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Research Article

Prognostic Analysis on Different Tumor Sizes for 14634 Hepatocellular Carcinoma Patients

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Aim. This study investigated the effect of tumor size and other factors on the survival and prognosis of hepatocellular carcinoma (HCC). *Methods*. All HCC populations based on the National Cancer Institute's SEER database to receive from 2010 to 2016 were employed in the study. *Results*. This study enrolled a total of 14,634 HCC. Among them, 1,686 patients had tumors ≤ 2 cm, 6,169 patients had tumors 2–5 cm, and 6,779 patients had tumors > 5 cm. The results using univariate analysis showed that all factors were significant prognostic factors for overall survival and specific survival. Patients with tumor size ≤ 2 cm were more likely to survive, while patients with tumor size > 5 cm had a lower survival rate. Patients who had surgery or surgery plus chemotherapy had a higher chance of survival in stages I-II, and the survival rate declined smoothly during the 80 months. The change rate of the mortality rate increased rapidly during the period of 1–12 cm; afterwards, the mortality rate's HR was basically and smoothly maintained at a high level. *Conclusions*. Tumor size was positively correlated with the mortality rate of HCC. Survival rates were greater in patients with tumors ≤ 2 cm who underwent surgery or surgery plus chemotherapy. Patients with HCC in the early stage had a higher survival probability particularly when they had experienced surgery or surgery plus chemotherapy.

1. Introduction

Hepatocellular carcinoma (HCC) with an extremely high mortality rate is one of the most common malignant tumors. Previous study [1] showed the HCC has the poor of prognosis, and its survival rate of 5-year was under 20%. HCC has a special feature: growth with metastasis to distant organs, which accounts for poor survival. The HCC with distant metastasis is commonly found in the lungs, bones, and brain [2]. Moreover, the most common risk factor for HCC globally is the hepatitis B virus. In a previous study, the most common causative agent was the hepatitis C virus [3]. More than 90% of primary liver cancers are HCC [4]. In recent years, relevant research studies confirmed that specific therapeutic regimens, including surgical resection, chemotherapy, and radiotherapy, provided HCC patients favorable prognosis and long-term survival. The current meta-analysis from Francesca's study [5] found that regorafenib was a safe and effective treatment option for patients with advanced HCC. In addition, the efficacy and safety of microwave ablation and radiofrequency ablation were similar, but microwave ablation reduced the long-term recurrence rate [6]. A review summarized the trajectory of various aspects of HCC management over the last 15 years, providing additional information for clinicians to aggregate [7]. Previous research studies [8] found that HCC patients were more likely to feel hopeless, depressed, and even have serious suicidal thoughts. HCC monitoring for national minority and individuals of lower

socioeconomic status was poorly performed, further exacerbating the difference in HCC prognosis among these disadvantaged populations [9]. Current therapeutic regimens, including surgery of liver resection, transplantation, radiotherapy, percutaneous ethanol injection, transarterial chemoembolization, microwave ablation, radiofrequency ablation, cryoablation, irreversible electroporation, combination therapies (such as postoperative adjuvant chemoradiotherapy and nutrition supportive therapy) and palliative care, will create high costs for HCC [10].

The hepatic artery gives off the proper hepatic artery, and the portal vein repeatedly branches into the interlobular artery and interlobular vein after passing through the hepatic portal into the liver, which then branch into the hepatic lobule and drain into the blood sinus. The proper hepatic artery and portal vein contribute to the metabolism of liver substances and regeneration of liver tissues, and they also provide abundant blood supply for the growth of liver tumors [11]. Larger liver tumors are prone to vascular infiltration and nodules, and the possibility of advanced HCC and tumor proliferation is also increased, which directly affects the prognosis of patients with HCC [12]. At present, liver resection and liver transplantation are relatively feasible methods in the surgical treatment. The prognosis of surgical treatment is related to tumor size, which may serve as an alternative marker of vascular infiltration. Relevant researchers have shown that clinicians should be concerned about the HCC patients with tumor size ≥ 5.8 cm [2]. However, another study [13] showed that HCC > 50 mm have a high degree of vascular infiltration which was associated with a poor prognosis. This study will further investigate tumor size and other factors on survival and prognosis of HCC.

2. Methods

2.1. Data Source. All data of population-based cancer registries for this study were from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) database, and all data were extracted by SEER*Stat (Version 8.3.8).

2.2. Population Selection and Classification. This study selected patients who were diagnosed with HCC between 2010 and 2016. The exclusion criteria in this study were as follows: (1) unknown of race; (2) unknown of survival time; (3) unknown of *T*, *N*, or *M* stage; (4) unknown of follow-up; (5) diagnosis at autopsy.

We enrolled 14,634 patients who were assigned in groups with tumors ≤ 2 cm, tumors between 2 and 5 cm, and tumors greater than 5 cm. Age were divided in 0–50, 51–60, 61–70, and 70 + four. The AJCC stage was also included, and the histological classification of liver cancer was performed. Patients diagnosed with HCC were grouped under the HCC-special survival if the cause of death was also HCC. HCC-special survival was calculated as the time from diagnosis to death from HCC.

2.3. Statistical Analysis. The Kaplan–Meier method and log-rank testing were employed for evaluating overall all-cause HCC survival and HCC-special survival. Different tumor sizes and intervention regimens were discussed as important prognostic survival factors. Regression analysis was employed to estimate the relationship between hepatocyte tumor size and overall survival (OS). Univariate and multivariate Cox proportional risk models were used to assess the probability of death. The hazard ratio (HR) was used as the statistical effect size. All statistical analyses were performed using *R* software (Version 4.0.0, *R* Foundation).

3. Results

3.1. Baseline Characteristics. In our study, 14,634 HCC patients were eligible and information is given in Table 1. The number of patients with tumor size ≤ 2 cm was 1,686, patients with tumor size 2–5 cm accounted for 6,169, and the most part went to patients with tumor size > 5 cm who were 6,779. In terms of age, 61–70 years old (33.8%) was the most common patient, and 51–60 years old (41.0%) was the most common among patients with tumors ≤ 2 cm, 61–70 years old (36.9%) was the most common among patients with tumor size 2–5 cm, and over 70 years old (36.4%) was the most common among patients with tumor size > 5 cm. In all three tumor size subgroups, males accounted for the largest proportion (72.8%, 75.7%, and 78.1%). A large proportion of study were white (68.6%), and the majority of the patients were white in different tumor sizes (72.1%, 69.6%, and 66.9%). For tumor stage, patients with tumor size ≤2 cm (61.2%) and 2–5 cm (53.6%) had the most patients in the stage I, and patients with tumors greater than 5 cm had the most patients in the stage III (37.5%). Patients with tumor size ≤2 cm (63.5%) and 2–5 cm (56.5%) had the most at stage T1, while patients with tumor size > 5 cm (49.6%) had the most at stage T3. In the three tumor size groups, patients at stage N0 and stage M0 had the largest proportion. Patients with tumor size ≤2 cm (66.0%) and 2–5 cm (53.3%) were more likely to have had surgery, while patients with tumor size > 5 cm (74.5%) were have no surgery or unknown conditions. Among the subgroups of different tumor sizes, the percentage of patients who did not undergo chemotherapy, radiation, or unknown conditions were higher. For the HCC-special survival liver cancer patients, the distribution of each factor in different tumor sizes was consistent with OS.

3.2. Cox Proportional Hazards Model. Univariate and multivariate analyses details are shown in Table 2. The results showed that all factors ($P < 0.001$), including age, gender, race, marital status, tumor size, AJCC stage, TNM stage, surgery, radiation, and chemotherapy ($P = 0.049$), were significant prognostic factors for OS and specific survival.

In multivariable analysis, the male (HR = 1.06, 95% CI: 1.01–1.12) was more likely to get cancer than the female. The risk increases when patients are older than 50, and they are most likely to develop the disease when they were older than 70 (HR = 1.40, 95% CI: 1.28–1.53). Among race

Table 1: Baseline characteristics of different tumor sizes in whole cohort.

	Hepatocellular carcinoma-overall survival				Hepatocellular carcinoma-specific survival			
	≤2 cm (*N* = 1686)	2–5 cm (*N* = 6169)	>5 cm (*N* = 6779)	Overall (*N* = 14634)	≤2 cm (*N* = 1281)	2–5 cm (*N* = 4534)	>5 cm (*N* = 5204)	Overall (*N* = 11019)
Age (years)								
0–50	156 (9.3%)	385 (6.2%)	561 (8.3%)	1102 (7.5%)	137 (10.7%)	334 (7.4%)	500 (9.6%)	971 (8.8%)
51–60	692 (41.0%)	1948 (31.6%)	1663 (24.5%)	4303 (29.4%)	559 (43.6%)	1567 (34.6%)	1426 (27.4%)	3552 (32.2%)
61–70	576 (34.2%)	2277 (36.9%)	2087 (30.8%)	4940 (33.8%)	425 (33.2%)	1715 (37.8%)	1632 (31.4%)	3772 (34.2%)
70+	262 (15.5%)	1559 (25.3%)	2468 (36.4%)	4289 (29.3%)	160 (12.5%)	918 (20.2%)	1646 (31.6%)	2724 (24.7%)
Gender								
Female	459 (27.2%)	1496 (24.3%)	1483 (21.9%)	3438 (23.5%)	330 (25.8%)	1069 (23.6%)	1114 (21.4%)	2513 (22.8%)
Male	1227 (72.8%)	4673 (75.7%)	5296 (78.1%)	11196 (76.5%)	951 (74.2%)	3465 (76.4%)	4090 (78.6%)	8506 (77.2%)
Race								
Black	207 (12.3%)	824 (13.4%)	975 (14.4%)	2006 (13.7%)	159 (12.4%)	605 (13.3%)	761 (14.6%)	1525 (13.8%)
White	1216 (72.1%)	4296 (69.6%)	4534 (66.9%)	10046 (68.6%)	917 (71.6%)	3091 (68.2%)	3417 (65.7%)	7425 (67.4%)
Others	263 (15.6%)	1049 (17.0%)	1270 (18.7%)	2582 (17.6%)	205 (16.0%)	838 (18.5%)	1026 (19.7%)	2069 (18.8%)
Marital status								
Married	966 (57.3%)	3494 (56.6%)	3740 (55.2%)	8200 (56.0%)	735 (57.4%)	2587 (57.1%)	2847 (54.7%)	6169 (56.0%)
Single	720 (42.7%)	2675 (43.4%)	3039 (44.8%)	6434 (44.0%)	546 (42.6%)	1947 (42.9%)	2357 (45.3%)	4850 (44.0%)
AJCC stage								
I	1031 (61.2%)	3305 (53.6%)	2116 (31.2%)	6452 (44.1%)	767 (59.9%)	2364 (52.1%)	1536 (29.5%)	4667 (42.4%)
II	510 (30.2%)	2049 (33.2%)	381 (5.6%)	2940 (20.1%)	402 (31.4%)	1533 (33.8%)	294 (5.6%)	2229 (20.2%)
III	45 (2.7%)	226 (3.7%)	2541 (37.5%)	2812 (19.2%)	37 (2.9%)	180 (4.0%)	1941 (37.3%)	2158 (19.6%)
IV	100 (5.9%)	589 (9.5%)	1741 (25.7%)	2430 (16.6%)	75 (5.9%)	457 (10.1%)	1433 (27.5%)	1965 (17.8%)
T stage								
*T*1	1070 (63.5%)	3486 (56.5%)	2541 (37.5%)	7097 (48.5%)	797 (62.2%)	2500 (55.1%)	1873 (36.0%)	5170 (46.9%)
*T*2	550 (32.6%)	2339 (37.9%)	447 (6.6%)	3336 (22.8%)	432 (33.7%)	1757 (38.8%)	350 (6.7%)	2539 (23.0%)
*T*3	53 (3.1%)	261 (4.2%)	3361 (49.6%)	3675 (25.1%)	43 (3.4%)	210 (4.6%)	2628 (50.5%)	2881 (26.1%)
*T*4	13 (0.8%)	83 (1.3%)	430 (6.3%)	526 (3.6%)	9 (0.7%)	67 (1.5%)	353 (6.8%)	429 (3.9%)
N stage								
*N*0	1645 (97.6%)	5913 (95.9%)	5963 (88.0%)	13521 (92.4%)	1248 (97.4%)	4337 (95.7%)	4538 (87.2%)	10123 (91.9%)
*N*1	41 (2.4%)	256 (4.1%)	816 (12.0%)	1113 (7.6%)	33 (2.6%)	197 (4.3%)	666 (12.8%)	896 (8.1%)
M stage								
*M*0	1602 (95.0%)	5735 (93.0%)	5444 (80.3%)	12781 (87.3%)	1217 (95.0%)	4190 (92.4%)	4091 (78.6%)	9498 (86.2%)
*M*1	84 (5.0%)	434 (7.0%)	1335 (19.7%)	1853 (12.7%)	64 (5.0%)	344 (7.6%)	1113 (21.4%)	1521 (13.8%)
Surgery								
No/unknown	573 (34.0%)	2883 (46.7%)	5047 (74.5%)	8503 (58.1%)	410 (32.0%)	2032 (44.8%)	3843 (73.8%)	6285 (57.0%)
Yes	1113 (66.0%)	3286 (53.3%)	1732 (25.5%)	6131 (41.9%)	871 (68.0%)	2502 (55.2%)	1361 (26.2%)	4734 (43.0%)
Radiation								
No/unknown	1616 (95.8%)	5648 (91.6%)	5940 (87.6%)	13204 (90.2%)	1235 (96.4%)	4138 (91.3%)	4551 (87.5%)	9924 (90.1%)
Yes	70 (4.2%)	521 (8.4%)	839 (12.4%)	1430 (9.8%)	46 (3.6%)	396 (8.7%)	653 (12.5%)	1095 (9.9%)
Chemotherapy								
No/unknown	1207 (71.6%)	3693 (59.9%)	3886 (57.3%)	8786 (60.0%)	898 (70.1%)	2648 (58.4%)	2935 (56.4%)	6481 (58.8%)
Yes	479 (28.4%)	2476 (40.1%)	2893 (42.7%)	5848 (40.0%)	383 (29.9%)	1886 (41.6%)	2269 (43.6%)	4538 (41.2%)
Histology								
Hepatocellular carcinoma, clear cell type	15 (0.9%)	69 (1.1%)	82 (1.2%)	166 (1.1%)	10 (0.8%)	40 (0.9%)	62 (1.2%)	112 (1.0%)

Table 1: Continued.

	Hepatocellular carcinoma-overall survival				Hepatocellular carcinoma-specific survival			
	≤2 cm ($N = 1686$)	2–5 cm ($N = 6169$)	>5 cm ($N = 6779$)	Overall ($N = 14634$)	≤2 cm ($N = 1281$)	2–5 cm ($N = 4534$)	>5 cm ($N = 5204$)	Overall ($N = 11019$)
Hepatocellular carcinoma, fibrolamellar	5 (0.3%)	17 (0.3%)	58 (0.9%)	80 (0.5%)	5 (0.4%)	13 (0.3%)	55 (1.1%)	73 (0.7%)
Hepatocellular carcinoma, not otherwise specified	1662 (98.6%)	6067 (98.3%)	6607 (97.5%)	14336 (98.0%)	1264 (98.7%)	4465 (98.5%)	5062 (97.3%)	10791 (97.9%)
Hepatocellular carcinoma, scirrhous	2 (0.1%)	10 (0.2%)	12 (0.2%)	24 (0.2%)	2 (0.2%)	10 (0.2%)	10 (0.2%)	22 (0.2%)
Hepatocellular carcinoma, spindle cell variant	2 (0.1%)	5 (0.1%)	15 (0.2%)	22 (0.2%)	0 (0%)	1 (0.0%)	3 (0.1%)	4 (0.0%)
Hepatocellular carcinoma, pleomorphic type	0 (0%)	1 (0.0%)	5 (0.1%)	6 (0.0%)	0 (0%)	5 (0.1%)	12 (0.2%)	17 (0.2%)

Table 2: Cox proportional-danger model analysis for hepatocellular carcinoma.

	Univariable analysis				Multivariable analysis			
	Hepatocellular carcinoma-overall survival		Hepatocellular carcinoma-specific survival		Hepatocellular carcinoma-overall survival		Hepatocellular carcinoma-specific survival	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Age (years)		<0.001		<0.001				
00–50	Reference		Reference		Reference	<0.001	Reference	
51–60	1.14 (1.05–1.25)	0.003	1.15 (1.04–1.27)	0.006	1.22 (1.12.1.33)	<0.001	1.12 (1.09–1.33)	<0.001
61–70	1.17 (1.07–1.27)	0.001	1.15 (1.04–1.27)	0.005	1.19 (1.09–1.30)	<0.001	1.15 (1.04–1.27)	0.005
70+	1.69 (1.54–1.84)	<0.001	1.75 (1.58–1.93)	<0.001	1.40 (1.28–1.53)	<0.001	1.36 (1.23–1.50)	<0.001
Gender		<0.001		<0.001				
Female	Reference		Reference		Reference		Reference	
Male	1.12 (1.07–1.18)	<0.001	1.14 (1.07–1.20)	<0.001	1.06 (1.01–1.12)	0.018	1.07 (1.01–1.14)	0.023
Race		<0.001		<0.001				
White	Reference		Reference		Reference		Reference	
Black	0.84 (0.80–0.87)	<0.001	0.84 (0.80–0.88)	<0.001	0.91 (0.87–0.95)	<0.001	0.92 (0.88–0.97)	0.001
Others	0.80 (0.76–0.84)	<0.001	0.78 (0.74–0.83)	<0.001	0.91 (0.86–0.95)	<0.001	0.90 (0.84–0.95)	<0.001
Marital status		<0.001		<0.001				
Married	Reference		Reference		Reference		Reference	
Single	1.29 (1.24–1.35)	<0.001	1.31 (1.25–1.37)	<0.001	1.11 (1.06–116)	<0.001	1.10 (1.05–1.16)	<0.001
Tumor size (cm)		<0.001		<0.001				
0–2	Reference		Reference		Reference		Reference	
2–5	0.28 (0.26–0.30)	<0.001	0.22 (0.20–0.25)	<0.001	1.61 (1.52–1.72)	<0.001	1.79 (1.66–1.94)	<0.001
5+	0.44 (0.42–0.46)	<0.001	0.40 (0.38–0.42)	<0.001	0.99 (0.95–1.04)	0.654	0.97 (0.92–1.03)	0.357
AJCC stage		<0.001		<0.001				
I	Reference		Reference		Reference		Reference	
II	1.03 (0.97–1.10)	0.226	1.09 (1.01–1.17)	0.027	1.11 (0.96–1.28)	0.170	1.20 (1.01–1.42)\	0.035
III	2.82 (2.67–2.97)	<0.001	3.30 (3.09–3.52)	<0.001	1.58 (1.41–1.77)	<0.001	1.78 (1.56–2.03)	<0.001
IV	4.76 (4.51–5.03)	<0.001	5.80 (5.43–6.19)	<0.001	1.87 (1.61–2.18)	<0.001	2.23 (1.88–2.66)	<0.001
T stage		<0.001		<0.001				
*T*1	Reference	<0.001	Reference		Reference		Reference	
*T*2	1.06 (1.00–1.12)	0.039	1.11 (1.03–1.18)	0.003	1.12 (0.98–1.29)	0.094	1.13 (0.97–1.32)	0.125
*T*3	2.90 (2.77–3.05)	<0.001	3.30 (3.13–3.50)	<0.001	1.17 (1.06–1.30)	0.002	1.11 (0.99–1.25)	0.072
*T*4	3.41 (3.10–3.75)	<0.001	3.89 (3.49–4.34)	<0.001	1.35 (1.18–1.53)	<0.001	1.30 (1.13–1.50)	<0.001
N stage		<0.001		<0.001				
*N*0	Reference		Reference		Reference		Reference	
*N*1	2.95 (2.76–3.75)	<0.001	3.18 (2.95–3.42)	<0.001	1.07 (0.97–1.19)	0.184	1.04 (0.93–1.17)	0.506
M stage		<0.001		<0.001				
*M*0	Reference		Reference		Reference		Reference	
*M*1	3.81 (3.61–4.02)	<0.001	4.22 (3.97–4.49)	<0.001	1.54 (1.36–1.75)	<0.001	1.48 (1.28–1.70)	<0.001
Surgery		<0.001		<0.001				
No/unknown	Reference		Reference		Reference		Reference	
Performed	0.21 (0.20–0.23)	<0.001	0.18 (0.17–0.19)	<0.001	0.24 (0.22–0.25)	<0.001	0.21 (0.19–0.22)	<0.001
Radiation therapy		<0.001		<0.001				
No/unknown	Reference		Reference		Reference		Reference	
Performed	1.28 (1.20–1.36)	<0.001	1.36 (1.26–1.46)	<0.001	0.63 (0.59–0.67)	<0.001	0.62 (0.58–0.67)	<0.001
Chemotherapy		0.049		0.049				
No/unknown	Reference		Reference		Reference		Reference	
Performed	1.04 (1.00–1.09)	0.049	1.06 (1.01–1.12)	0.014	0.57 (0.54–0.59)	<0.001	0.55 (0.53–0.58)	<0.001

Note. HR, hazard ratio; CI, confidence interval.

comparisons, whites had a higher risk than the other two races. In the results, tumors had a high mortality rate at 2–5 cm (HR = 1.61, 95% CI: 1.52–1.72), but not at more than 5 cm (HR = 0.99, 95% CI: 0.95–1.04) based on the small number of HCC. Compared to stage T1, patients in stage IV (HR = 1.87, 95% CI: 1.61–2.18) were more at risk. Compared to stage N0 and M0, patients in stage N1 (HR = 1.07, 95% CI: 0.97–1.19) and stage M1 (HR = 1.54, 95% CI: 1.36–1.75) had higher rates of mortality. Regardless of the type of treatment, patients who did not participate in the treatment were at greater risk than those who did. Single patients (HR = 1.11, 95% CI: 1.06–1.16) were at greater risk than married patients.

3.3. Kaplan–Meier Survival Analysis. Figures 1(a) and 1(b) show the rate of OS and special survival for three different tumor sizes of HCC. Figures 1(a) and 1(b) show that patients with tumor size ≤2 cm had relatively high survival rates, while patients with tumor size > 5 cm had low survival rate.

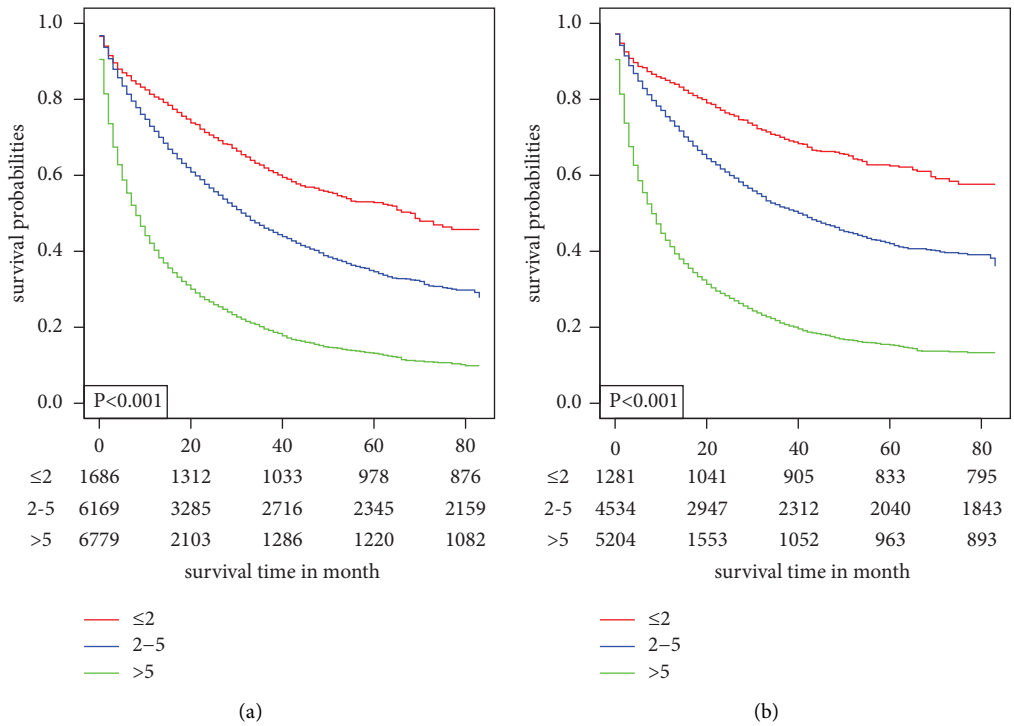

Figure 1: Kaplan–Meier survival curves of hepatocellular carcinoma based on different tumor sizes. (a) The overall survival. (b) The special survival.

Figure 2 shows that survival was higher in patients who underwent suboptimal treatment (combination of three treatments: surgery plus chemotherapy, surgery plus radiotherapy, and only surgery) during the first 20 months and highest after 80 months in patients who underwent surgery alone and in combination with chemotherapy but very low in patients who underwent radiotherapy combined with chemotherapy or no treatment at all. Figures 2(a) and 2(b) display the rate of overall and special survival with HCC using univariable and multivariable analyses. Figures 2(a) and 2(b) show that only surgery and surgery plus chemotherapy were the most effective intervention therapy for overall and special survival.

Figure 3 shows the survival of patients with tumor size ≤2 cm, 2–5 cm, and > 5 cm under different treatment strategies, respectively. In each tumor size study, patients who underwent surgery and surgery plus chemotherapy had the highest survival rates within 80 months (Figure 3). Figures 3(a), 3(c), and 3(e) illustrate that the survival rate of patients undergoing surgery or undergoing surgery plus chemotherapy was higher, while the survival rate of patients receiving no treatment was always lower than that of patients receiving different treatment strategies in all three different tumor sizes for HCC-OS. On the other aspects, Figures 3(b), 3(d), and 3(f) illustrate HCC-specific survival in different treatment strategies. Figure 3(b) displays that the survival rate of patients receiving surgery alone and surgery plus chemotherapy was higher than that of other patients up to the first 80 months for tumor size ≤2 cm. Figure 3(d) demonstrates that the survival rate of patients undergoing surgery plus chemotherapy and surgery plus radiotherapy in the first 80 months was basically higher than that of other patients, while the survival rate of patients receiving no treatment was the lowest for tumor size 2–5 cm. Figure 3(f) shows that patients who underwent surgery had higher survival rates at 20 months than those who received other treatments for tumor > 5 cm. As for survival probability in different stages, Figures 4(a), 4(c), 4(e), and 4(g) describe HCC-OS in different stages, and Figures 4(b), 4(d), 4(f), and 4(h) illustrate HCC-specific survival. Figures 4(a)–4(d) display that patients who had surgery or surgery plus chemotherapy had a higher chance to survival in stages I-II; thus, the survival rate declined smoothly during the 80 months. On the contrary, Figures 4(e)–4(h) show a sharp drop of survival rate during the 80 months for patients in stages III-IV. Compared to the tumor size of 1 cm, Figure 5 shows that tumor size was positively correlated with a mortality rate of HCC. Figure 5 displays that the change rate of the mortality rate's HR increased rapidly during the period of 1–12 cm. Afterwards, the mortality rate's HR basically and smoothly was maintained at a high level.

4. Discussion

HCC is a malignant tumor frequently seen worldwide with an extremely high mortality rate [1]. Therefore, the accurate diagnosis and the most appropriate treatment are crucially important. Senior patients were often considered to be the easy targets because of complex diseases and altered drug metabolism. Aging and chromosomal changes within the liver were proofed to be connected. Otherwise, shortening of the telomeres is also associated with aging in the liver [14].

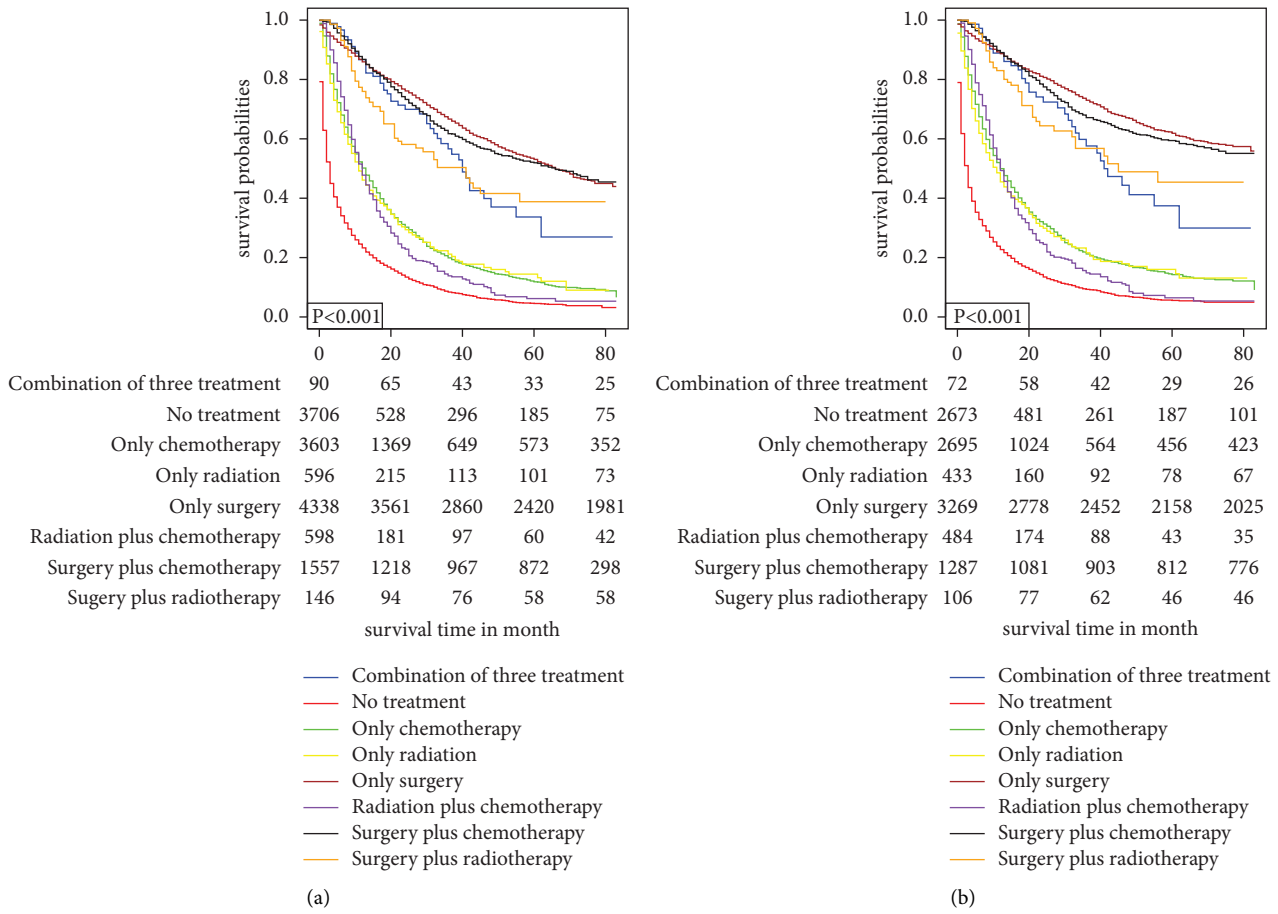

Figure 2: Kaplan–Meier survival curves of hepatocellular carcinoma based on different treatment strategies. (a) The overall survival. (b) The special survival.

DNA copy number changes, gene mutations, a weak immune system, and limited treatment options are a combination which can lead to lower survival rates in senior patients [15]. The past 3 decades of experimental studies have witnessed the death rate of people ≥ 60 years with liver cancer sharply increasing in more than 50% of people worldwide [16]. Previous cohort analyses had found a gradual increase in the mortality of HCC patients aged ≥ 75 years [17].

Scientists proofed that male population was prone to develop HCC than the female worldwide [18]. Social activities of males in life were more than that of females and drinking was inevitable in social situations, the action of which contributes to the generation and acceleration of reactive oxygen species. These highly reactive particles may have a huge impact on your organs and readily deposited in the brain, liver, heart, and kidneys [19]. Recent studies have shown alcoholics of all ages were subjected to elevated blood endotoxin levels, more active inflammatory cascades, and increased oxidative stress and lipid peroxidation [20]. Meanwhile, inherent diversities in genes and hormone levels between both genders were also contributing to these factors [16]. In the 2013 investigation, 21,143 male and 8,330 female from the US were diagnosed with HCC, and male deaths of HCC also increased the most during the year [21]. According to the latest estimates from the World Health Organization, the death toll of the male patients was 2.35 times more than that of the women [22].

In the expert's study from 2003 to 2009, the absolute rate of HCC increased by 2.6 percent for whites and 2.3 percent for blacks [21]. This conclusion was consistent with the conclusion of our study that whites stand higher possibility. On the contrary, other studies had found that blacks were worse than whites in terms of insurance, medicaid, and the likelihood of having surgery.

Marriage had a beneficial effect on survival outcomes for primary liver cancer. Good survival outcomes for married people were not due to early detection; the reason was that unmarried women had lower rates of surgery and radiation than married women. Importantly, unmarried people were likely to have lower overall economic conditions than married populations; consequently, the disposable income they can spend on health care is relatively lower. Single cancer patients without a spouse who can provide adequate mental support and share the emotional burden had a higher risk of psychological distress, anxiety, and depression than married cancer patients.

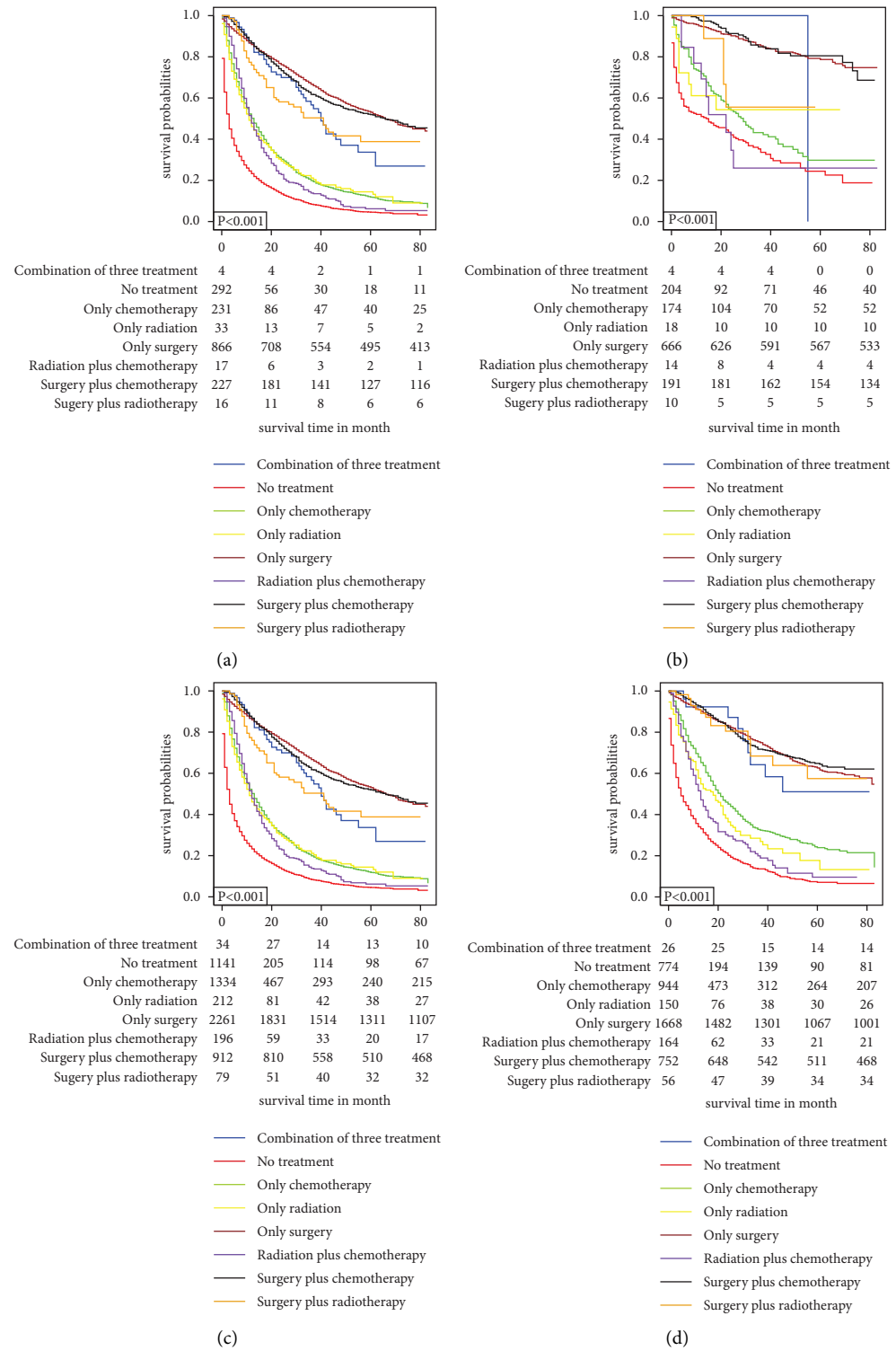

Figure 3: Continued.

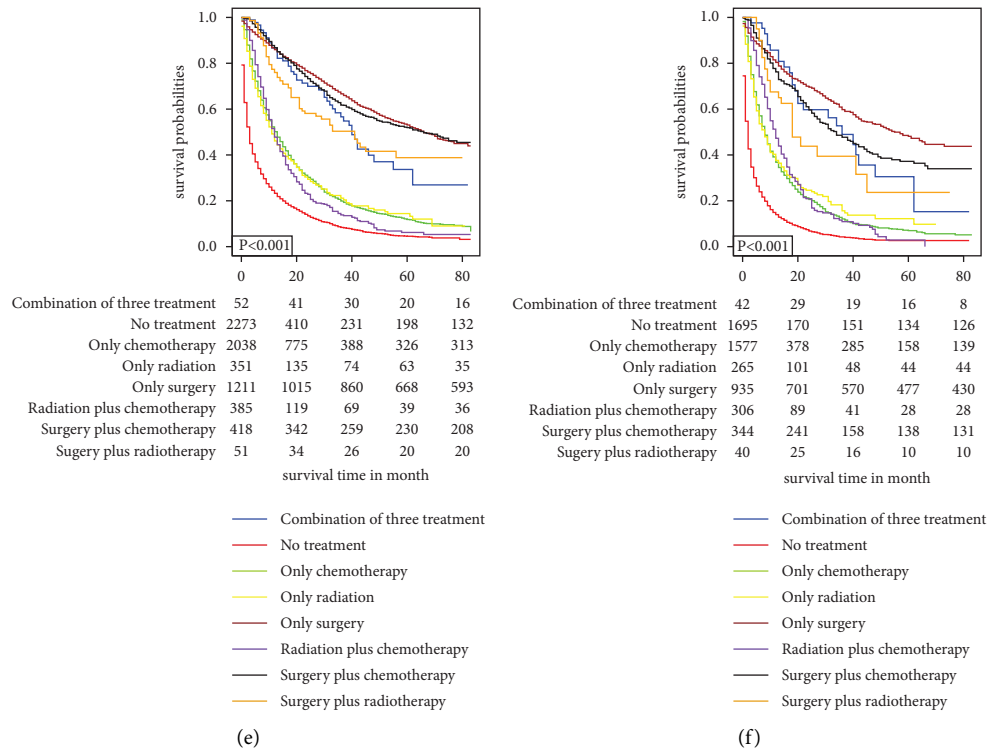

Figure 3: Kaplan–Meier survival curve of hepatocellular carcinoma with different treatment strategies based on different tumor sizes. (a) The tumor ≤2 cm of overall survival. (b) The tumor ≤2 cm of special survival. (c) The tumor 2–5 cm of overall survival. (d) The tumor 2–5 cm of special survival. (e) The tumor > 5 cm of overall survival. (f) The tumor >5 cm of special survival.

In addition to the above factors, drug-related factors had also been noted. The updated meta-analysis [23] demonstrated the beneficial chemoprophylaxis effect of statins on HCC development, which was dose-dependent, was more obvious with lipophile statins. A systematic review and meta-analysis [24] supported the use of aspirin to reduce HCC incidence and liver-related mortality in high-risk populations, and HCC recurrence was lower after nonsteroidal anti-inflammatory drugs treatment. Related research studies [25, 26] found that type 2 diabetes mellitus had 3 times the risk of HCC. More controversial was the role of sulfonylureas in reducing HCC incidence in patients with diabetes [27].

This study showed that the 5-year survival rate in stage I of the AJCC for HCC was about 50%. HCC in stage I was nothing to be sneezed at, and the more advanced it was, the greater the risk was [28]. Patients diagnosed with HCC usually had obvious signs of cancer and liver failure. The disease at the advanced stage was tough to be treated which makes most patients die within 3–6 months [29]. Surgery may be curative which coincided with this result in the early stages and had a better survival rate [30]. In our study, we had testified that the bigger the tumor, the greater the risk. HCC features a growth with metastasis to distant organs. Bone metastasis may be the main manifestation of HCC, and it was very aggressive [31]. The brain hemorrhage was the third prognostic factor for HCC patients. In the previous clinical study, the mortality rate of 10,000 HCC patients in Japan was HCC ≤ 2 cm (34%), 2–5 cm (48%), and HCC ≥ 5 cm (63%), which proofed that mortality increased with tumor growth. What is more, 5-year of all-cause mortality was about 50% [32]. It was widely accepted that patients with larger tumors had a worse prognosis than those with smaller tumors [2].

In other studies, patients who received liver transplantation had a 5-year OS rate up to 72%, suggesting that liver transplantation is an optimal treatment [33]. A study from Park et al. reported that among 224 inoperable non-metastatic HCC patients, 1-year and 2-year locally progress-free rates were 97.4% in stereotactic ablative body radiotherapy, 83.8% in radiofrequency ablation, and 83.6% and 80.2% in radiofrequency ablation, respectively. Observational studies had displayed outcomes in patients with liver cancer treated with proton or carbon beam therapy with 90% control rate over 2–5 years [34]. The study witnessed that survival rates were highest for patients who underwent surgery or who underwent surgery combined with other treatments in each size group.

At present, the main local treatment options include percutaneous ethanol injection, radiofrequency ablation, microwave ablation, cryoablation, and irreversible electroporation [35]. A propensity score matching analysis [36] revealed that the injection of ethanol near peritumoral vessels significantly reduced the risk of local tumor progression following peritumoral radiofrequency ablation of HCC. Radiofrequency ablation with 67–84% of 3-year OS, 3.2–28.5% of 3-year local recurrence rates, and 90–98.5% of complete response for tumors < 3 cm was the

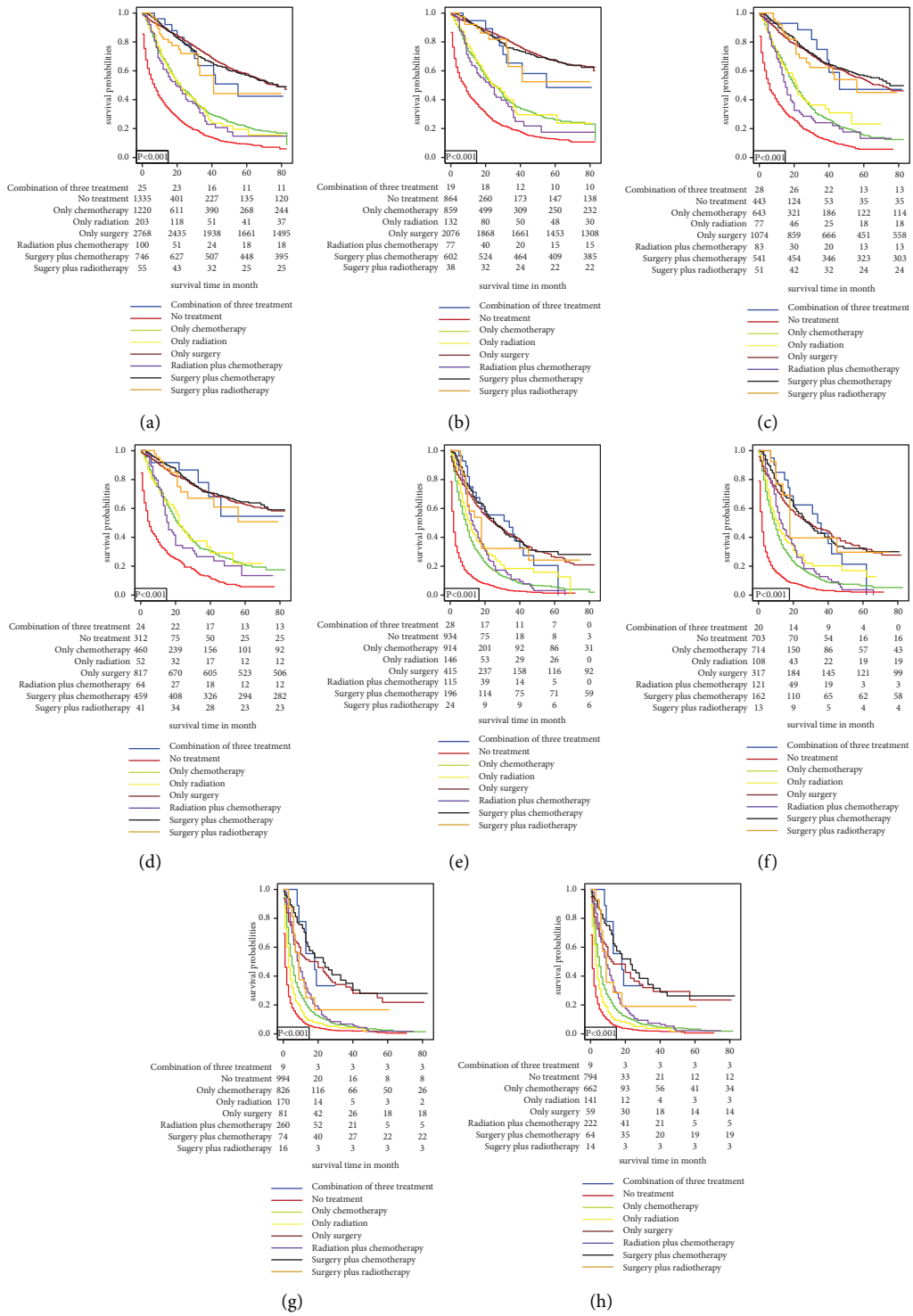

FIGURE 4: Kaplan–Meier survival curves of hepatocellular carcinoma with different treatment strategies based on different AJCC stages. (a) The AJCC stage I of overall survival. (b) The AJCC stage I of special survival. (c) The AJCC stage II of overall survival. (d) The AJCC stage II of special survival. (e) The AJCC stage III of overall survival. (f) The AJCC stage III of special survival. (g) The AJCC stage IV of overall survival. (h) The AJCC stage IV of special survival.

most commonly used medical technology [35]. The cohort study [37] revealed that HCC within 3 cm and 3 nodules after operative microwave ablation had good long-term outcomes. Systematic review and meta-analysis [38] indicated that the microwave ablation had superiority in larger neoplasms. A prospective single-center study [39] with a total of 26 participants and 39 tumors showed for the first time that percutaneous irreversible

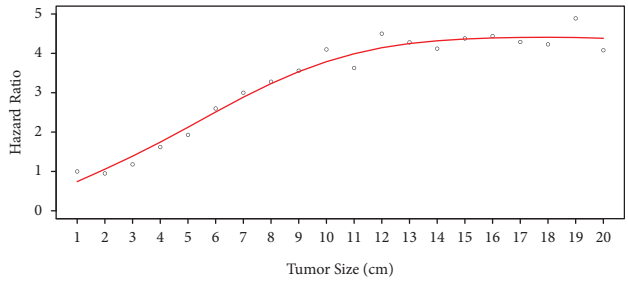

Figure 5: Cox regression of hazard ratio of mortality based on different tumor sizes.

electroporation was a safe and effective ablation technology for HCC abutting the diaphragm. A narrative review [40] disclosed that palliative care had the potential to improve outcomes for HCC. In addition, liver transplantation offered a glimmer of hope and possibility for patients with advanced HCC. Clinical decision makers can refer to the results from this study when choosing the ideal treatment options which can enhance effectiveness and decline the time and cost for the treatment.

There were certain limitations though. It referred to chemotherapy in the study as a generalization, without specific classification studies, including the timing of medication, drug selection and compatibility, drug order, drug dosages, course of treatment, and interval time. In addition, lack of information about specific treatment options for HCC, including liver surgery, liver transplantation, radiotherapy, percutaneous ethanol injection, transarterial chemoembolization, microwave ablation, radiofrequency ablation, postoperative adjuvant chemoradiotherapy, nutrition supportive therapy, and palliative care, can lead to instability and bias in outcomes. Furthermore, some other factors were not mentioned in this article, such as alcohol consumption, obesity, diabetes, income, whether the patient was exposed to aflatoxin-contaminated food, and so on. Despite these limitations, the results from this study generally proved the relationship between tumor size and survival prognosis and testified to the relatively optimal treat proposal for HCC.

5. Conclusions

This study revealed that the age of majority in HCC was over 50 years old, and the majority of HCC had solid tumor sizes of 2–5 cm and not otherwise specified histology. The incidence of HCC in males was much higher than that in females, and whites also proved to be more than half the population at risk for HCC. Based on different stages, the majority of patients were in the early stages of HCC. Furthermore, HCC patients were distributed in above 2 cm, and the distribution of basic information for different tumor sizes was consistent with the overall populations. Single patients had more challenges than married patients. Otherwise, survival rates were greater in patients with tumor size ≤2 cm who underwent surgery or surgery with chemotherapy. Patients with HCC in the early stage had a higher survival probability, particularly when they had undergone surgery or surgery plus chemotherapy. The most important thing was that we further determined that the larger the tumor, the greater the risk, and that surgical treatment was the major and critical of the three methods.

Data Availability

All data were obtained from the SEER*Stat software (version 8.3.5) (https://seer.cancer.gov/seerstat/).

Ethical Approval

This study has been approved by the institution review board (IRB), and there are no ethical requirements involved (KY 2022-002-05).

Disclosure

He Zheng and Zilin Chen are the co-first authors. All funders had no roles in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

Authors' Contributions

YC had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. HZ designed the study. ZC and ML developed and tested the data collection forms. HZ, ZC, and ML acquired the data. HZ and WZ conducted the analysis and interpreted the data. WZ and YC drafted the manuscript. All authors critically revised the manuscript. YC and WZ had guarantor. All authors read and approved the final manuscript.

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