Original Article

No expenditure difference among patients with liver cancer at stage I–IV: Findings from a multicenter cross-sectional study in China

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Abstract

Objective: The number of liver cancer patients in China accounts for more than half of the world. However, China currently lacks national, multicenter economic burden data, and meanwhile, measuring the differences among different subgroups will be informative to formulate corresponding policies in liver cancer control. Thus, the aim of the study was to measure the economic burden of liver cancer by various subgroups.

Methods: A hospital-based, multicenter and cross-sectional survey was conducted during 2012-2014, covering 39 hospitals and 21 project sites in 13 provinces across China. The questionnaire covers clinical information, sociology, expenditure, and related variables. All expenditure data were reported in Chinese Yuan (CNY) using 2014 values.

Results: A total of 2,223 liver cancer patients were enrolled, of whom 59.61% were late-stage cases (III-IV), and 53.8% were hepatocellular carcinoma. The average total expenditure per liver cancer patient was estimated as 53,220 CNY, including 48,612 CNY of medical expenditures (91.3%) and 4,608 CNY of non-medical expenditures (8.7%). The average total expenditures in stage I, II, III and stage IV were 52,817 CNY, 50,877 CNY, 50,678 CNY and 54,089 CNY (P>0.05), respectively. Non-medical expenditures including additional meals, additional nutrition care, transportation, accommodation and hired informal nursing were 1,453 CNY, 839 CNY, 946 CNY, 679 CNY and 200 CNY, respectively. The one-year out-of-pocket expenditure of a newly diagnosed patient was 24,953 CNY, and 77.2% of the patients suffered an unmanageable financial burden. Multivariate analysis showed that overall expenditure differed in almost all subgroups (P<0.05), except for sex, clinical stage, and pathologic type.

Conclusions: There was no difference in treatment expenditure for liver cancer patients at different clinical stages, which suggests that maintaining efforts on treatment efficacy improvement is important but not enough. To furtherly reduce the overall economic burden from liver cancer, more effort should be given to primary and secondary prevention strategies.

Keywords: Liver cancer; medical expenditure; non-medical expenditure; economic burden

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Introduction

The GLOBOCAN estimates that liver cancer is listed as the sixth most frequently diagnosed cancer and the fourth leading cause of cancer death worldwide in 2018, with 841,000 new cases and 782,000 deaths each year; the number of liver cancer patients in China accounts for more than half of the world (1). The National Cancer Center of China estimated that the number of new liver cancer cases was 466,100 in China in 2015, and the number of deaths was 422,100 (2). However, China currently lacks national, multicenter economic burden data, and meanwhile measuring the differences among different subgroups will be informative to formulate corresponding policies in liver cancer control.

World Health Organization (WHO) emphasizes that the most effective strategies for the prevention and control of cancer are early detection, diagnosis and treatment. The central government of China has been providing continuous support to the early detection and treatment research of cancers, which eventually led this to become one of national major public health projects in 2012. The project, officially named the Cancer Screening Program in Urban China (CanSPUC), has mainly covered population aged 40–69 years, and expanded to 17 provinces and regions since August 2012. The project consists of three parts, assessment of high-risk groups (community-based), hospital-based clinical screening, and a multi-stage comprehensive health economic evaluation.

As a part of the overall health economic evaluation component, the aim of the current study was to measure the economic burden of liver cancer by various subgroups.

Materials and methods

Overall design and study sites selection

This is a hospital-based, multicenter, cross-sectional survey. From 2012 to 2014, a total of 39 hospitals and 21 project sites were designated by the government from 13 provinces or cities, including Beijing, Chongqing, Jinan in Shandong province, Nantong, Xuzhou in Jiangsu province, Guangzhou, Dongguan, Foshan, Shenzhen and Zhongshan in Guangdong province, Hangzhou, Ningbo in Zhejiang province, Tangshan in Hebei province, Tieling in Liaoning province, Changsha in Hunan province, Harbin, Daqing in Heilongjiang province, Zhengzhou in Henan province, Urumqi in Xinjiang province, Lanzhou, Jinchang in Gansu province. Summary of study sites and hospitals involved is listed in *Supplementary Table S1*.

Considering the budget from the government and previous experience, a total of 3,120 liver cancer patients were expected for the 13 study provinces. For each province, in accordance with a uniform design scheme, a stratified convenience sampling approach was used for selecting 240 clinically confirmed, primary prevalent liver cancer patients who were undergoing treatment in the study hospitals (including both newly and previously diagnosed patients). All respondents were interviewed face-to-face using a structured questionnaire at the time of discharge when most treatment expenditures were incurred. Prior to the survey, we registered participation of all invited patients; we also recorded basic information including age, sex and cancer stage to facilitate exclusion. For patients who were in very poor condition, family member(s) or other caregivers helped with the interview; all the other interviewees were the patients themselves.

This study was approved by the Institutional Review Board of Cancer Hospital, Chinese Academy of Medical Sciences, as part of a broader health economic evaluation project based on the CanSPUC program. All subjects participated were aware of the investigation process and signed informed consent forms.

Data collection

The designed questionnaire mainly covered the following parts: 1) demographic and societal information (e.g. name, sex, age, education, occupation, previous-year household income, and healthcare insurance type); 2) clinical information (e.g. clinical stage, pathologic diagnosis and therapeutic regimen); 3) by-clinical-visit expenditure occurred until the survey date, covering both outpatient and inpatient, occurring either within or outside the study hospitals, e.g. the start date of treatment, hospitalization duration, overall medical expenditure, overall and detailed non-medical expenditure (e.g. transportation, additional meals and nutrition, accommodation, fee of hiring informal

nursing), predicted reimbursement ratio, and self-reported financial pressure; and 4) time loss of the to-date whole course to clinical visits, including working days loss of patients and of accompanying persons or informal caregivers (relatives and friends).

Quality control

All the investigators have received the standard consultants and training program. One-on-one, face-to-face interview form was conducted by trained interviewers. The interviewers record the details of each participant and their collaboration rating at the end of the questionnaire. Then they evaluate by segment the reliability of the data collected. The questionnaire consists of a multilevel quality control procedure: first of all, the interviewer conducts the self-evaluation, then the quality control staff will check the result again within 2 d after the interview. If necessary, we correct the mistakes and fill in the missing parts of the clinical information not obtained by using the electronic medical system.

Several rounds of verification of on-site input data and EpiData software (Version 3.1; The EpiData Association, Odense, Denmark) were used to conduct the double entry. Furthermore, they process the logical verification and data analysis on SAS software (Version 9.2; SAS Institute Inc., Cary, USA), eliminating records of all variables like sex, age, total medical and non-medical expenditures that did not come from first-tier hospitals.

Statistical analysis

Group variables include clinical stage, type of hospital, age, sex, education, occupation, health insurance type, family income, pathological types, therapeutic regimen and region. The medical and non-medical expenditures, average total expenditures of each patient were compared between subgroups. Analyzing successively possible factors of average total expenditures, the economic pressure on patient families after average total expenditures reimbursement, the composition of non-medical expenditures and time loss of patients and their family members, we defined a newly diagnosed course as 2 months before diagnosis and 10 months after diagnosis, and all patient-paid medical expenditure items and non-medical expenditure of a newly diagnosed course as out-of-pocket expenditure. At the same time, we used generalized linear models-gamma conjugate (A1) for multivariate analysis, applied the natural logarithmic conversion for expenditures data that has larger degree of dispersion, compared two independent samples with the student's *t* test, compared more than two groups by using variance-analysis and using Student-Newman-Keuls Test (SNK) test pairwise comparisons within the group, and compared rates with Chi-square test. All data statistics were tested bilaterally, and $P<0.05$ was considered statistically significant. All expenditure data were converted using local consumer price index in 2014.

Results

A total of 2,223 patients with liver cancer were included in the current analysis, and mean age at diagnosis was 55.7±11.2 years. Of the overall patients, 79.2% were males, 75.6% were from specialized hospitals, 40.0% owned a New Cooperative Medical Scheme (NCMS) medical insurance and the median income per patient in last 5 years was 20,000 Chinese Yuan (CNY) (P_{25}–P_{75}: 10,000–40,000). Patients with liver cancer at stage I, II, III and IV accounted for 13.5%, 22.2%, 42.6 and 17.1% of the overall cases (remaining were reported), respectively. More than half (53.8%) of the overall pathological types were hepatocellular carcinoma (HCC) and more than half (50.2%) of the patients received symptomatic treatment or palliative care alone. *Table 1* shows additional details.

The average total expenditure per liver cancer patient was estimated as 53,220 CNY, including 48,612 CNY of medical expenditure and 4,608 CNY of non-medical expenditure. There are significantly differences among different subgroups, including hospital type, age, education, occupation, insurance type, household income and treatment (all P values <0.005). *Table 2* shows more subgroup results on the overall, medical and non-medical expenditure. Further, the multivariate analysis (*Table 3*) confirmed that patients in specialized hospitals, patients who were diagnosed <45 years, patients with education level of university or higher, patients who were public sector employee, patients with urban employee basic medical insurance or patients with higher household income were likely to spend more on treatment, whereas patients with commercial insurance, patients received surgery and postoperative chemotherapy or neoadjuvant chemotherapy and surgery spent less on treatment compared with patients received only surgery.

However, no statistical difference of average total expenditure was found among patients with liver cancer at stage I–IV, which were 52,817 CNY, 50,877 CNY, 50,678

Table 1 Characteristics of included liver cancer patients (N=2,223)

Variables	n (%)
Hospital type	
General	543 (24.4)
Specialized	1,680 (75.6)
Age at diagnosis (year)	
Mean age at diagnosis ($\bar{x}\pm s$)	55.7±11.2
<45	362 (16.3)
45–54	633 (28.5)
55–64	745 (33.5)
≥65	483 (21.7)
Gender	
Male	1,760 (79.2)
Female	463 (20.8)
Education	
Primary school or below	652 (29.3)
Junior high school	800 (36.0)
Senior high school	565 (25.4)
Undergraduate or over	206 (9.3)
Occupation	
Farmer	902 (40.6)
Enterprise or company employee/worker	567 (25.5)
Self-employed or unemployed	312 (14.0)
Retiree	236 (10.6)
Staff in institution/civil servant	173 (7.8)
Other	33 (1.5)
Previous year household income (N=2,153) ($\bar{x}\pm s$) (CNY)	56,468±42,696
Previous year household income (N=2,153) [median (P_{25}–P_{75})] (CNY)	48,000 (28,000–75,000)
Previous year household income (CNY)	
<20,000	250 (11.6)
20,000–39,999	606 (28.1)
40,000–69,999	654 (30.4)
≥70,000	643 (29.9)
Average income per patient in last 5 years (N=2,188) ($\bar{x}\pm s$) (CNY)	29,958±27,692
Median income per patient in last 5 years (N=2,188) [median (P_{25}–P_{75})] (CNY)	20,000 (10,000–40,000)
Number of family members (N=2,195) [median (P_{25}–P_{75})]	4 (2–5)
Health-care insurance type	
Urban employees basic medical insurance	852 (38.3)
Urban residents basic medical insurance	400 (18.0)
New rural cooperative medical scheme	890 (40.0)
Commercial insurance	19 (0.9)
Self-financed	40 (1.8)
Other	22 (1.0)
Clinical stage	
I	299 (13.5)
II	493 (22.2)
III	946 (42.6)
IV	379 (17.1)
Not reported	106 (4.8)
Pathological type	
Hepatocellular carcinoma	1,196 (53.8)
Other	235 (10.6)
Not reported	792 (35.6)
Therapeutic regimen (N=2,040)	
Surgery	438 (21.5)
Chemotherapy	354 (17.4)
Surgery and postoperative chemotherapy	127 (6.2)
Symptomatic treatment	1,024 (50.2)
Concurrent chemoradiotherapy	20 (1.0)
Radiotherapy	33 (1.6)
Neoadjuvant chemoradiotherapy and surgery	44 (2.2)
Number of clinical visits [median (P_5–P_{95})]	2 (1–5)
Number of admissions [median (P_5–P_{95})]	1 (1–5)
Length of stay per case (N=2,222) ($\bar{x}\pm s$) (d)	27±33
Length of stay per case (N=2,222) [median (P_{25}–P_{75})] (d)	19 (11–32)

CNY, Chinese Yuan.

CNY and 54,089 CNY, respectively (P=0.198 in *Table 2* and all P values >0.05 in the multivariate analysis in *Table 3*). There is only about 300 CNY difference between stage I and IV, which is also less clinically significant. *Figure 1* presents more details on the medical and non-medical expenditures in different clinical stages. In addition, there was also no expenditure difference among patients with different genders and pathological types (*Table 2*,*3*).

Expenditure heterogeneity was observed among regions. Expenditures of 8 provinces appeared higher and 6

Table 2 Overall and subgroup analysis of medical and non-medical expenditure for liver cancer diagnosis and treatment per case

Variables	Medical expenditure (CNY)	Non-medical expenditure (CNY)	Overall expenditure		
			Value (CNY)	Statistics*	P*
Total	48,612	4,608	53,220	–	–
Hospital type					
General	40,570	3,773	44,343	−5.56	<0.001
Specialized	51,211	4,878	56,089		
Age at diagnosis (year)					
<45	52,605	4,880	57,485	2.65	0.047
45–54	50,595	4,779	55,374		
55–64	46,474	4,745	51,219		
≥65	46,318	3,967	50,285		
Gender					
Male	49,294	4,630	53,924	1.28	0.201
Female	46,018	4,525	50,543		
Education					
Primary school or below	43,080	3,597	46,677	23.21	<0.001
Junior high school	45,280	3,994	49,274		
Senior high school	52,873	5,381	58,254		
Undergraduate or over	67,373	8,073	75,446		
Occupation					
Farmer	42,643	3,702	46,345	9.55	<0.001
Enterprise or company employee/worker	49,453	4,508	53,961		
Self-employed or unemployed	48,402	4,738	53,140		
Retiree	56,053	7,255	63,308		
Staff in institution/civil servant	67,797	5,794	73,591		
Other	45,513	4,696	50,209		
Health-care insurance type					
Urban employees basic medical insurance	53,250	5,286	58,536	8.49	<0.001
Urban residents basic medical insurance	51,452	4,798	56,250		
New rural cooperative medical scheme	43,515	3,933	47,448		
Commercial insurance	20,876	1,345	22,221		
Self-financed	44,158	4,345	48,503		
Other	55,604	5,513	61,117		
Previous year household income					
<20,000	40,684	4,212	44,896	8.57	<0.001
20,000–39,999	45,170	4,390	49,560		
40,000–69,999	50,461	4,814	55,275		
≥70,000	53,402	4,720	58,122		
Clinical stage					
I	48,644	4,173	52,817	1.56	0.198
II	46,616	4,261	50,877		

Table 2 (*continued*)

Table 2 (*continued*)

Variables	Medical expenditure (CNY)	Non-medical expenditure (CNY)	Overall expenditure		
			Value (CNY)	Statistics*	P*
III	46,319	4,359	50,678		
IV	49,063	5,026	54,089		
Therapeutic regimen					
Surgery	57,641	4,970	62,611	19.82	<0.001
Chemotherapy	45,773	4,652	50,425		
Surgery and postoperative chemotherapy	55,042	5,070	60,112		
Symptomatic treatment	44,837	4,644	49,481		
Concurrent chemoradiotherapy	50,892	4,524	55,416		
Radiotherapy	56,251	4,943	61,194		
Neoadjuvant chemoradiotherapy and surgery	42,449	4,747	47,196		
Pathological type					
Hepatocellular carcinoma	50,937	4,592	55,529	0.96	0.338
Other	48,143	4,213	52,356		

*, Two-sample Student test after logarithm transition for two groups comparative analysis, analysis of variance (ANOVA) test after logarithm transition for more than two groups comparative analysis.

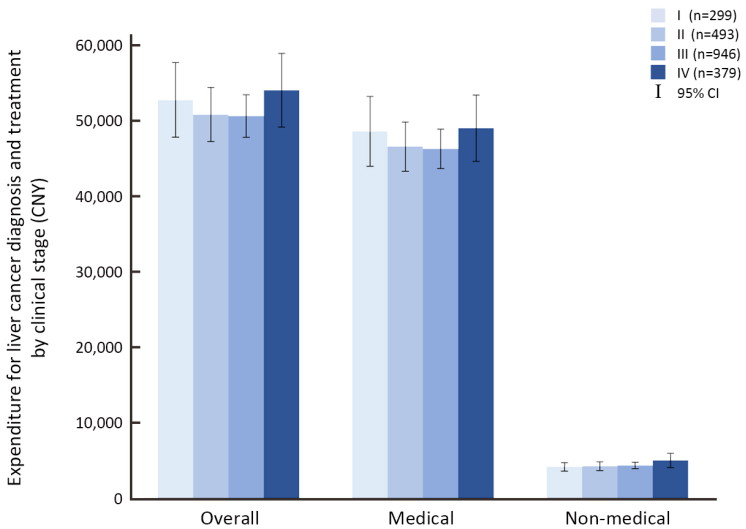

Figure 1 Medical and non-medical expenditure for liver cancer diagnosis and treatment, by clinical stage. 95% CI, 95% confidence interval; CNY, Chinese Yuan.

provinces seemed lower than the national average. Live cancer patients treated in Beijing, Xinjiang and Shandong usually spent more on treatment; while, live cancer patients treated in Hebei, Chongqing and Heilongjiang usually spent less on treatment. *Figure 2* shows more information of more provinces.

Table 4 shows the overall expenditure of a newly diagnosed course, the pocket expenditures of the patients and their situation of economic pressure. The total expenditure of a newly diagnosed course is equal to 46,070 CNY, among which the reimbursed medical expenditures account for 46.9%. The average of pocket expenditures is 24,953 CNY. And 77.2% of the patients cannot afford the non-reimbursed expenditures, 45.8% of them have lots of pressure and 31.4% have a certain pressure.

The estimated reimbursement percentage of medical expenditures varies with different variables. Among all the variables, general hospital, diagnosed age ≥65 years old,

Table 3 Multivariate analysis of overall expenditure for diagnosis and treatment of patients with liver cancer

Characteristic	Estimate (95% CI)	P
Intercept	10.4 (10.2, 10.7)	<0.001
Hospital type (Ref=general)		
Specialized	0.2 (0.1, 0.3)	<0.001
Age at diagnosis (year) (Ref≥65)		
<45	0.2 (0.0, 0.3)	0.030
45–54	0.1 (0.0, 0.3)	0.080
55–64	0.0 (−0.2, 0.1)	0.443
Sex (Ref=females)		
Males	0.0 (−0.1, 0.1)	0.828
Education (Ref=primary school or below)		
Junior high school	0.0 (−0.1, 0.1)	0.573
Senior high school	0.1 (−0.1, 0.2)	0.388
Undergraduate or higher	0.2 (0.0, 0.4)	0.015
Occupation (Ref=self-employee or unemployee)		
Farmer	0.0 (−0.2, 0.1)	0.604
Enterprise or company employee/worker	0.1 (−0.1, 0.2)	0.248
Retiree	0.0 (−0.2, 0.2)	0.983
Staff in institution/civil servant	0.5 (0.3, 0.7)	<0.001
Other	0.0 (−0.3, 0.4)	0.879
Healthcare insurance type (Ref=new rural cooperative medical scheme)		
Urban employee basic medical insurance	0.2 (0.0, 0.3)	0.034
Urban resident basic medical insurance	0.1 (0.0, 0.2)	0.196
Commercial insurance	−0.6 (−1.1, −0.1)	0.031
Self-financed	0.1 (−0.3, 0.4)	0.663
Other	0.3 (−0.1, 0.7)	0.132
Previous-year household income (CNY) (Ref<20,000)		
20,000–39,999	0.1 (−0.1, 0.3)	0.240
40,000–69,999	0.2 (0.0, 0.3)	0.032
≥70,000	0.2 (0.0, 0.4)	0.022
Clinical stage (Ref=I)		
II	−0.1 (−0.2, 0.0)	0.100
III	0.1 (−0.1, 0.2)	0.375
IV	0.1 (−0.1, 0.3)	0.183
Pathologic type (Ref=others)		
Adenocarcinoma	0.0 (−0.1, 0.1)	0.810
Therapeutic regimen (Ref=surgery)		
Chemotherapy	−0.1 (−0.4, 0.2)	0.493
Surgery and postoperative chemotherapy	−0.2 (−0.4, −0.1)	<0.001
Symptomatic treatment	−0.1 (−0.2, 0.1)	0.552
Concurrent chemoradiotherapy	−0.1 (−0.4, 0.1)	0.289
Radiotherapy	0.0 (−0.5, 0.5)	0.934
Neoadjuvant chemotherapy and surgery	−0.2 (−0.3, −0.1)	<0.001

95% CI, 95% confidence interval.

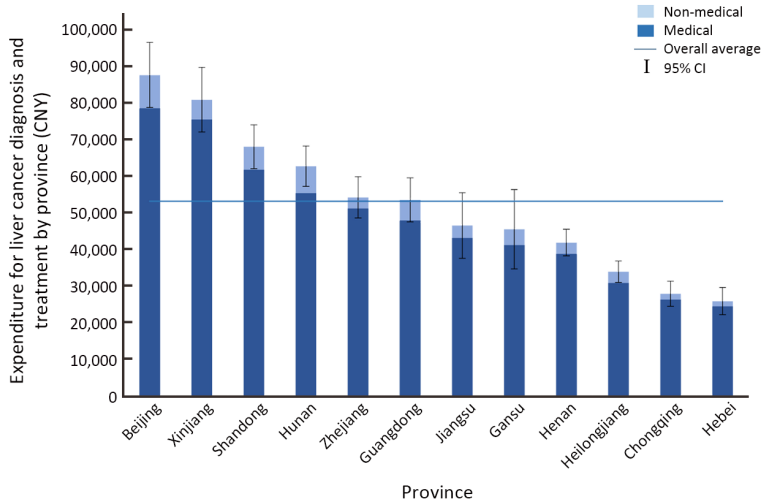

Figure 2 Medical and non-medical expenditure for liver cancer diagnosis and treatment, by province. 95% CI, 95% confidence interval; CNY, Chinese Yuan.

females (sex subgroup), education of university and higher, staff in institution/civil servant (occupation), other (medical insurance types subgroup), family income of last year ≥ 70,000 CNY, phase IV (clinical stage), neoadjuvant chemoradiotherapy and surgery (therapeutic regimen), other (pathological types subgroup) have the largest proportion in each subgroup.

The same, the ratio of self-financed expenditures to total household income varies in different subgroups. Among all the variables, specialist hospital, diagnosed age <45 years old, males (sex subgroup), education of primary school and below, farmers (occupation), NCMS (medical insurance types subgroup), family income of last 5 year <20,000 CNY, phase II (clinical stage), concurrent chemoradiotherapy (therapeutic regimen), and HCC (pathological types subgroup) have higher ratio.

Table 5 shows the status of working time loss of patients and their accompanying persons (relatives or friends) due to medical treatment. In total, it takes about 73.1 d per person, including 41.7 d for patients and 31.4 d for accompanying persons. The statistical result shows that the loss of working time among sex, occupation, clinical stage and pathological types are not statistically significant. Among all the variables, specialist hospital, diagnosed age from 45 to 54 years old, males (sex subgroup), education of university and higher, staff in institution/civil servant (occupation), other (medical insurance types subgroup), family income of last year (40,000–69,999) CNY, phase II (clinical stage), radiotherapy (therapeutic regimen), and HCC (pathological types subgroup) have more loss of working days in each subgroup.

Figure 3 shows the specific composition ratio of non-medical expenditures. Additional meals, additional nutrition care, transportation, accommodation, hired informal nursing and other expenditures are 1,453 CNY, 839 CNY, 946 CNY, 679 CNY, 200 CNY and 616 CNY, respectively. These suggests that the economic burden of non-medical expenditure on liver cancer cannot be ignored.

Discussion

As a major cancer in China, the medical expenditure of liver cancer accounts for a large proportion of the health economic burden. According to the analysis of Chinese malignant tumor registration data, the estimated age-standardized incidence rate of liver cancer in 2015 was 17.64 per 100,000, and the age-standardized incidence rate of liver cancer in urban China was 15.90 per 100,000. The age-standardized incidence rate of liver cancer in the Chinese male population was 26.74 per 100,000, only second to lung cancer and stomach cancer. It was estimated that the age-standardized mortality rate of liver cancer in China was only second to lung cancer (3). A comparative analysis of liver cancer shows that the incidence and mortality rate of liver cancer in Chinese men and women were both higher than the world average (4). Due to its large population and high incidence, China is the country with the largest number of liver cancer patients in the world, which places a heavy burden on people's health and social wealth. Our results indicate that HCC is the major

Table 4 Economic impact of overall expenditure on liver cancer patient's family

Variables	Expenditure of newly diagnosed course/Annual expenditure of illness* (CNY) (N=2,175)	Self-reported predicted reimbursement ratio (%) (N=2,175)	Out-of-pocket expenditure**(A) (CNY) (N=2,175)	Previous year household income (N=2,153)		Self-reported degree of economic pressure (%) (N=2,210)				
				Amount (B) (CNY)	Ratio (A/B)	Not at all	Somewhat but manageable	Heavy	Overwhelmed	P***
Total	46,070	46.9	24,953	56,468	0.4	7.8	15.0	31.4	45.8	–
Hospital type										
General	38,207	57.5	18,562	73,501	0.3	12.8	20.0	32.9	34.4	<0.001
Specialized	48,611	43.3	27,074	50,961	0.5	6.2	13.4	31.0	49.5	
Age at diagnosis (year)										
<45	51,019	43.2	29,796	62,202	0.5	6.4	11.7	31.1	50.8	<0.001
45–54	46,775	44.3	26,440	56,066	0.5	5.3	15.4	29.5	49.8	
55–64	45,170	48.5	24,050	54,510	0.4	8.0	14.3	32.8	44.9	
≥65	42,824	50.5	20,660	55,676	0.4	11.9	17.9	32.2	38.0	
Gender										
Male	46,569	46.7	25,183	56,622	0.4	7.9	14.6	31.5	45.9	0.800
Female	44,171	47.4	24,065	55,873	0.4	7.2	16.3	31.3	45.2	
Education										
Primary school or below	40,974	41.4	23,906	43,198	0.6	6.3	11.0	32.7	50.0	<0.001
Junior high school	42,973	44.2	24,388	54,542	0.4	5.2	16.2	32.5	46.1	
Senior high school	49,755	52.0	25,614	63,641	0.4	10.9	15.5	29.1	44.5	
Undergraduate or over	64,114	61.2	28,879	85,523	0.3	14.1	21.4	29.6	35.0	
Occupation										
Farmer	41,180	36.1	26,514	41,770	0.6	2.0	8.4	33.4	56.2	<0.001
Enterprise or company employee/worker	45,802	56.1	21,044	62,700	0.3	13.6	20.0	27.7	38.7	
Self-employed or unemployed	46,555	41.6	27,577	72,497	0.4	8.0	15.1	30.9	46.0	
Retiree	54,054	60.7	25,236	67,599	0.4	15.0	20.1	29.5	35.5	
Staff in institution/civil servant	60,834	64.6	24,240	68,698	0.4	9.2	26.6	31.8	32.4	
Other	45,245	42.7	26,482	56,242	0.5	3.0	9.1	60.6	27.3	
Health-care insurance type										
Urban employees basic medical insurance	49,419	58.6	22,234	64,584	0.3	14.6	18.5	27.3	39.6	<0.001
Urban residents basic medical insurance	47,668	49.8	23,591	60,320	0.4	6.0	18.8	33.8	41.4	

Table 4 (*continued*)

Table 4 (*continued*)

Variables	Expenditure of newly diagnosed course/Annual expenditure of illness* (CNY) (N=2,175)	Self-reported predicted reimbursement ratio (%) (N=2,175)	Out-of-pocket expenditure**(A) (CNY) (N=2,175)	Previous year household income (N=2,153)		Self-reported degree of economic pressure (%) (N=2,210)				
				Amount (B) (CNY)	Ratio (A/B)	Not at all	Somewhat but manageable	Heavy	Overwhelmed	P***
New rural cooperative medical scheme	42,510	36.8	27,571	44,620	0.6	1.9	9.6	33.6	54.8	
Commercial insurance	22,221	10.6	20,336	46,842	0.4	5.3	5.3	36.8	52.6	
Self-financed	41,799	0.0	41,799	104,514	0.4	7.5	22.5	40.0	30.0	
Other	59,682	69.9	20,257	72,136	0.3	13.6	18.2	40.9	27.3	
Previous year household income (CNY)										
<20,000	39,281	38.0	24,624	10,888	2.3	0.4	4.9	20.6	74.1	<0.001
20,000–39,999	44,199	42.0	26,124	26,983	1.0	2.7	8.1	31.6	57.6	
40,000–69,999	45,246	46.9	24,011	50,150	0.5	8.1	16.6	31.0	44.2	
≥70,000	51,529	55.5	25,012	108,404	0.2	15.0	24.3	35.3	25.4	
Clinical stage										
I	45,032	48.0	23,118	57,594	0.4	5.7	15.8	28.3	50.2	0.004
II	44,479	47.9	24,062	53,461	0.5	6.5	15.5	26.0	51.9	
III	44,573	44.6	24,592	54,950	0.5	9.0	13.7	34.9	42.5	
IV	45,446	48.1	25,102	61,929	0.4	7.2	17.3	29.9	45.6	
Therapeutic regimen										
Surgery	59,301	47.0	32,520	61,581	0.5	8.5	14.2	36.9	40.4	0.005
Chemotherapy	42,480	50.3	21,726	59,854	0.4	9.4	15.9	25.3	49.4	
Surgery and postoperative chemotherapy	52,035	48.5	27,420	60,440	0.5	2.4	17.3	40.2	40.2	
Symptomatic treatment	41,113	44.5	22,958	53,408	0.4	8.26	14.65	30.68	46.4	
Concurrent chemoradiotherapy	52,664	39.1	35,458	59,800	0.6	15.8	26.3	36.8	21.1	
Radiotherapy	49,076	52.7	24,359	54,040	0.5	6.3	21.9	25.0	46.9	
Neoadjuvant chemoradiotherapy and surgery	44,756	56.5	23,002	61,135	0.4	0.00	18.2	45.5	36.4	
Pathological type										
Hepatocellular carcinoma	48,150	48.1	25,896	56,536	0.5	5.2	15.2	30.5	49.1	<0.001
Other	47,567	50.2	23,787	69,449	0.3	21.5	22.3	36.5	19.7	

*, The 12-month duration covers 2 months before and 10 months after the diagnosis; **, Out-of-pocket expenditure=(∑(1 − Self-reported predicted reimbursement ratio) × Medical expenditure of newly diagnosed course + Non-medical expenditure of newly diagnosed course)/n; ***, Chi-square tests; CNY, Chinese Yuan.

Table 5 Time lost due to liver cancer diagnosis and treatment

Variables	Patients (N=2,139) (d)	Caregivers* (N=2,139) (d)	Overall number of days lost		
			Value (d)	Statistics**	P**
Total	41.7	31.4	73.1	–	–
Hospital type					
General	40.5	27.9	68.4	−4.21	<0.001
Specialized	42.1	32.5	74.7		
Age at diagnosis (year)					
<45	45.2	28.6	73.8	3.45	0.016
45–54	45.9	34.4	80.3		
55–64	38.0	31.3	69.3		
≥65	39.3	29.6	68.9		
Sex					
Male	42.4	31.8	74.2	0.94	0.346
Female	38.9	29.9	68.8		
Education					
Primary school or below	38.2	30.9	69.1	2.95	0.031
Junior high school	42.8	29.9	72.7		
Senior high school	41.7	33.4	75.1		
Undergraduate or over	49.0	32.8	81.8		
Occupation					
Farmer	40.0	31.0	70.9	1.17	0.320
Enterprise or company employee/worker	40.8	32.1	72.8		
Self-employed or unemployee	42.1	27.1	69.2		
Retiree	45.8	31.8	77.6		
Staff in institution/civil servant	48.9	38.8	87.7		
Other	37.1	29.3	66.4		
Health-care insurance type					
Urban employees' basic medical insurance	47.4	33.4	80.9	5.93	<0.001
Urban residents' basic medical insurance	37.8	32.5	70.3		
New rural cooperative medical scheme	39.0	29.5	68.5		
Commercial insurance	24.5	15.0	39.5		
Self-financed	24.4	21.7	46.1		
Other	46.3	37.6	84.0		
Previous year household income (CNY)					
<20,000	37.2	32.7	69.9	4.70	0.003
20,000–39,999	43.1	32.0	75.1		
40,000–69,999	45.9	32.2	78.1		
≥70,000	39.3	30.0	69.3		
Clinical stage					
I	39.2	27.1	66.3	2.60	0.050
II	44.7	34.0	78.7		
III	42.6	30.0	72.6		

Table 5 (*continued*)

Table 5 (*continued*)

Variables	Patients (N=2,139) (d)	Caregivers* (N=2,139) (d)	Overall number of days lost		
			Value (d)	Statistics**	P**
IV	39.5	35.2	74.7		
Therapeutic regimen					
Surgery	42.6	25.5	68.1	4.05	<0.001
Chemotherapy	41.2	35.4	76.6		
Surgery and postoperative chemotherapy	38.7	28.4	67.1		
Symptomatic treatment	43.8	32.3	76.1		
Concurrent chemoradiotherapy	36.6	47.2	83.8		
Radiotherapy	53.5	42.0	95.5		
Neoadjuvant chemoradiotherapy and surgery	63.8	31.7	95.5		
Pathological type					
Hepatocellular carcinoma	41.4	29.1	70.5	1.17	0.243
Other	41.1	27.9	69.0		

*, Patients' relatives and friends; **, Two-sample Student test after logarithm transition for two groups comparative analysis; analysis of variance (ANOVA) test after logarithm transition for more than two groups comparison; CNY, Chinese Yuan.

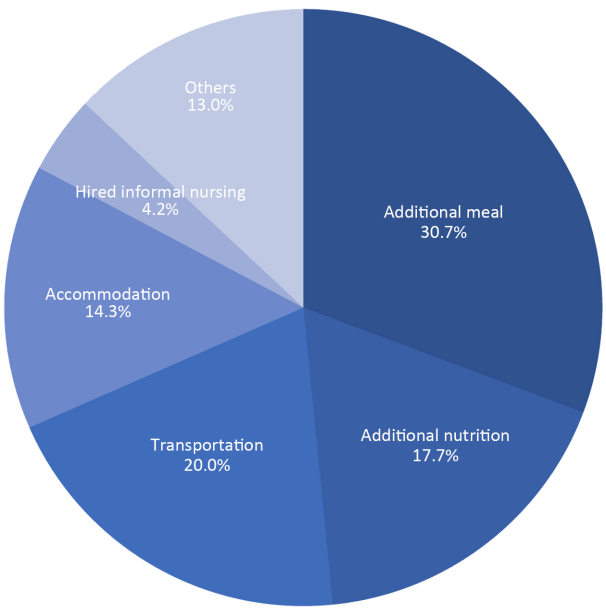

Figure 3 Proportional breakdown of non-medical expenditure for liver cancer diagnosis and treatment.

pathological type of liver cancer, accounting for approximately 54% of all cases in this study. In recent years, the average total expenditure per HCC patient is significantly higher than that of other pathological types of liver cancer in China. The United States also has a similar economic burden of HCC (5).

For most Chinese families, expensive medical expenditures were a heavy economic burden. From 2012 to 2014, the average medical expenditure of liver cancer was 48,612 CNY per case, and the average medical expenditure of patients with the pathological type of HCC was 50,937 CNY per case. The expenditure in this study was higher than that in previous systematic review and original articles on the economic burden of liver cancer in mainland China (6-9). However, a retrospective survey conducted in 2010 in Shandong, China found that direct medical expenditure in US dollars for inpatients with primary liver cancer amounted to $10,635 (10). According to the China Statistical Yearbook, the medical expenditure for each liver cancer clinic visit was almost equal to the one-year disposable income of urban residents (11). In Taiwan, China, the average 10-year expenditure of liver cancer patients was NT$ 418,554 (~82,706 CNY), which was higher than that in this study (12). For low-income families who usually do not have formal jobs and have lower health insurance, their economic burden on liver cancer will increase and may lead to poverty caused by disease.

The medical treatment expenditure in specialized hospitals is higher than the one in general hospitals. Because specialized hospitals have more various means of cancer treatment, more advanced treatment equipment, and more professional medical staff. In China, the vast majority of cancer patients are willing to choose a specialized hospital for their treatment. Patients with higher education levels have more knowledge about cancer and believe it can be cured, so they want to spend more time and money on cancer treatment. People with higher education levels normally have higher incomes and are able to afford the medical treatment expenditure than those

with a lower education level. The total medical expenditures are related to the reimbursement rate and the ability to pay. Patients with high medical insurance reimbursement rates are more willing to receive treatment and spend more money on treatment. Urban employee basic medical insurance has the highest reimbursement rate, which is also consistent with the higher medical expenditure for the staff in the institution or civil servants and highly educated patients.

We found not statistical difference in diagnosis and treatment expenditure for liver cancer patients at different clinical stages, which indicates that liver cancer control in China is more challenging, compared with breast cancer and colorectal cancer (13,14). Maintaining efforts on treatment efficacy improvement is important but not enough. To furtherly reduce the overall economic burden from liver cancer, more effort should be given to primary and secondary prevention strategies.

In addition to calculating direct expenditure by consulting the medical bills of patients with liver cancer, indirect losses such as labor loss caused by liver cancer are huge. Five studies calculated individual-based indirect economic burdens, using the human capital method to combine the time of missed work and early death of liver cancer patients and the time of missed work of caregivers. The results showed that the median indirect economic burden was 73,440 CNY per case, distributed between 35,815 CNY and 166,967 CNY per case (15-19).

Patients with stage IV liver cancer have low survival rates, and high direct expenditure (medical and non-medical expenditures) and indirect expenditure associated with diagnosis and treatment imposes a heavy burden on individuals and families. Therefore, early detection, early diagnosis and early treatment of liver cancer are particularly important.

This study has some limitations. First, only tertiary and secondary hospitals were included in the survey, the situation in lower level hospitals is still not clear. Second, other than the direct medical expenditure for the current hospitalization, which was obtained from hospital financial data, all other outpatient and inpatient expenditures were self-reported and may be subjected to recall bias. Third, the questionnaire was adopted at hospital when patents completed most of the treatments before discharge, which to certain extent missed the expenditure occurred afterwards. Forth, there is a possible selection bias, which might occur because the study was not randomized. This study also has a potential limitation of retrospective nature. Since this study is currently the largest in China about the medical and non-medical expenditure of patients with liver cancer. Although there is a little design flaw, it is still very valuable. It is indeed the first study on the estimation of the economic burden of liver cancer, including medical expenditures and labor value losses.

These results provide evidence to help health policymakers understand the scale of economic burden of liver cancer in China so that the Chinese government can adjust relevant disease prevention and control strategies. In addition, the evidence from our study also contributes to our understanding of potential benefits to society in allocating more resources to prevent and treat liver cancer, as well as increasing insurance coverage in China. These findings have important policy implications for health care reform which is currently underway in China and focuses on how to reduce the burden of catastrophic disease for its citizens.

Conclusions

The findings indicate that there was no difference in treatment expenditure for liver cancer patients at different clinical stages, which suggests that maintaining efforts on treatment efficacy improvement is important but not enough. To further reduce the overall economic burden from liver cancer, more effort should be given to primary and secondary prevention strategies.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Table S1 Summary of study sites and hospitals involved in 13 provinces or cities in China

Province	General information at provincial level		Specific information on study sites and hospitals involved			
	Population size in 2013* ($\times 10^4$)	GDP per capita in 2013* (CNY)	No. of sites (city)	Total No. of hospitals	General hospitals (n)	Specialized hospitals (n)
Shandong	9,733	56,323	1 (Jinan)	1	0	1
Beijing	2,115	93,213	1 (Beijing)	3	1	2
Jiangsu	7,939	74,607	2 (Nantong, Xuzhou)	2	0	2
Guangdong	10,644	58,540	5 (Five cities**)	6	5	1
Zhejiang	5,498	68,462	2 (Hangzhou, Ningbo)	2	1	1
Hebei	7,333	38,716	1 (Tangshan)	3	3	0
Liaoning	4,390	61,686	1 (Tieling)	1	1	0
Hunan	6,691	36,763	1 (Changsha)	1	0	1
Heilongjiang	3,835	37,509	2 (Harbin, Daqing)	6	5	1
Henan	9,413	34,174	1 (Zhengzhou)	1	0	1
Xinjiang	2,264	37,181	1 (Urumchi)	1	0	1
Gansu	2,582	24,296	2 (Lanzhou, Jinchang)	9	7	2
Chongqing	2,970	42,795	1 (Chongqing)	1	0	1
Overall	–	–	21	37	23	14

*, Based on China Statistical Yearbook 2014, available from http://www.stats.gov.cn/tjsj/ndsj/2014/indexce.htm; **, Including Guangzhou, Shenzhen, Zhongshan, Dongguan and Foshan.