical treatment or transplantation, but we observed a trend towards less surgical treatment over the study period. Between 2004–2007 and 2008–2011, less patients received surgery or transplantation, but this was not statistically significant (chi-squared test  $p=0.104$ ). Half of the patients received chemotherapy in this study cohort. The detailed demographics of the study sample are shown in [Table 1](#).

## Univariate Analysis

We performed a univariate analysis of covariates regarding surgical approaches in order to infer which factors affect surgical treatment in FLC. Chemotherapy was added as both a variable and a factor in separate analyses in order to ascertain the effect of chemotherapy on whether surgical treatment is chosen. In the analysis of surgery, the majority of patients presented with a single lesion (70.1%). Apart from tumor multiplicity, the tumor nodal status and size were of significance; however, most patients in the surgical treatment group presented with lesions larger than 5cm (75.9% vs 19.5% with ≤5cm) ([Table 2](#)).

Patients with distant metastases were treated more often with chemotherapy, although the database findings showed that 16 patients underwent resection and 2 underwent transplantation while distant metastasis was present. In the univariate analysis of chemotherapy, only age, N1,

**Table 2** Univariate Association with Study Cohort and Surgery

Covariate	Level	No Surgery N=71	Surgery		P-value*
			Liver Resection/Ablation N=87	Transplantation N=12	
Age category	<18	13 (18.31)	25 (28.74)	4 (33.33)	0.128
	18–39	28 (39.44)	43 (49.43)	6 (50)	
	40–64	18 (25.35)	12 (13.79)	2 (16.67)	
	>65	12 (16.9)	7 (8.05)	0 (0)	
Gender	Male	42 (59.15)	56 (64.37)	8 (66.67)	0.758
	Female	29 (40.85)	31 (35.63)	4 (33.33)	
Year of diagnosis	2004–2007	23 (32.39)	40 (45.98)	4 (33.33)	0.120
	2008–2011	30 (42.25)	25 (28.74)	2 (16.67)	
	2012–2014	18 (25.35)	22 (25.29)	6 (50)	
Insurance status	Uninsured	2 (2.82)	1 (1.15)	0 (0)	0.451
	Insured	53 (74.65)	57 (65.52)	10 (83.33)	
	Unknown	16 (22.54)	29 (33.33)	2 (16.67)	
Ethnicity	Caucasian	51 (71.83)	69 (79.31)	11 (91.67)	0.625
	African-American	11 (15.49)	9 (10.34)	1 (8.33)	
	Other	9 (12.68)	9 (10.34)	0 (0)	
AFP	Negative	28 (39.44)	44 (50.57)	6 (50)	<b>0.030</b>
	Positive	30 (42.25)	18 (20.69)	5 (41.67)	
	Other	13 (18.31)	25 (28.74)	1 (8.33)	
Tumor size	≤5 cm	11 (15.49)	17 (19.54)	1 (8.33)	<b>&lt;0.001</b>
	>5 cm	40 (56.34)	66 (75.86)	10 (83.33)	
	Unknown	20 (28.17)	4 (4.6)	1 (8.33)	
Number of lesions	Single lesion	35 (49.3)	61 (70.11)	6 (50)	<b>0.022</b>
	Multiple lesions	23 (32.39)	17 (19.54)	6 (50)	
	Unknown	13 (18.31)	9 (10.34)	0 (0)	
Differentiation grade	G1	4 (5.63)	10 (11.49)	1 (8.33)	<b>0.011</b>
	G2	8 (11.27)	26 (29.89)	5 (41.67)	
	G3	7 (9.86)	10 (11.49)	0 (0)	
	Unknown	52 (73.24)	41 (47.13)	6 (50)	
Vascular invasion	No	34 (47.89)	45 (51.72)	3 (25)	0.096
	Yes	25 (35.21)	33 (37.93)	9 (75)	
	Unknown	12 (16.9)	9 (10.34)	0 (0)	
Tumor stage	T1	27 (38.03)	41 (47.13)	3 (25)	<b>&lt;0.001</b>
	T2	4 (5.63)	18 (20.69)	0 (0)	
	T3	21 (29.58)	18 (20.69)	8 (66.67)	
	T4	6 (8.45)	8 (9.2)	0 (0)	
	Tx	13 (18.31)	2 (2.3)	1 (8.33)	
Node stage	N0	41 (57.75)	58 (66.67)	8 (66.67)	<b>0.013</b>
	N1	16 (22.54)	26 (29.89)	4 (33.33)	
	Nx	14 (19.72)	3 (3.45)	0 (0)	
Distant metastasis	No	33 (46.48)	70 (80.46)	10 (83.33)	<b>&lt;0.001</b>
	Yes	33 (46.48)	16 (18.39)	2 (16.67)	
	Unknown	5 (7.04)	1 (1.15)	0 (0)	

(Continued)

**Table 2** (Continued).

Covariate	Level	Surgery			P-value*
		No Surgery N=71	Liver Resection/Ablation N=87	Transplantation N=12	
Chemotherapy	No	29 (40.85)	53 (60.92)	3 (25)	<b>0.009</b>
	Yes	42 (59.15)	34 (39.08)	9 (75)	
Age at diagnosis		39.21 ± 22.71	29.26 ± 17.75	27.25 ± 15.6	<b>0.005</b>
Survival months		14.46 ± 21.83	50.22 ± 34.43	29.42 ± 22.16	<b>&lt;0.001</b>

**Notes:** \*The p-value is calculated by ANOVA for numerical covariates; and chi-square test or Fisher's exact for categorical covariates, where appropriate. P-values are printed in bold when under the 0.05 threshold.

**Table 3** Univariate Association with Study Cohort and Chemotherapy

Covariate	Level	Chemotherapy			Parametric P-value*
		No N=85	Yes N=85		
Age category	<18	13 (15.29)	29 (34.12)	<b>0.023</b>	
	18–39	41 (48.24)	36 (42.35)		
	40–64	18 (21.18)	14 (16.47)		
	>65	13 (15.29)	6 (7.06)		
Gender	Male	55 (64.71)	51 (60)	0.527	
	Female	30 (35.29)	34 (40)		
Year of diagnosis	2004–2007	33 (38.82)	34 (40)	0.322	
	2008–2011	25 (29.41)	32 (37.65)		
	2012–2014	27 (31.76)	19 (22.35)		
Insurance status	Uninsured	2 (2.35)	1 (1.18)	0.128	
	Uninsured	54 (63.53)	66 (77.65)		
	Unknown	29 (34.12)	18 (21.18)		
Ethnicity	Caucasian	68 (80)	63 (74.12)	0.124	
	African-American	12 (14.12)	9 (10.59)		
	Other	5 (5.88)	13 (15.29)		
AFP	Negative	41 (48.24)	37 (43.53)	0.507	
	Positive	23 (27.06)	30 (35.29)		
	Other	21 (24.71)	18 (21.18)		
Tumor size	≤5 cm	19 (22.35)	10 (11.76)	0.158	
	>5 cm	53 (62.35)	63 (74.12)		
	Unknown	13 (15.29)	12 (14.12)		
Number of lesions	Single lesion	58 (68.24)	44 (51.76)	0.073	
	Multiple lesions	17 (20)	29 (34.12)		
	Unknown	10 (11.76)	12 (14.12)		
Differentiation grade	G1	5 (5.88)	10 (11.76)	0.145	
	G2	25 (29.41)	14 (16.47)		
	G3	7 (8.24)	10 (11.76)		
	Unknown	48 (56.47)	51 (60)		
Vascular invasion	No	47 (55.29)	35 (41.18)	0.183	
	Yes	29 (34.12)	38 (44.71)		
	Unknown	9 (10.59)	12 (14.12)		

(Continued)

**Table 3** (Continued).

Covariate	Level	Chemotherapy		
		No N=85	Yes N=85	Parametric P-value*
Tumor stage	T1	42 (49.41)	29 (34.12)	<b>0.041</b>
	T2	14 (16.47)	8 (9.41)	
	T3	16 (18.82)	31 (36.47)	
	T4	5 (5.88)	9 (10.59)	
	Tx	8 (9.41)	8 (9.41)	
Node stage	N0	68 (80)	39 (45.88)	<b>&lt;0.001</b>
	N1	11 (12.94)	35 (41.18)	
	Nx	6 (7.06)	11 (12.94)	
Distant metastasis	No	68 (80)	45 (52.94)	<b>&lt;0.001</b>
	Yes	14 (16.47)	37 (43.53)	
	Unknown	3 (3.53)	3 (3.53)	
Age at diagnosis		37.46 ±21.48	29.09 ±18.41	<b>0.007</b>
Survival months		34.33 ±36.75	33.31 ±30.36	0.843

**Notes:** \*The parametric p-value is calculated by ANOVA for numerical covariates and chi-square test for categorical covariates. P-values are printed in bold when under the 0.05 threshold.

M1 and T were significantly associated with this treatment (Table 3).

We performed a univariate association analysis of surgery and chemotherapy with the other covariates in our dataset. This revealed that with no chemotherapy only the tumor multiplicity, size and T stage are the only covariates with significant differences between surgical treatment groups. Patients receiving no chemotherapy and no surgical treatment were noticeably older than patients receiving resection or transplantation (mean age of 53.2±20.7 Vs 29.4±17.4 and 26.7 ±8.1 years of age,  $p < 0.001$ ) (Table 2 and Supplementary Table 1). Another interesting finding in this cohort is that pediatric and adolescent patients did not receive chemotherapy when not being resected, whereas the opposite was the case for patients with liver resection/ablation. The positivity of AFP was comparable in patients with and without metastases (Supplementary Table 2).

## Survival Analysis

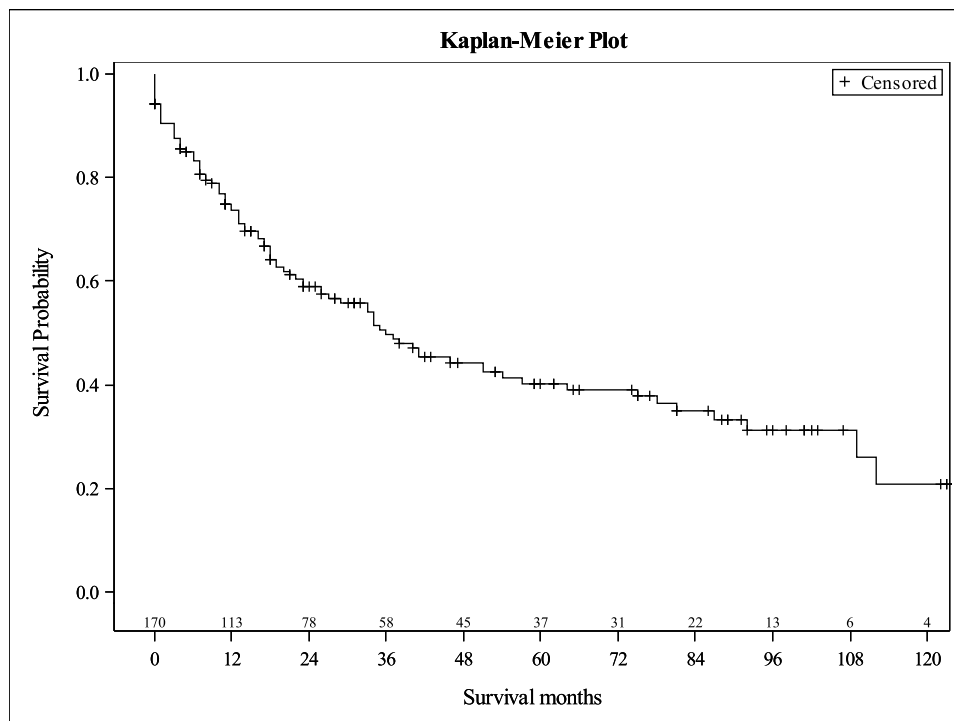
We evaluated survival trends in the univariate analysis of both surgery and chemotherapy (Figures 1 and 2). The results have been in favor of surgery with a mean survival of 50 months. Chemotherapy alone did not show any influence on survival. Still, patients receiving

both surgery and chemotherapy had a mean survival of 34 months, while patients with just resection and no chemotherapy showed a mean of 50.5 months. This finding was significant in both the chemotherapy and non –chemotherapy groups (Supplementary Table 1).

The 5-year overall survival (OS) rate of all patients was 40.3% while for those who had undergone surgery it was 60.7%. The overall 10-year survival was 20.8%. We examined univariate associations between each variable of interest and the time-to-event survival using Cox proportional hazards models. Out of all patients' characteristics, young age was the significant factor for better prognosis with an HR of 0.15 (95% CI 0.06–0.35) for patients under 18 years of age (Supplementary Table 3).

These results were incorporated in a multivariate Cox proportional hazards model and a Cox proportional hazards model with backward selection at a specified significance  $\alpha$  level of 0.05.

There was no influence of gender, race, or nodal status on survival. Surgery and chemotherapy were the most significant independent prognostic factors for survival with an HR of 0.18 for resection, 0.14 for transplantation and 0.58 for chemotherapy (Table 4). Histologically undifferentiated tumors, distant metastases and age over 40 were independent negative factors of survival predictions. The factor with the highest



No. of Subject	Event	Censored	Median Survival (95% CI)
170	93 (55%)	77 (45%)	36 (26, 54)

Survival months	Survival Rate(95% CI)
12	73.6% (66.1%, 79.7%)
60	40.3% (31.7%, 48.7%)
120	20.8% (9.4%, 35.2%)

**Figure 1** Overall survival plot.

impact on negative prognosis was the tumor stage with T4 showing an HR=5.91 (95% CI 1.19–29.33).

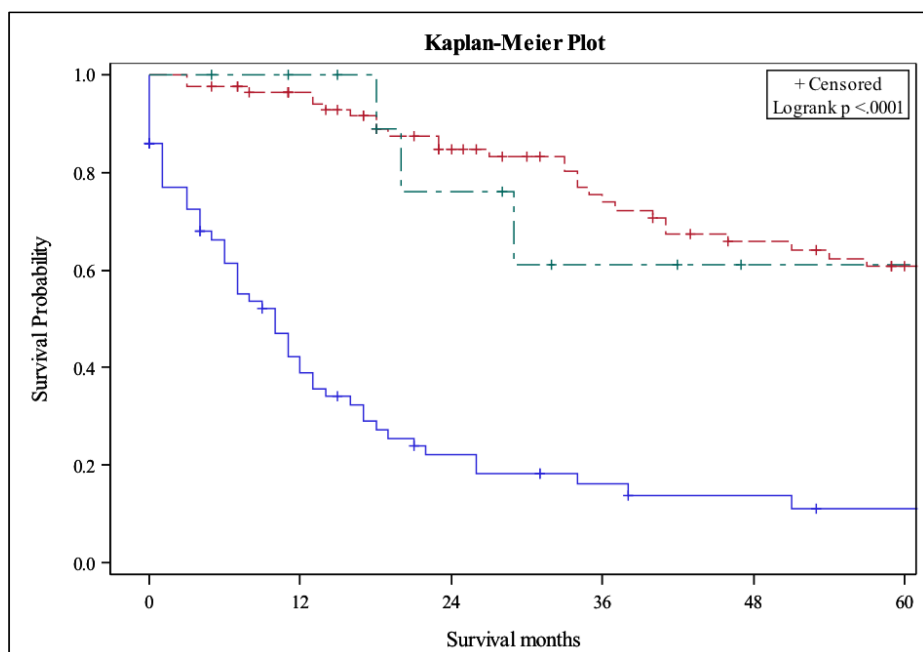
When utilizing a backward model of high significance with the last values as reference, the presence of distant metastases (HR=3.64; 95% CI 1.20–11.00) and the lack of surgical treatment (HR=4.64; 95% CI 1.40–15.37) were the most harmful prognostic factors. On the other hand, the age under 18 (HR 0.15; 95% CI 0.06–0.35) and under 35 (HR=0.30; 95% CI 0.14–0.64) as well as a T2 stage (HR=0.31; 95% CI 0.11–0.87) had the highest positive factor predictability. A good (G1) histological differentiation (HR=0.39; 95% CI 0.16–0.98) was also marginally an independent predictive factor of positive prognostic value while a G3 differentiation (HR=2.45; 95% CI 1.20–5.01) of

negative one. Based on these findings, we created a survival nomogram with validation in 1-, 3- and 5-year survival (Figures 3 and 4). The nomogram showed that age was the largest predictor of OS, followed by surgery and tumor stage.

## Discussion

FLC is a disease with unique molecular characteristics affecting children and young adults, with a slow progression.<sup>6,23–26</sup> Recent studies have identified a fusion gene that could provide with liquid biopsy alternatives or even therapeutic targets in the future.<sup>11,27,28</sup> However, despite higher diagnostic rates and better understanding in its pathophysiology, FLC remains a disease with enigmatic prognosis. At present,





Treatment : — No surgery — Surgery or ablation — Transplantation

Treatment	No. of Subjects	Events	Censored	Median Survival (95% CI)
No surgery	71	56 (79%)	15 (21%)	10 (6, 13)
Surgery or ablation	87	34 (39%)	53 (61%)	92 (54, NA)
Transplantation	12	3 (25%)	9 (75%)	NA (18, NA)

Treatment	Survival months	Survival Rate(95% CI)
No surgery	12	39.0% (27.2%, 50.7%)
	60	11.0% (4.2%, 21.6%)
Surgery or ablation	12	96.5% (89.6%, 98.9%)
	60	60.7% (47.8%, 71.3%)
Transplantation	12	100.0% (NA, NA)
	60	61.0% (20.2%, 85.8%)

Figure 2 Survival plot depending on surgery, no resection and transplantation.

surgical resection remains the main aim of treatment with a reported OS of 75–88 months.<sup>1</sup> Our study showed that resection offers a median OS of 92 months with a 5-year overall survival rate of 60.7%. A very interesting finding proved the difference in survival among cases with a combination of chemotherapy and transplantation (27.44 months) versus cases treated with transplantation only (26.67 months), a finding that has not been described in extent before. Patients not undergoing surgery and not receiving treatment

with chemotherapy showed a mean survival of 5.9 months, significantly lower than patients with chemotherapy. These were the only two groups with significant differences in patients’ mean age. This is an interesting finding that hints that patients who are not staged timely for chemotherapy tend to be older and survive much less. In a univariate association between chemotherapy and distant metastases, the only significant association was the age difference between patients who received chemotherapy while having



**Table 4** Univariable Analysis and Cox Proportional Hazards Regression Analysis<sup>a</sup>

	Univariable Analysis with OS			Cox Proportional Hazards Regression Analysis with OS *,**		
	HR	95% CI	P value	HR	95% CI	P value
Sex						
Male	Ref			Ref		
Female	1.18	0.76–1.81	0.462			
Age at diagnosis			<b>0.001</b>			<b>0.002</b>
<18	Ref			Ref		
18–39	1.74	0.98–3.10	0.060	1.89	1.00–3.58	0.050
40–64	2.22	1.12–4.40	<b>0.023</b>	3.55	1.58–8.01	<b>0.002</b>
>65	4.34	2.07–9.11	<b>&lt;0.001</b>	5.85	2.26–15.11	<b>&lt;0.001</b>
Race			0.303			
Caucasian	Ref					
African-American	1.35	0.73–2.51	0.337			
Other	1.55	0.82–2.95	0.179			
Year of diagnosis			0.422			
2004–2007	Ref					
2008–2011	1.21	0.76–1.93	0.418			
2012–2014	0.78	0.39–1.56	0.483			
Insurance status			0.953			
Uninsured	Ref					
Ininsured	1.11	0.15–8.06	0.915			
Unknown	1.19	0.16–8.76	0.865			
Tumor size			<b>&lt;0.001</b>			0.083
≤5cm	Ref			Ref		
>5 cm	1.02	0.57–1.84	0.965	0.97	0.45–2.10	0.931
Unknown	3.02	1.52–6.01	<b>0.002</b>	2.46	0.86–7.06	0.093
Tumor multiplicity			<b>&lt;0.001</b>			
Single lesion	Ref					
Multiple lesions	2.16	1.33–3.51	<b>0.002</b>			
Unknown	2.66	1.53–4.65	<b>0.001</b>			
AFP status			<b>0.003</b>			
Negative	Ref					
Positive	2.26	1.39–3.67	<b>0.001</b>			
Unknown	1.17	0.67–2.02	0.586			
Tumor stage			<b>&lt;0.001</b>			<b>0.015</b>
T1	Ref			Ref		
T2	0.61	0.27–1.39	0.241	0.67	0.25–1.77	0.415
T3	2.04	1.20–3.46	<b>0.009</b>	2.02	1.04–4.35	<b>0.042</b>
T4	2.42	1.23–4.76	<b>0.011</b>	5.91	1.19–29.33	<b>0.030</b>
Tx	3.44	1.73–6.82	<b>&lt;0.001</b>	1.03	0.22–4.49	0.997
Differentiation grade			<b>0.016</b>			<b>0.001</b>

(Continued)

Table 4 (Continued).

	Univariable Analysis with OS			Cox Proportional Hazards Regression Analysis with OS <sup>*,**</sup>		
	HR	95% CI	P value	HR	95% CI	P value
G1	Ref			Ref		
G2	1.32	0.52–3.39	0.559	1.73	0.62–4.79	0.292
G3	3.45	1.27–9.40	<b>0.015</b>	7.48	2.44–22.95	<b>&lt;0.001</b>
Unknown	2.4	1.03–5.58	<b>0.042</b>	2.90	1.16–7.25	<b>0.022</b>
Node stage			0.816			
N0	Ref					
N1	1.09	0.68–1.75	0.714			
Nx	1.25	0.59–2.63	0.557			
Distant metastasis						
No	Ref			Ref		
Yes	2.98	1.95–4.57	<b>&lt;0.001</b>	2.56	1.52–4.32	<b>&lt;0.001</b>
Chemotherapy						
No	Ref			Ref		
Yes	1.34	0.88–2.06	0.173	0.58	0.34–0.99	<b>0.049</b>
Surgery or ablation			<b>&lt;0.001</b>			<b>&lt;0.001</b>
No surgery or ablation	Ref			Ref		
Liver resection or ablation	0.17	0.11–0.26	<b>&lt;0.001</b>	0.18	0.11–0.31	<b>&lt;0.001</b>
Liver transplantation	0.16	0.05–0.53	<b>0.002</b>	0.14	0.04–0.49	<b>0.002</b>

Notes: <sup>a</sup>Unknown data on distant metastasis were excluded (n=6). <sup>\*</sup>Number of observations in the original data set = 170. Number of observations used = 170. <sup>\*\*</sup>Selection with an alpha level of removal of 0.05 was used. P-values are printed in bold when under the 0.05 threshold.

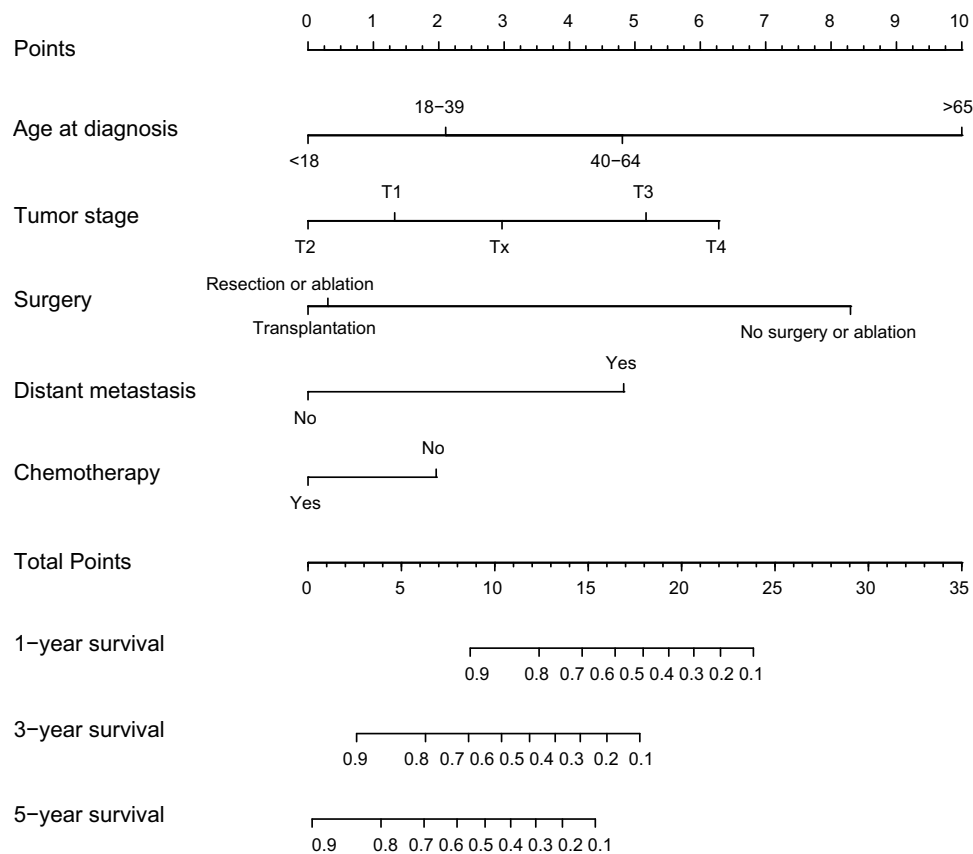
a positive metastasis status (mean age  $24.6 \pm 12.7$  vs  $38.1 \pm 20.7$ ;  $p=0.007$ ); nonetheless, the survival of patients with distant metastases was comparable regardless of receiving chemotherapy treatment. This finding is significant when comparing metastasis and age in other cancer groups, where the mean age of oncological treatment is much higher.

The incidence of FLC has been previously described as low as 0.2/100,000 and previous publications on the SEER database have been reporting variable annual incidence.<sup>14,29,30</sup> In our analysis, where patients were stratified in four categories we accounted for more than 30 new cases per year.

The already described factors predicting OS and DFS in FLC have been quite variable during the past years since most publications are based on case series with small sample size.<sup>31</sup> Matching previous data, metastases and the differentiation of tumors were

negative predictive factors. Furthermore, age and the lack of surgical treatment were factors with negative predictive value. Our most impressive finding was that larger tumors had a negative prognostic value, although one can see that most of these patients were surgically treated. This can be a case of small sample size (5 patients in total) but also a situation where recurrence occurred.

Concerning the diagnosis of FLC, multimodal imaging is of paramount importance since the clinical symptoms are inconstant and the diagnostic value of AFP is marginal. Our study confirmed that the levels of AFP are not indicative of disease or even of distant metastases. However, the null association of AFP with distant metastases at baseline in a univariate analysis has been demonstrated for the first time in this study. This finding may have more than the hypothesized limited clinical significance. A combination of this



**Figure 3** Predictive survival nomogram.

marker with other biomarkers should be tried in larger datasets.

The value of aggressive surgery has been demonstrated since the first publications on FLC and although even high-volume centers report a significant proportion of recurrent disease, the 5-year prognosis remains higher than this of not resected/ablated tumors. Our study was consistent with the findings of other analyses, which showed better survival for surgery/ablation, but in the present study, the effect of chemotherapy in combination with surgery showed actually a lower OS. This may be attributable to advanced disease, because due to age of diagnosis, one can postulate that the patients had few underlying conditions.

This study has a number of limitations apart from possible selection bias, with the database-derived factors being the most important ones. We had a relatively large sample size; however, due to the fact that other databases are not open for validation, we could not validate the analysis presented here. Another limitation is that some transplantation cases were not classified as patients who had received chemotherapy before or after

transplantation, which would be a novel approach to this disease. Furthermore, the SEER does not contain data on recurrence, which would help specify our findings on the role of surgery or transplantation on survival. Finally, data on chemotherapy type/duration are required in order to assess its influence on survival.

## Conclusions

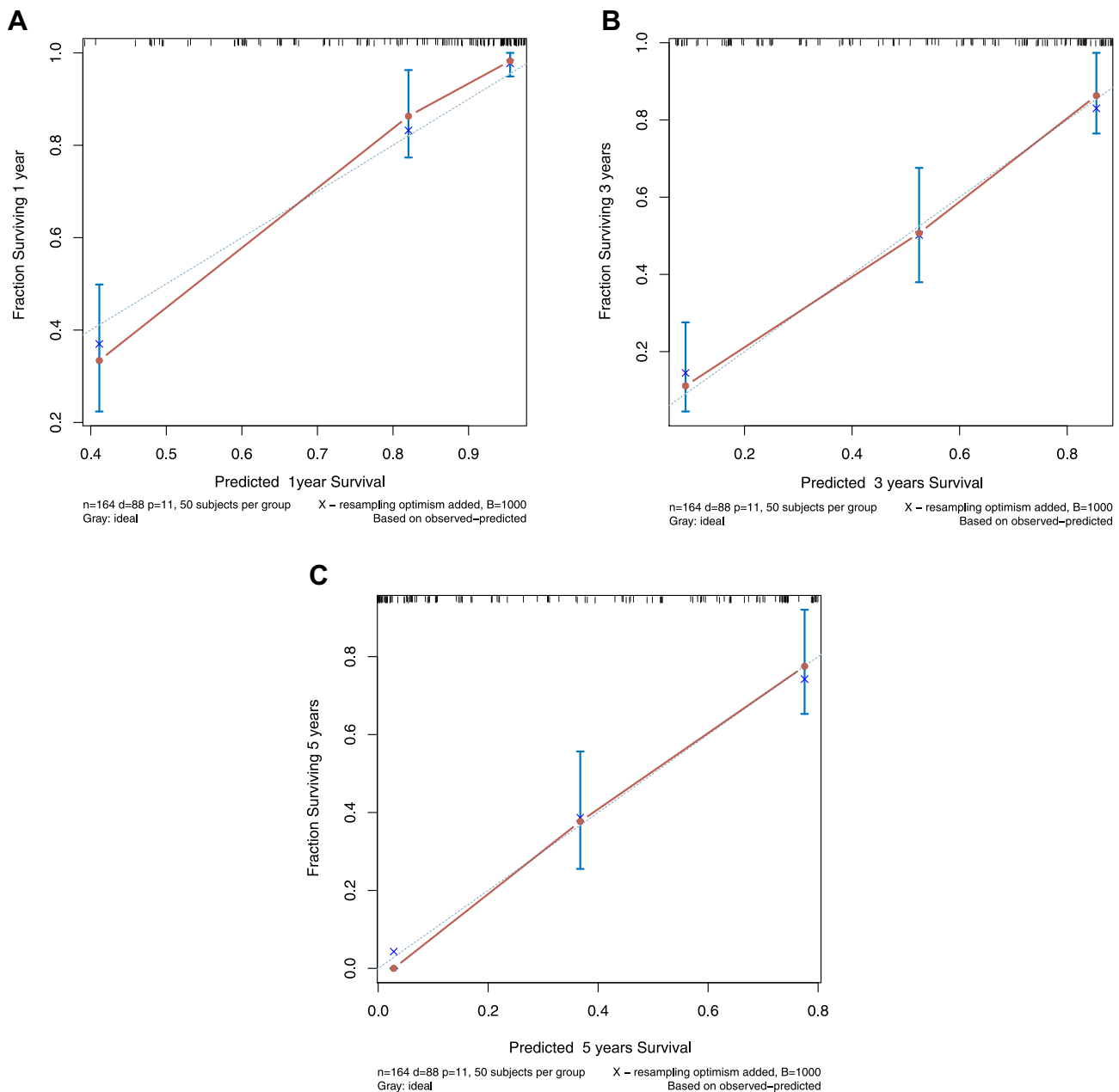
The prognosis of FLC depends greatly on its surgical management. Surgery irrespective of combination with (neo-) adjuvant chemotherapy offers significantly better survival than systemic therapy alone.

## Abbreviations

FLC, fibrolamellar hepatocellular carcinoma; HCC, hepatocellular carcinoma; OS, overall survival.

## Data Sharing Statement

SEER data are available after registration. The authors will provide any additional data, including the analysis dataset at reasonable request.



**Figure 4** Predicted 1-year (A), 3-year (B) and 5-year (C) survival based on the nomogram.

### Ethics Approval and Consent to Participate

N/A (The SEER database did not prerequisite any ethics approval since patient data are pseudonymised). Studies in which exclusively anonymous data are collected and evaluated are not required to be submitted to the ethics committee of the Medical Faculty of Heidelberg University.

Research with anonymous data does not fall under the consultation and submission obligation of Section 15 (1) of the Professional Code for Doctors in Baden-Württemberg.

### Consent for Publication

The authors have consented to publication after having read the final manuscript.

### 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 by China Scholarship Council [File No.201708080137].

## Disclosure

The authors have declared no conflicts of interest.

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