Research Paper

Lower Education and Household Income Contribute to Advanced Disease, Less Treatment Received and Poorer Prognosis in Patients with Hepatocellular Carcinoma

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Abstract

Understanding the ways in which socioeconomic status affects prognosis of hepatocellular carcinoma (HCC) is important for building up strategies eliminating the inequalities in cancer diagnosis and treatments among different groups, which, remains undetermined. In the present study, 1485 newly diagnosed HCC patients with complete demographic and clinical data were included. Socioeconomic data, including education, annual household income and residency was also reported by patients or families. In the present study, less educated patients were older, more female involved, poorly paid, more living in rural places, had more advanced tumor burden, received less curative and loco-regional therapies, and thus showed poorer short-term and long-term outcomes (in total or after surgical resection) than the highly educated. Patients with lower income were less educated, less treated, and more likely to live in rural places, had more advanced stages of HCC and thus poorer long-term survival (in total or after surgical resection) than higher income groups. In Cox regression analysis, lower household income was independently associated with poorer outcome (HR=1.2, 95% CI: 1.0-1.4, *p*=0.036). These results indicate that education and income are critically associated with early diagnosis, treatments and prognosis of HCC. Much more efforts should be taken to support the patients with less education and lower income to improve the outcomes of HCC.

Key words: Hepatocellular carcinoma; surgery; education; income; survival.

Introduction

Hepatocellular carcinoma (HCC) is the second most common cause of cancer-related death all over the world, with China alone accounting for more than 50% of the total number of cases and deaths [1-3]. Fewer than 20% of patients with HCC are amendable to curative surgical resection and liver transplantation [4]. Most patients presented with advanced staged HCC were treated with loco-regional therapies (LRT) or only supportive care. Despite the availability and improvement of different therapies, overall survival of patients with HCC remains poor with an overall 1-year survival rate of less than 50% [5].

Despite the substantial advances in knowledge concerning risk factors of patient survival including

demographic, tumor- and treatments-related factors, socioeconomic inequalities which persist in cancer incidence, morbidity, mortality, and survival, have been largely neglected [6-8]. Some socioeconomic factors, such as education and household income, can be closely related to comorbidity status, health awareness and adherence to treatments, which are also likely to affect the timing of referral, tumor stage at diagnosis and treatment choices after diagnosis. Some studies have implied that higher education level and household income were associated with a beneficial effect of survival of certain cancer patients [6, 9-12]. However, some studies indicated that the effects of socioeconomic status might be restricted in some high-mortality cancers [11, 13].

As a type of malignancy with high mortality associated, HCC has not been thoroughly studied about potential influence of socioeconomic status on diagnosis, treatments and prognosis. One study using Surveillance, Epidemiology and End Results (SEER) database demonstrated that higher income, longer education and living in large urban areas were correlated with prolonged survival of patients with unresectable HCC [14]. However, HCC staging (Barcelona Clinic Liver Cancer [BCLC]) and actual treatments were unavailable in the study [14]. Therefore, the present study aimed to identify whether socioeconomic disparities as measured by education and household income affect BCLC stages at diagnosis, receipt of treatments, and overall survival among patients with HCC.

Patients and Methods

1622 patients firstly diagnosed as HCC January 2008 to September 2013 in our hospital were included retrospectively. The demographic information, Child-Pugh class, hepatitis status and residence place were documented before the primary treatments. Primary treatments were defined as liver transplant and surgical resection when the patients underwent liver transplant surgical resection during follow up regardless of other treatments received. LRT included radiofrequency ablation, microwave ablation, ethanol intratumoral injection, transarterial chemoembolization (TACE) and palliative resection. Supportive treatments were defined as those with no tumor-target therapy but only nutritional support or no specific treatments.

The education level and household income were reported by the patients or their family members, and documented during follow up. The information was obtained with the understanding of the patients and/or their relatives that it might be published with no identified personal information. The education level were classified as below high school level (less than 9 years of education), high school level (10-12 years of education), and above high school level (≥ 13 years of education). The household income included the self-reported annual income of the patients and their spouses, which were categorized as low income (≤ 50,000 Chinese Yuan [CNY]), moderate income (50,000-200,000 CNY) and high income (>200,000 CNY).

15 patients younger than 25 years old were excluded, since they were still studying in school and had no personal income yet. 122 patients unresponsive to the education and income information were excluded. Finally, 1485 patients were included in the present study. The study has been approved by the ethics committee of the First Affiliated Hospital Xi'an Jiaotong University. A waiver of informed consent was obtained, since the data were analyzed from the electronic medical record and reported without personal identifiers.

Statistical analysis

Numerical variables were expressed as mean ± standard deviation, and compared with One-way ANOVA test among the groups, and with student t test or Mann-Whitney U test between the two groups. Nominal variables were expressed as number and percentages, and compared with Chi-squared test or Fisher's exact test. Kaplan–Meier survival analysis was used to compare survival with log-rank test among the three groups and between any two groups. Cox regression was used to assess the association of potential risk factors including education and income of overall survival expressed by hazard ratio (HR) and 95% confidence interval (CI). Two-tailed p value $<$ 0.05 was considered statistically significant. Statistical analysis was carried out using SPSS 22.0 (Chicago, IL, USA).

Results

Correlation of education level with clinical parameters

Among the 1485 patients, most (60.7%) had education for 10 to 12 years equal to high school level, 21.1% were educated for more than 13 years, and 18.1% for less than 9 years. Patients educated below high school level were older, more female involved, less paid, more living in rural places, and less curatively or loco-regionally treated with a higher 90-day mortality than other two groups, respectively (all $p<0.05$, Table 1). Child-Pugh class of liver function was similar among the three groups. However, patients educated for at least 13 years equal to college level were much more highly paid and more likely to live in large cities than other two less educated groups

(all *p*<0.05, Table 1). Patients educated above high school level were more likely to have early BCLC staged HCC at diagnosis, and receive curative and loco-regional therapies than other two groups (all *p*<0.05, Table 1).

Table 1. Demographic and treatments of the patients at different education level

Variables	Below high school (n=269)	High school level (n=902)	Above high school (n=314)	P value
Age (years)	57±11[1,2;1,3]	54±12	55±14	<0.001
Male gender	192 (71.4%)[1,2; 1,3]	744 (82.5%)	269 (85.7%)	<0.001
Child-Pugh class				0.204
A	232 (8.6%)	799 (8.9%)	263 (8.4%)	
B	32 (11.9%)	92 (10.2%)	47 (15.0%)	
C	5 (1.9%)	11 (1.2%)	4 (1.3%)	
Household income* [1,2; 1,3]		[2,3]		<0.001
≤ 50,000 CNY	136 (50.6%)	189 (10.9%)	15 (4.8%)	
50,000-200,000 CNY	110 (40.9%)	529 (58.6%)	123 (39.2%)	
>200,000 CNY	20 (7.4%)	178 (19.7%)	176 (56.1%)	
Residence [1,2; 1,3]		[2,3]		<0.001
Rural/small urban	221 (82.2%)	434 (48.1%)	27 (8.6%)	
Large urban	48 (17.8%)	468 (51.9%)	287 (91.4%)	
Hepatitis status [1,3]				0.021
Hepatitis B/C	192 (71.4%)	705 (78.2%)	253 (80.5%)	
None	77 (28.6%)	197 (21.8%)	61 (19.4%)	
First Dept. admitted				0.408
Surgery Dept.	166 (61.7%)	690 (76.5%)	260 (82.8%)	
Internal Medical Dept.	91 (33.8%)	198 (22.0%)	50 (15.9%)	
Other Dept.	12 (4.5%)	14 (15.5%)	4 (1.3%)	
BCLC stages [1,3]		[2,3]		0.027
0-A	105 (39.0%)	336 (37.3%)	144 (45.9%)	
B-D	164 (61.0%)	566 (62.7%)	170 (54.1%)	
Primary treatments [1,2; 1,3]		[2,3]		<0.001
Liver transplant	2 (0.7%)	15 (1.7%)	17 (5.4%)	
Surgical resection	117 (43.5%)	384 (42.6%)	122 (38.9%)	
Locoregional therapies	117 (43.5%)	437 (48.4%)	148 (47.1%)	
Supportive treatments	33 (12.3%)	66 (7.3%)	27 (8.6%)	
30-day mortality	16 (5.9%)	47 (5.2%)	12 (3.8%)	0.475
90-day mortality	39 (14.5%)[1,2;1,3]	88 (9.8%)	28 (8.9%)	0.045

* Data unavailable in 9 patients; BCLC, Barcelona Liver Cancer; CNY, Chinese Yuan (1 CNY≈0.146 USD); 1,2 *p*<0.05 when compared between group 1 and 2; 1,3 *p*<0.05 when compared between group 1 and 3; 2,3 *p*<0.05 when compared between group 2 and 3.

Correlation of household income with clinical parameters

The self-reported annual household income was categorized as low, moderate and high in 1476 patients (9 patients declined to report their household incomes). Patients with low income were less educated, more likely to live in rural places and had more advanced BCLC stages of HCC than either moderate or high income patients (all *p*<0.05, Table 2). Moreover, patients with low income were less treated (although not statistically different) and displayed higher 30-day mortality than other two groups (both *p*<0.05, Table 2). Patients with high income had better liver function classified by Child-Pugh score at admission, and were more likely to live in large cities than those with low and moderate income (all *p*<0.05, Table 2).

Table 2. Demographic and treatments of the 1476 patients with different household income

Variables	Low income (n=340)	Moderate income (n=762)	High income (n=374)	P value
Age (years)	55±12	54±12[2,3]	56±13	0.020
Male gender	270 (79.4%)	625 (82.0%)	303 (81.0%)	0.590
Child-Pugh class [1,3]		[2,3]		<0.001
A	309 (90.9%)	672 (88.2%)	304 (81.3%)	
B	28 (8.2%)	77 (10.1%)	66 (17.6%)	
C	3 (0.8%)	13 (1.7%)	4 (1.1%)	
Residence [1,2; 1,3]		[2,3]		<0.001
Rural/small urban	236 (69.4%)	334 (43.8%)	103 (27.5%)	
Large urban	104 (30.6%)	428 (56.2%)	271 (72.5%)	
Hepatitis status				0.083
Hepatitis B/C	249 (73.3%)	595 (78.0%)	299 (80.0%)	
Others	91 (26.8%)	167 (21.9%)	75 (20.1%)	
First Dept. admitted				0.449
Surgery Dept.	235 (69.1%)	564 (74.0%)	308 (82.4%)	
Internal Medical Dept.	98 (28.8%)	183 (24.0%)	58 (15.5%)	
Other Dept.	7 (2.1%)	15 (2.0%)	8 (2.1%)	
BCLC stages [1,2; 1,3]				0.001
0-A	105 (30.9%)	310 (40.7%)	165 (44.1%)	
B-D	235 (69.1%)	452 (59.3%)	209 (55.9%)	
Primary treatments				0.081
Liver transplant	2 (0.6%)	19 (2.5%)	13 (3.5%)	
Surgical resection	150 (44.1%)	312 (41.0%)	154 (41.1%)	
Locoregional therapies	151 (44.4%)	369 (48.4%)	180 (48.1%)	
Supportive treatments	37 (10.9%)	62 (8.1%)	27 (7.2%)	
30-day mortality	26 (7.6%)[1,2;1,3]	33 (4.3%)	16 (4.3%)	0.049
90-day mortality	44 (12.9%)	79 (10.4%)	32 (8.6%)	0.159

BCLC, Barcelona Liver Cancer; 1,2 *p*<0.05 when compared between group 1 and 2; 1,3 *p*<0.05 when compared between group 1 and 3; 2,3 *p*<0.05 when compared between group 2 and 3.

Socioeconomic factors and patients survival

The overall 1-, 3- and 5-year survival rates of all the patients were 77%, 43% and 20%, respectively. The survival curves of the patients at different education level were plotted by Kaplan–Meier method in Figure 1A. Patients educated above high school had significant prolonged survival than those educated at or below high school level (Median survival 47 vs. 37 months, *p*=0.028; and 47 vs. 35 months, *p*=0.010) (Figure 1A). The 1-, 3- and 5-year survival rates were 72%, 41% and 17% in patients educated below high school, 78%, 43% and 17% at high school level, and 81%, 47% and 31% above high school level, respectively (*p*=0.019, , Figure 1A).

When stratified by household income, patients with high income had significantly better prognosis than other two groups (Median survival, 46 months vs. 37 months and 34 months, *p*=0.003 and *p*<0.001, respectively) (Figure 1B). The 1-, 3- and 5-year survival rates were 75%, 39% and 14% in patients with

low income, 77%, 41% and 18% in patients with moderate income, and 80%, 50% and 30% in patients
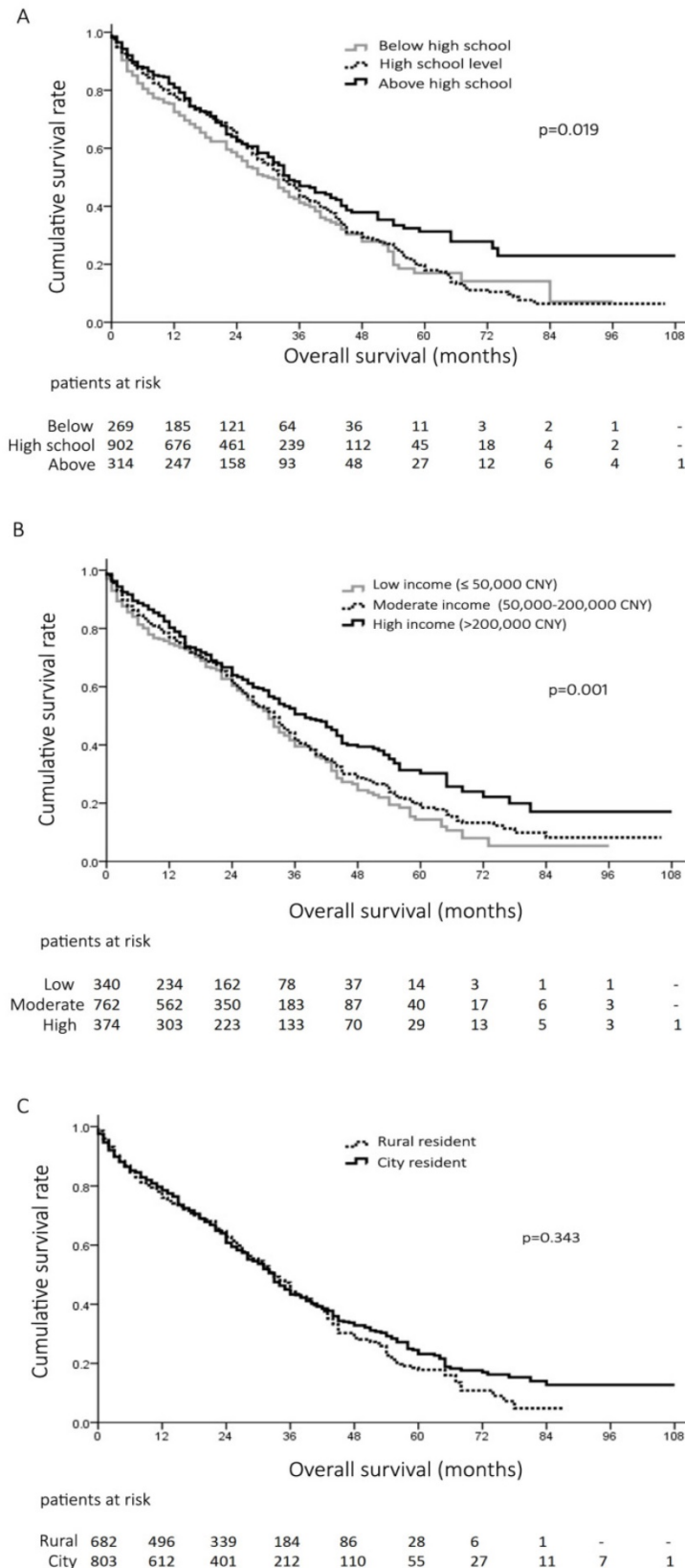

A

B

C

Figure 1. A, overall survival of 1485 patients with hepatocellular carcinoma (HCC) at different education level; B, overall survival of 1476 HCC patients with different annual household income; C, overall survival of 1485 HCC patients living in rural areas and city.

with high income, respectively (*p*=0.001, Figure 1B). In contrast, the survival was not different between the patients living in the rural/small urban and large urbans, (Median survival, 36 months vs. 41 months, *p*=0.343) (Figure 1C).

Socioeconomic factors and patients survival after curative resection

Totally, there were 623 (42%) patients receiving curative surgical resection of HCC. Interestingly, there was no significant difference of the overall survival of the patients at different education background after curative resection (*p*=0.410, Figure 2A). However, after surgical resection, patients with high income showed better prognosis than those with low and moderate income (Median survival, 45 months vs. 37 months and 35 months, *p*=0.003 and *p*=0.015, respectively) (Figure 2B). The 1-, 3- and 5-year survival rates after surgery were 89%, 47% and 20% in patients with low income, 88%, 51% and 25% in patients with moderate income, and 92%, 66% and 30% in patients with high income, respectively (*p*=0.010, Figure 2B). Moreover, there was no difference of the overall survival of the HCC patients undergoing surgical resection living in large cities and those living in rural places (p=0.111, Figure 2C).

Risk factors of HCC patient survival

To better understand the potential risk factors associated with overall survival of patients, we performed univariate and multivariate analysis by Cox regression model (Table 3). By univariate analysis, Child-Pugh class B/C, lower education and household income, tumor size larger than 5cm, portal vein tumor thrombosis, and BCLC B, C and D versus 0-A were risk factors associated with poorer long-term survival (all *p*<0.05, Table 3), while radical and locoregional treatments were selected as protective factors associated with improved outcome versus supportive treatments (all *p*<0.05, Table 3). By multivariate analysis, Child-Pugh class B/C, advanced BCLC stages and lower household income were independently associated with poorer outcome (all *p*<0.05, Table 3), while HCC-directed therapies were associated with prolonged survival (all *p*<0.05, Table 3).

Discussion

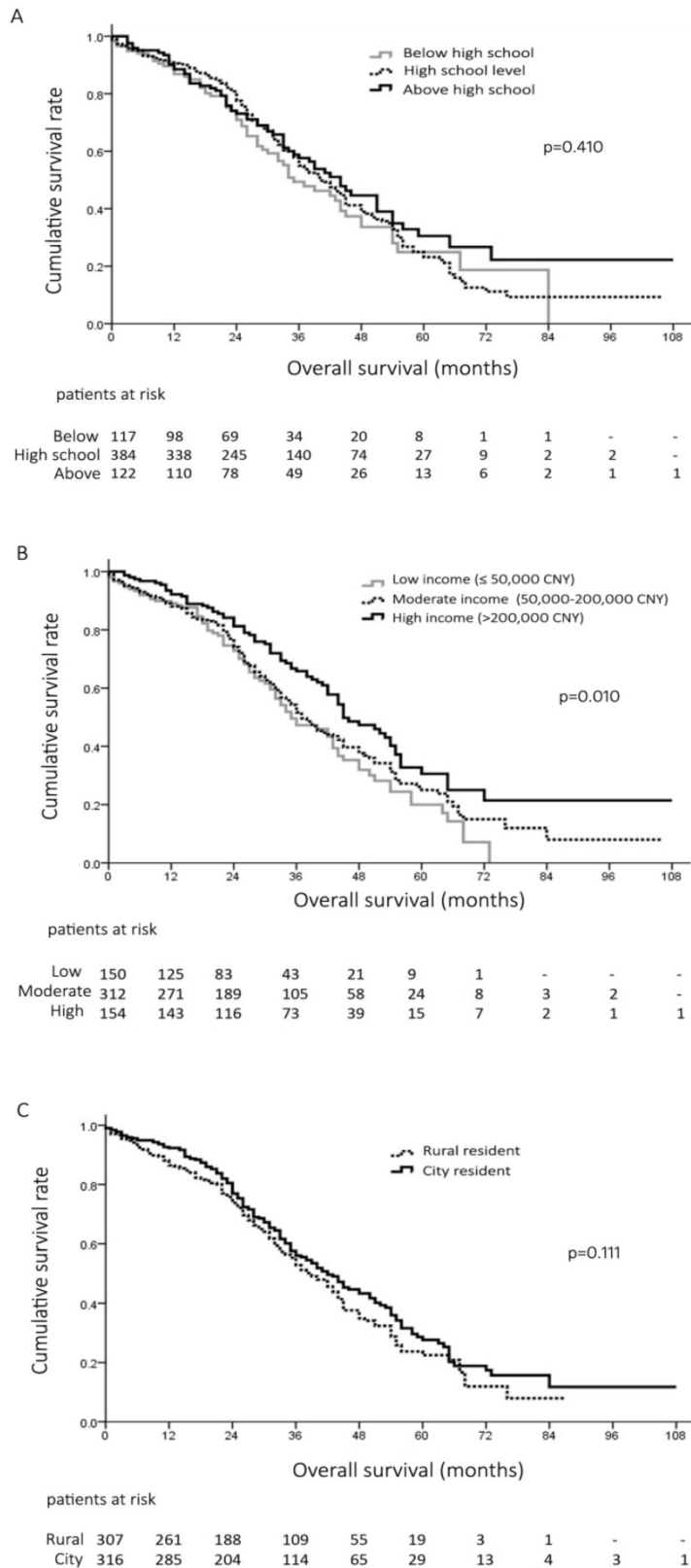Few studies have been able to examine the

Figure 2. A, overall survival of 623 patients at different education level undergoing surgical resection hepatocellular carcinoma (HCC); B, overall survival of 616 patients with different household income after surgical resection for HCC; C, overall survival of 623 patients living rural areas and city after surgical resection for HCC.

influence of socioeconomic status on prognosis of HCC patients. The present study demonstrated that in hospitalized HCC patients, lower education and household income were consistently associated with advanced BCLC stages at diagnosis, less treatment received and poorer long-term survival. It was well accepted that tumor stage and treatments were the most significant factors affecting prognosis of cancer patients. However, socioeconomic status has been neglected in determining screening, diagnosis, major and adjuvant treatments of cancer [6, 11, 12, 14-18]. Several studies using SEER-Medicare database have suggested that persistently poor long-term outcome across HCC population might be partially correlated with underutilization of effective HCC-directed therapies due to sociodemographic and economic factors [14-18]. Underutilization of effective therapies of HCC must be more severe in developing countries, such as China, because of traditional views of incurability of cancers, financial difficulties, and limited healthcare resources.

It is not surprising that education level is closely related to residency place, living habits, income, health insurance available, health care and disease treatments [6, 11, 12, 14-18]. However, due to the historical and social reasons, most patients (902/1485, 61%) in the present study (born before 1960s) were educated at high school level. The National College Entrance Examination of China had been restored since 1977, but with an average enrollment rate less than 5% at the beginning [19]. This was also confirmed by that highly educated patients were younger and more male predominant than less educated patients. Interestingly, less education was strongly correlated with more advanced disease, less HCC-target therapies received, higher 90-day mortality and poorer long-term survival. However, after surgical resection, no significant difference of survival was identified in patients at different education level (Figure 2A). These findings highlighted that less education was more likely to affect early detection of disease, access to care and choice of treatments of patients [16]. Once the patients were diagnosed and surgically treated, education level might be less important than other tumor- and treatment-related factors in affecting HCC outcome.

Table 3. Univariate and multivariate analysis of the risk factors of survival for hepatocellular carcinoma

Variables	n	events	Univariate analysis		Multivariate analysis	
			HR (95% CI)	P value	HR (95% CI)	P value
Age (years)						
≤ 50	560	307	1			
> 50	925	561	1.1 (1.0-1.3)	0.070		
Gender						
Female	280	159	1			
Male	1205	709	1.0 (0.8-1.2)	0.782		
Child-Pugh class						
A	1294	733	1		1	
B/C	191	135	1.9 (1.5-2.2)	<0.001	1.6 (1.3-1.9)	<0.001
Education						
Above high school	314	168	1		1	
High school level	902	537	1.2 (1.0-1.4)	0.031	1.2 (0.9-1.5)	0.217
Below high school	269	163	1.3 (1.1-1.7)	0.007	1.2 (1.0-1.4)	0.118
Residence						
Rural/small urban	682	401	1.1 (0.9-1.2)	0.349		
Large urban	803	467	1			
Household income						
>200,000 CNY	374	211	1		1	
50,000-200,000 CNY	762	443	1.3 (1.1-1.5)	0.004	1.2 (1.0-1.4)	0.069
≤ 50,000 CNY	340	210	1.4 (1.2-1.7)	0.001	1.2 (1.0-1.4)	0.036
Tumor size						
< 5 cm	808	448	1		1	
≥ 5 cm	677	420	1.3 (1.2-1.5)	<0.001	1.1 (0.8-1.3)	0.507
Tumor number						
≤ 3	1296	750	1			
> 3	189	118	1.2 (0.9-1.4)	0.157		
Portal vein thrombosis						
No	1176	678	1		1	
Yes	309	190	1.2 (1.0-1.4)	0.048	1.1 (0.7-1.6)	0.084
BCLC stages						
0-A	585	305	1		1	
B	542	330	1.4 (1.2-1.6)	<0.001	2.6 (1.6-4.3)	<0.001
C	318	203	1.5 (1.3-1.8)	<0.001	2.8 (1.6-4.9)	<0.001
D	40	30	2.5 (1.7-3.6)	<0.001	3.1 (1.9-5.0)	<0.001
Primary treatments						
Supportive treatments	126	107	1		1	
Locoregional therapies	702	413	0.2 (0.1-0.2)	<0.001	0.2 (0.1-0.2)	<0.001
Surgical resection	623	333	0.1 (0.1-0.2)	<0.001	0.1 (0.1-0.2)	<0.001
Liver transplant	34	15	0.1 (0.1-0.2)	<0.001	0.1 (0.1-0.2)	<0.001

Events, patient death during follow-up; HR, hazard ratio; CI, confidence interval; BCLC, Barcelona Liver Cancer; CNY, Chinese Yuan (1 CNY≈0.146 USD)

Household income was closely relevant to, but not determined by education level. Similar to some previous studies on other tumor types [6, 16, 20], patients with low income had more advanced HCC stages, less aggressive treatments received, higher 30-day mortality and poorer long-term survival than those with high income. This association was also manifested in surgical resected HCC patients. Lower household income, but not education level, was identified as independent risk factor of the survival of HCC patients. Patients with low income may be exposed to unhealthy lifestyle or environmental factors, be less intensively screened for HCC, less adherent to any treatments, which lead to more aggressive disease and poorer outcome [6, 16, 20, 21].

Although closely correlated to each other, education and income are separate constructs and have different impacts on diagnosis, treatment and prognosis of HCC. While both education and income may be associated with economic resources, education can also reflect noneconomic social characteristics that influence health such as health-related knowledge, acceptance of invasive treatments, and influence one's lifestyle [21, 22]. Income can reflect "ability to pay" in cancer screening, diagnosis, treatment and post-treatment checkup [23]. Therefore, more effort should be placed on the lower educated patients, as they could have more risk of late diagnosis, less treatment, higher mortality, as presented in our study. Moreover, efforts from the whole society should be made continuously to support the patients in poverty in cancer screening, diagnosis, and treatments.

Residence of the patients was closely associated with education and income. People with higher education and income are more likely to live in large

cities, while those with lower education and income are more likely to live in rural places. This is called "Urban-Rural Gap" which has been noticed for several decades by the whole society and government [24]. Interestingly, we found no significant difference of long-term outcome between the patients living in urban and in rural places as whole or after surgical resection. These findings might imply certain socioeconomic changes in the country that the urban-rural gap is narrowing, although the imbalance of education, health and living resources is still huge [25]. To reduce the long-standing gap and insuring the rural population against health and economic risk, the Chinese government launched the New Rural Cooperative Medical System in 2003, which covers 95.3% of the rural population of China by 2011 [26, 27].

There are several limitations of the present study. First, this is a retrospective study conducted in one single center. All the data were collected retrospectively, thus weakened by certain inherent biases. Second, education level was documented only for the patients at admission. However, in China, concealment of diagnosis and prognosis from cancer patients is still common and not all the cancer patients would be fully informed of their diagnosis, treatment and expected prognosis [28]. Diagnosis and treatments are usually discussed by family members of the patients and physicians. Therefore, the impact of education level of patients on cancer prognosis would be substantially weakened. However, education level of their families is hard to collect and determine. Third, income is rather complex to measure. Patients and their family members tended to underreport the household income, since some income as bonus might not be reported. Last, the present study has been conducted based on hospitalized patients who were eager to be treated. As we believe, there were still many HCC patients, especially those with low education level and household income, and living in rural places, refusing any invasive treatments in hospital but relying on some folk remedies. Therefore, impacts of socioeconomic status on cancer patient survival should be more significant if taking all the inpatients and outpatients into account.

Conclusion

The present study has shown that HCC patients with less education and lower household income presented with more advanced disease progression at diagnosis, received less effective treatments, and had higher mortality and poorer long-term survival. Intervention strategies targeting patients with less education and lower income should be evaluated to improve the outcomes of HCC by routine screening, early diagnosis and effective treatments. Further studies based on national health database with enrollment of both inpatients and outpatients should be performed, especially in China with great changes in society, law and economics in recent 40 years.

Acknowledgement

Competing Interests

The authors have declared that no competing interest exists.

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