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## Inpatient Treatment Patterns and Health Care Expenditures for Hepatocellular Carcinoma among the Population with Urban Basic Health Insurance in China

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### ABSTRACT

**Objective:** To identify inpatient treatment patterns and health care expenditures for hepatocellular carcinoma (HCC) among the population with urban basic health insurance (BHI) in China. **Methods:** Hospitalizations for patients 18 years or older with discharge diagnosis of HCC from 2008 to 2011 and enrolled in the Chinese BHI plan were identified from the Chinese Health Insurance Research Association database. Treatment approaches and hospital expenditures were assessed for the full sample, and according to city level and hospital tier. Analyses were extrapolated to the national urban BHI population. **Results:** A total of 3679 HCC hospitalizations were identified in the period 2008 to 2011, representing 615,359 hospitalizations among the urban BHI population. More than two-thirds of the patients received active treatment during hospitalization (68%, N = 418,394), most commonly with traditional Chinese medicine (51%) and/or transarterial intervention therapy (21%). Cases from larger level 1 cities and larger tier 3 hospitals reported greater use of active treatments (81% and 83%, respectively) than did those from smaller

level 3 cities (46%) or tier 1 hospitals (56%). Hospital expenditures were higher in level 1 cities (mean [95% confidence interval] Chinese currency renminbi [¥] 17,119 [¥16,292–¥17,946]; US \$2,506 [\$2,385–\$2,628]) than in level 3 cities (mean [95% confidence interval] ¥7,870 [¥5,775–¥9,964]; \$1,152 [\$846–\$1,459]). **Conclusions:** Most patients with HCC received active treatment during hospitalization in China. There were substantial disparities, however, in the use of HCC treatments across different economic regions, and nearly a third received only palliative care. With the recent launch of health care reform, this study provides valuable insights into current resource use and costs for HCC in China to help prioritize areas of improvement.

**Keywords:** basic health insurance, China, cost, health care expenditures, hepatocellular carcinoma, treatment.

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### Introduction

Hepatocellular carcinoma (HCC) is one of the most prevalent and deadly cancers worldwide [1,2]. It is particularly common in Asian-Pacific countries, resulting from a higher prevalence of hepatitis B virus infection, and more than half of all global cases occur in China alone [3]. In China, HCC is the third most frequent cancer and the second leading cause of cancer-related death; an estimated 402,000 new cases were diagnosed and 372,000 HCC-related deaths occurred in 2008 [1]. HCC presents a significant economic and societal burden in China, and it is the highest contributing factor to hospital expenditures related to hepatitis B virus infection [4–7].

In recent years, the China Ministry of Health has declared HCC as one of five tumors of high national importance and has published its newest Diagnosis and Treatment Guidelines for Primary Liver Cancers (2011 edition) [8]. Largely consistent with consensus recommendations published by other developed nations [9–11], guideline-recommended therapeutic options for HCC are administered on the basis of tumor stage and liver function [8]. Patients with HCC diagnosed at an early stage are eligible for curative surgical therapies, which include liver resection and liver transplantation, and, in some cases, receive local ablation therapy. Most of the patients, however, are diagnosed with intermediate to advanced HCC for which curative treatment

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is not an option [12]. For intermediate to advanced HCC, treatment options include palliative resection, local treatments, such as local ablation and transarterial intervention therapy, radiotherapy, systemic therapy, and palliative care [8]. Recommended systemic therapies include molecular targeted therapy, systemic chemotherapy, as well as traditional Chinese medicine (TCM).

Although multiple treatment options are available, little is known about current treatment approaches and associated costs for HCC at the national level in China [12–14]. A better understanding of current treatment patterns and expenditures for HCC using real-world data in China can help guide interventions to increase compliance with clinical guideline recommendations and minimize health care costs. Therefore, the objective of this study was to identify inpatient treatment patterns and health care expenditures for HCC among the population with urban basic health insurance (BHI) in China. As secondary objectives, the study also explored differences in treatment patterns and associated HCC-related expenditures according to city-level size and hospital type.

The urban BHI plan is required by the government and currently covers more than 90% of China's population in urban areas nationwide [15]. The urban population in China represents approximately 51% of the total population in China [16]. Knowledge of HCC treatment patterns and costs among the urban population can help identify current areas of unmet medical need across different economic regions and inform current health care reform efforts to improve long-term outcomes for this patient population in China.

## Methods

### Study Subjects

Eighteen years or older inpatients with a discharge diagnosis of HCC from 2008 to 2011 were identified from the Chinese Health Insurance Research Association (CHIRA) database. CHIRA conducts a national survey of health care services utilization and costs for hospitalizations among urban BHI inpatients annually. For each hospitalization, the integrated database includes information on hospital-level characteristics, patients' demographic characteristics, health insurance type, and inpatient diagnoses, procedures, and expenses.

Hospitalizations are selected annually from approximately 60 local health insurance departments using multistage stratified sampling in terms of geographic location (East, Central, and West; excluding Hong Kong, Taiwan, and Macau), city level (levels 1–3), and hospital tier (tiers 1–3). Level 1 cities are defined as provincial capitals (e.g., Guangzhou, Hangzhou, Nanjing, and Wuhan) and municipalities (i.e., Beijing, Chongqing, Shanghai, and Tianjin), level 2 includes prefecture- (e.g., Baoding and Weihai) and sub-prefecture-level cities (e.g., Jiyuan in Henan), and level 3 includes the less heavily populated county-level cities (e.g., Yiwu in Zhejiang). Tier 1 hospitals indicate small community hospitals, tier 2 intermediate volume hospitals, and tier 3 large/academic hospital centers.

### Data Collection

Study inclusion criteria included hospitalizations for individuals who were 1) 18 years or older, 2) enrolled in the Chinese urban resident or employee BHI plan, 3) were admitted to a hospital during the calendar years 2008 to 2011, and 4) had a diagnosis of HCC at patient discharge. HCC diagnosis was identified using the *International Classification of Diseases, Tenth Revision* codes: C22.0 (liver cell carcinoma) and C22.9 (liver, unspecified) [12].

HCC-related treatments were categorized into five categories on the basis of China Ministry of Health's Diagnosis and Treatment Guidelines for Primary Liver Cancers (2011 edition) [8]: surgical therapy, local therapy, radiotherapy, systemic therapy, and palliative therapy. Surgical therapies included liver resection and liver transplant. Local therapies included local ablation (radiofrequency ablation, microwave ablation, cryoablation, high-intensity focused ultrasound ablation, and percutaneous ethanol injection) and transarterial intervention therapy (transcatheter arterial infusion chemotherapy, transcatheter arterial embolization, and transarterial chemoembolization). Systemic therapies included molecular targeted therapy (sorafenib, sunitinib, bevacizumab, cetuximab, and erlotinib), systemic chemotherapy (most commonly doxorubicine, gemcitabine, cisplatin, oxaliplatin, capecitabine, fluorouracil, epirubicin, mitomycin C, carboplatin, lobaplatin, floxuridine, and thalidomide, among others), TCM (e.g., aidi injection, anduolin jiaonang, ankangxin-jiaonang, antike jiaonang, macao wessing particles, barbadian, corbrin capsule, shen lian capsule, and chansu injection), and other systemic therapies (interferon, thymosin  $\alpha$ 1, and interferon- $\alpha$ ). Individuals who did not receive active treatment with any of the above therapies were categorized as having received palliative therapy. Palliative therapy was additionally verified on the basis of common palliative therapeutic regimens to treat HCC-related symptoms: narcotic analgesics, nonnarcotic analgesics, laxatives, antidiarrhea medications, antihistamines, antidepressants, anxiolytics, sedative/hypnotics, oxygen, and others.

To identify all inpatient therapies and procedures, the CHIRA database contains detailed charge lists for all hospital resources and related expenditures categorized by service type: diagnostic, medical device/supply, nursing care, surgical treatment, and medication. The above-mentioned HCC-related treatments were identified and characterized using a combination of records from the medication, medical device/supply, and surgical treatment charge lists. Medications for systemic therapies were mapped using the corresponding Anatomical Therapeutic Chemical Classification System codes for each generic name in cases in which systemic therapies were entered in text [15]. For most treatments, rather than providing the name of the procedure, the charge list showed only the device and agents used. Therefore, active treatments were categorized according to detailed device/agent lists (more than 50,000 items). Physician experts were then asked to verify the full list for each active treatment category.

### Data Analysis and Extrapolation

Descriptive characteristics and treatment patterns for all hospitalizations with a discharge diagnosis of HCC were summarized using frequencies and percentages. Relevant characteristics included patients' demographic characteristics (sex, age, and insurance type), hospital level, city characteristics (city level and region), and year of hospitalization (2008–2011). Active and palliative treatment approaches were examined for the full study sample and according to city level and hospital tier.

Average inpatient hospital expenditures (in Chinese currency renminbi [¥]) and length of stay (in days) were calculated for all hospitalizations and across city level. Average hospital expenditures were further analyzed according to the above-mentioned active and palliative treatment categories. Additional analyses assessed average BHI reimbursement and cost-sharing for all hospital expenditures, defined as the ratio of costs for each BHI reimbursement category (BHI reimbursed, co-payment, and out-of-pocket costs for treatments ineligible for co-payment) over the total hospitalization cost for each event, according to year, city level, and insurance type.

Study analyses were extrapolated to reflect the national population with urban BHI. As exceptions, frequencies and

associated hospital expenditures for certain treatment approaches were not extrapolated because the sample groups were too small to provide reliable projections. Two levels of data projection were conducted to account for the multistage stratified sampling design (Table 1). To achieve the target sample size for each city level, hospitalization records were disproportionately sampled according to city size using systematic randomized sampling methods, by the date of patient discharge; 2% of hospitalization records were selected from level 1 cities, 5% from level 2 cities, and 10% from level 3 cities. The second level of projection intends to convert sampled city volume/value to national level. A city projection factor was recalculated and applied on a yearly basis on the basis of the population of BHI enrollees, inpatient volume, as well as annual urban BHI expenditures. Every sampled observation was, in turn, assigned weighting variables according to the total numbers of enrollees and hospitalizations, total expenditures by health insurance funds, hospital and city levels, and geographic locations to make accurate national estimates.

Statistical analyses were conducted using STATA v12 (Stata-Corp, 2011) and Microsoft Excel (Microsoft, 2010) software. The Kolmogorov-Smirnov test was conducted to test the normality assumption for hospital expenditures and length of stay. Both variables displayed a right-skewed distribution ( $P > 0.05$  for normality test); thus, the median and interquartile range were reported to provide an assessment of dispersion in hospital expenditures, in addition to the mean and the 95% confidence interval (95% CI). The mean and the 95% CI in hospital expenditures (in ¥) were approximated to US dollars (US \$) using the World Bank–reported exchange rates for the study period [17]. Comparisons of inpatient treatment approaches, according to city level and hospital tier, were conducted using chi-square tests. Differences in hospital expenditures and length of stay across city levels were assessed on the basis of overlap in the 95% CIs. Statistical analyses were considered significant if  $P < 0.05$ .

## Results

A total of 3679 cases of hospitalizations with a discharge diagnosis of HCC were identified in the period 2008 to 2011, representing an estimated 615,359 HCC hospitalizations extrapolated to the national population with urban BHI (Table 2). Most of the

cases were men (79%), between the ages of 40 and 79 years (89%), and covered under the urban employee BHI plan (83%). Patients with HCC tended to be hospitalized and treated in larger hospitals; 50% of HCC hospitalizations were from tier 3 and 42% from tier 2 hospitals. Most of the HCC hospitalizations were from the more populated and affluent geographical regions in China. An estimated 40% of the hospitalizations were from level 1 ( $n = 243,176$ ) and 43% from level 2 ( $n = 267,255$ ) cities, and 61% ( $n = 377,966$ ) were from Eastern China.

## HCC Treatment Patterns

More than two-thirds of the patients received active treatment during hospitalization (68%,  $n = 418,394$ ), whereas the remaining received palliative therapy (Table 3). Among active treatments, most patients received systemic therapy (63%,  $n = 386,624$ ) or local therapy using transarterial interventions (21%,  $n = 130,511$ ); use of curative surgical treatments (2%) or radiotherapy (2%) was rather limited. TCM was the most common systemic therapy, administered at approximately half of all hospitalizations (51%,  $n = 313,056$ ), followed by other systemic therapies (24%,  $n = 150,092$ ) and chemotherapy (16%,  $n = 98,175$ ). TCM was generally administered in combination with other active treatments (61%), and less commonly used alone (data not shown).

There were substantial and highly significant differences in treatment patterns across city level and hospital tier, after extrapolation to the national level (Table 4; all comparisons  $P < 0.0001$ ). Cases from the more heavily populated level 1 cities reported the greatest use of active treatments (81%), whereas only 46% of the cases from level 3 cities received active treatment ( $P < 0.0001$ ). Level 1 cities also showed higher use of local therapies (35%) and surgical treatments (3%) than did level 3 cities (local therapies 9%; surgical treatments 1%). Statistically significant differences in the use of treatment approaches were also observed across hospital tiers (all  $P < 0.0001$ ). A greater number of HCC cases treated at larger tier 3 hospitals received active treatment (83%) compared with those treated in smaller tier 1 hospitals (56%).

Across all HCC hospitalizations, approximately 41% of the patients who received active treatment during hospitalization received only one therapy, whereas the remaining were treated using combination therapies (Table 5, numbers represent the study sample). TCM was commonly used as a supplementary

**Table 1 – Multistage stratified sampling scheme for cases of HCC-related hospitalizations according to city level for individuals with urban BHI (2008–2011).**

Year, city level	Total cities, n	Sampled cities, n (%)	Total hospitalizations, n	HCC cases, n (%)
2008	646	60 (9.29)	98,979	589 (0.60)
Level 1	31	26 (83.87)	48,845	366 (0.75)
Level 2	249	22 (8.84)	38,799	180 (0.46)
Level 3	366	12 (3.28)	11,335	43 (0.38)
2009	646	50 (7.74)	157,577	876 (0.56)
Level 1	31	24 (77.42)	100,074	598 (0.60)
Level 2	249	15 (6.02)	48,720	253 (0.52)
Level 3	366	11 (3.01)	8,783	25 (0.28)
2010	646	67 (10.37)	236,366	1283 (0.54)
Level 1	31	27 (87.10)	152,476	909 (0.60)
Level 2	249	20 (8.03)	64,219	305 (0.47)
Level 3	366	20 (5.46)	19,671	69 (0.35)
2011	646	62 (9.60)	375,822	931 (0.25)
Level 1	31	27 (87.10)	245,707	634 (0.26)
Level 2	249	19 (7.63)	112,023	292 (0.26)
Level 3	366	16 (4.37)	18,092	5 (0.03)

BHI, basic health insurance; HCC, hepatocellular carcinoma.

**Table 2 – Patient and demographic characteristics among cases of HCC-related hospitalizations, extrapolated to reflect HCC hospitalizations among the national population with urban BHI (2008–2011).**

Characteristic	Sample (n = 3679)		Estimated urban hospitalizations (n = 615,359)	
	Cases	%	Cases	%
Sex				
Male	2876	78.17	487,011	79.14
Female	803	21.83	128,348	20.86
Age group (y)				
18–39	221	6.00	32,860	5.34
40–59	1677	45.58	285,106	46.33
60–79	1574	42.79	267,274	43.43
≥80	194	5.27	26,866	4.37
Unspecified	13	0.35	3,252	0.53
Insurance type				
Urban employee	3186	86.60	511,255	83.08
Urban resident	446	12.12	81,700	13.28
Unspecified	47	1.28	22,403	3.64
Hospital tier				
3	2460	66.87	307,546	49.98
2	956	25.99	260,459	42.33
1	241	6.55	45,603	7.41
Unspecified	22	0.60	1,751	0.28
City level				
1	2507	68.14	243,176	39.52
2	1030	28.00	267,255	43.43
3	142	3.86	104,928	17.05
Region				
East	2590	70.40	377,966	61.42
Central	566	15.38	166,019	26.98
West	523	14.22	71,374	11.60
Year				
2008	589	16.01	144,036	23.41
2009	876	23.81	149,001	24.21
2010	1283	34.87	147,586	23.98
2011	931	25.31	174,736	28.40

BHI, basic health insurance; HCC, hepatocellular carcinoma.

**Table 3 – Inpatient treatment approaches among cases of HCC-related hospitalizations, extrapolated to reflect HCC hospitalizations among the national population with urban BHI (2008–2011).**

Treatment approaches <sup>*</sup>	Sample (n = 3679)		Estimated urban hospitalizations (n = 615,359)	
	Cases	%	Cases	%
Active treatment	2907	79.02	418,394	67.99
Systemic therapy	2672	72.63	386,624	62.83
TCM	2173	59.06	313,056	50.87
Chemotherapy	618	16.80	98,175	15.95
MTD therapy	10	0.27	†	†
Others	1231	33.46	150,092	24.39
Local therapy	1148	31.20	150,106	24.39
TAI therapy	988	26.86	130,511	21.21
Local ablation	223	6.06	27,474	4.46
Surgical treatment	148	4.02	12,214	1.98
Liver resection	147	4.00	12,191	1.98
Liver transplant	1	0.03	†	†
Radiotherapy	107	2.91	13,233	2.15
Palliative therapy	772	20.98	196,965	32.01

BHI, basic health insurance; HCC, hepatocellular carcinoma; MTD, molecular targeted drug; TAI, transarterial intervention; TCM, traditional Chinese medicine.

\* Treatment categories are based on the Diagnosis and Treatment Guidelines for Primary Liver Cancers (2011 edition), published by the China Ministry of Health [4].

† Indicates that the sample size was too small for data extrapolation at the national level of estimated urban hospitalizations.

**Table 4 – Comparisons of inpatient treatment approaches among cases of HCC-related hospitalizations across city level and hospital tier, extrapolated to reflect HCC hospitalizations among the national population with urban BHI (2008–2011)**

Treatment approaches*	City level†						Hospital tier††					
	Level 1 (n = 243,176)		Level 2 (n = 267,255)		Level 3 (n = 104,928)		Tier 1 (n = 45,603)		Tier 2 (n = 260,459)		Tier 3 (n = 307,546)	
	Cases	%	Cases	%	Cases	%	Cases	%	Cases	%	Cases	%
Active treatment	197,604	81.26	172,524	64.55	48,266	46.00	25,434	55.77	135,776	52.13	255,712	83.15
Systemic therapy	181,949	74.82	159,793	59.79	44,882	42.77	24,943	54.70	127,314	48.88	232,911	75.73
TCM	150,116	61.73	122,178	45.72	40,762	38.85	21,986	48.21	97,374	37.39	192,487	62.59
Chemotherapy	42,763	17.59	47,663	17.83	7,749	7.38	4,864	10.67	37,047	14.22	55,402	18.01
MTD therapy	445	0.18	628	0.24	0	0.00	0	0.00	446	0.17	628	0.20
Others	83,737	34.43	51,960	19.44	14,395	13.72	7,105	15.58	37,028	14.22	105,589	34.33
Local therapy	84,737	34.85	55,923	20.92	9,445	9.00	4,085	8.96	37,241	14.30	108,130	35.16
TAI therapy	69,990	28.78	51,076	19.11	9,445	9.00	3,275	7.18	34,990	13.43	91,844	29.86
Local ablation	20,793	8.55	5,811	2.17	870	0.83	1,080	2.37	3,337	1.28	22,811	7.42
Surgical treatment	8,419	3.46	2,569	0.96	1,225	1.17	128	0.28	1,725	0.66	10,343	3.36
Liver resection	8,397	3.45	2,569	0.96	1,225	1.17	128	0.28	1,725	0.66	10,321	3.36
Liver transplant	22	0.01	0	0.00	0	0.00	0	0.00	0	0.00	22	0.01
Radiotherapy	6,751	2.78	6,038	2.26	444	0.42	128	0.28	2,416	0.93	10,566	3.44
Palliative therapy	45,573	18.74	94,731	35.45	56,661	54.00	20,169	44.23	124,683	47.87	51,834	16.85

BHI, basic health insurance; HCC, hepatocellular carcinoma; MTD, molecular targeted drug; TAI, transarterial intervention; TCM, traditional Chinese medicine.

\* Treatment categories are based on the Diagnosis and Treatment Guidelines for Primary Liver Cancers (2011 edition), published by the China Ministry of Health [4].

† Statistical comparisons of inpatient treatment approaches were highly significant across both city level (all  $P < 0.0001$ ) and hospital tier (all  $P < 0.0001$ ) groups.

‡ A total of 22 cases ( $N = 1751$  after extrapolation) were excluded because of missing hospital status information.

**Table 5 – Distribution of treatment approaches and hospital expenditures among cases of HCC-related hospitalizations (2008–2011).\***

Treatment approaches	Sample (n = 3679)		Hospital expenditures		
	Cases	%	Mean (95% CI) (¥)	Median (IQR) (¥)	Mean (95% CI) (US \$)
Palliative therapy	772	20.98	9,295 (7,956–10,633)	4,685 (7,161)	1361 (1165–1557)
Active treatment	2907	79.02	18,432 (17,662–19,202)	13,054 (15,406)	2699 (2586–2811)
Monotherapy	1187	40.83	12,544 (11,821–13,267)	8,977 (10,934)	1837 (1731–1942)
Systemic therapy	977	82.31	11,805 (11,004–12,606)	7,792 (10,486)	1728 (1611–1846)
TCM	681	57.37	11,408 (10,478–12,338)	7,611 (9,444)	1670 (1534–1806)
Chemotherapy	81	6.82	10,736 (8,357–13,115)	8,019 (7,363)	1572 (1224–1920)
Others	215	18.11	13,465 (11,515–15,415)	8,489 (14,653)	1971 (1686–2257)
Local therapy	180	15.16	14,259 (12,775–15,783)	11,946 (7,737)	2091 (1870–2311)
TAI therapy	151	12.72	13,575 (12,084–15,066)	11,554 (6,715)	1988 (1769–2206)
Local ablation	29	2.44	17,942 (12,684–23,200)	16,846 (12,541)	2627 (1857–3397)
Surgical resection	14	1.18	30,110 (19,941–40,279)	22,181 (10,599)	4408 (2920–5897)
Radiotherapy	16	1.35	22,785 (16,048–29,522)	21,878 (22,479)	3336 (2350–4322)
Combination therapy	1720	59.17	22,495 (21,332–23,658)	16,415 (16,401)	3294 (3123–3464)
TCM + OST	344	20.00	16,339 (14,664–18,014)	10,719 (15,857)	2392 (2147–2637)
TCM + TAI	253	14.71	16,559 (15,272–17,845)	14,908 (9,502)	2424 (2236–2613)
TCM + TAI + OST	202	11.74	25,395 (22,402–28,387)	19,728 (12,483)	3718 (3280–4156)
TCM + Chemo	154	8.95	10,958 (9,541–12,374)	8,647 (7,258)	1604 (1397–1812)
TCM + Chemo + OST	102	5.93	23,639 (15,144–32,135)	12,202 (17,280)	3461 (2217–4705)
TCM + TAI + Chemo	71	4.13	26,451 (18,809–34,092)	18,175 (12,363)	3873 (2754–4992)
TAI + OST	69	4.01	16,824 (14,650–18,999)	14,843 (11,068)	2463 (2145–2782)
TCM + TAI + Chemo + OST	57	3.31	33,301 (27,121–39,480)	25,523 (34,878)	4876 (3971–5780)
TCM + Local ablation	42	2.44	23,473 (18,242–28,703)	21,225 (16,218)	3437 (2671–4202)
Chemo + OST	36	2.09	17,149 (11,309–22,989)	9,758 (13,879)	2511 (1656–3366)
Other combinations	390	22.67	33,623 (30,441–36,805)	24,620 (22,202)	4923 (4457–5389)

Chemo, chemotherapy; CI, confidence interval; HCC, hepatocellular carcinoma; IQR, interquartile range; OST, other systemic therapy; TAI, transarterial intervention; TCM, traditional Chinese medicine.

\* Data were not extrapolated to the national level of estimated urban hospitalizations because many of the sample groups were too small.

therapy to other active treatments, primarily in combination with other systemic therapy (20%) or transarterial intervention therapy (15%).

### HCC Hospital Expenditures

Average health care expenditures for all HCC-related hospitalizations were ¥13,467 (95% CI ¥12,873–¥14,060; \$1,972 [\$1,885–\$2,059]) (Table 6). Median hospital expenditures were substantially lower than the median with a high level of dispersion (¥8,573; interquartile range ¥12,089), indicating a right-skewed distribution in health care costs. Hospital expenditures were substantially higher in level 1 (mean [95% CI] ¥17,119 [¥16,292–¥17,946]; \$2,506 [\$2,385–\$2,628]) than in level 3 (¥7,870 [¥5,775–

¥9,964]; \$1,152 [\$846–\$1,459]) cities, largely reflecting the higher adoption rate of active treatments in the more developed regions. In contrast, length of stay did not significantly differ according to city level, indicated by the overlap in the 95% CIs for length of stay across city levels.

Mean hospital expenditures were substantially lower for individuals who received palliative therapy (¥9,295 [¥7,956–¥10,633]; \$1,361 [\$1,165–\$1,557]) than for those who received active treatment during hospitalization (¥18,432 [¥17,662–¥19,202]; \$2,699 [\$2,586–\$2,811]) (Table 5). Among single active treatment approaches, average hospital expenditures for cases involving surgical resection (¥30,110 [¥19,941–¥40,279]; \$4,408 [\$2,920–\$5,897]) and radiotherapy were the highest (¥22,785 [¥16,048–¥29,522]; \$3,336 [\$2,350–\$4,322]), whereas hospital

**Table 6 – Hospital expenditures and length of stay among cases of HCC-related hospitalizations by year and city level, extrapolated to reflect HCC hospitalizations among the national population with urban BHI (N = 615,359).**

City level	Hospital expenditures			Length of stay (d)	
	Mean (95% CI) (¥)	Median (IQR) (¥)	% Change*	Mean (95% CI) (US \$)	Median (IQR)
All	13,467 (12,873–14,060)	8,573 (12,089)		1972 (1885–2059)	13 (15)
1	17,119 (16,292–17,946)	12,013 (15,722)		2506 (2385–2628)	13 (13)
2	12,341 (11,311–13,370)	8,489 (10,223)	–27.91	1807 (1656–1958)	13 (16)
3	7,870 (5,775–9,964)	4,560 (5,126)	–54.03	1152 (846–1459)	12 (21)

BHI, basic health insurance; CI, confidence interval; HCC, hepatocellular carcinoma; IQR, interquartile range.

\* Represents the % change in mean costs, in reference to city level 1 category.

expenditures for systemic therapy were generally the lowest (¥11,805 [¥11,821–¥13,267]; \$1,728 [\$1,611–\$1,846]). Average hospital expenditures for individuals who received multiple treatments during hospitalization were proportionately higher (¥22,495 [¥21,332–¥23,658]; \$3,294 [\$3,123–\$3,464]), mainly reflecting the added cost of the supplemental medical devices/supplies. The most common combination therapies involved the use of TCM as a supplement to other systemic treatment or transarterial intervention therapy, with average hospital expenditures totaling ¥16,339 (95% CI ¥14,664–¥18,014; \$2,392 [\$2,147–\$2,637]) and ¥16,559 (95% CI ¥15,272–¥17,845; \$2,424 [\$2,236–\$2,613]), respectively.

### BHI Reimbursement and Cost-Sharing

Most of the health care expenditures related to HCC hospitalizations were covered under the BHI plan (80%), and the remaining were paid out of pocket (9%) or through co-payments (11%) (Fig. 1). The ratio of BHI coverage fluctuated slightly over time (range 75%–86%), but co-payments generally remained consistent (range 8%–10%). Interestingly, hospitalizations from level 2 cities had the highest ratio of BHI coverage (85%) and the lowest ratio of out-of-pocket costs (6%), whereas those from level 1 cities had a much higher ratio of out-of-pocket expenses (18%). Trends in the BHI reimbursement ratios were consistent for individuals covered under employee versus resident BHI plans.

## Discussion

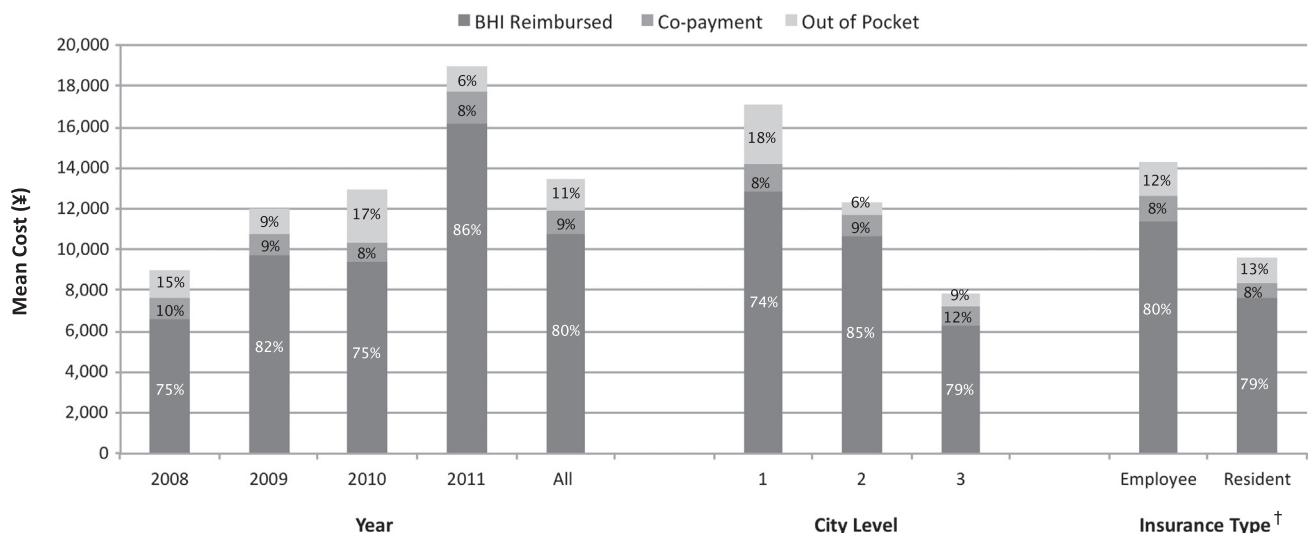
HCC is one of the most common and deadly cancers in East Asia, and China alone contributes more than half of all cases worldwide [3,18]. The China Ministry of Health has made great strides to improve the clinical management of HCC [8]; yet, little is known about current treatment approaches and associated costs in China [12–14]. The present study examined treatment patterns and health care expenditures for more than 3600 cases of HCC hospitalizations among the national population with urban BHI in China, representing more than 615,000 cases of HCC hospitalizations in the period 2008 to 2011. The results revealed that the

large majority received active treatment during hospitalization; however, nearly a third received only palliative care.

The results showed substantial disparities in the use of active treatments across different economic regions in China (all comparisons  $P < 0.0001$ ). More than 80% of the HCC cases from the heavily populated provincial capital and provincial-level cities (level 1) received active treatment during hospitalization, compared with only 46% of the cases from county-level cities (level 3). As a result, average hospital expenditures were substantially higher in level 1 (mean ¥17,119; \$2,506) than in level 3 (mean ¥7,870; \$1,152) cities, largely reflecting the higher adoption rate of active treatments.

Systemic and local therapies were the most common active treatments for HCC, administered at approximately 63% and 21% of hospitalizations, respectively. However, overall use of curative surgical treatments, including liver resection and liver transplant, was quite rare (2%). To some extent, the infrequent use of surgical treatments may reflect variations in availability across different geographic and economic regions in China, differences in hospital-level expertise, and an overall shortage in liver transplant donors. To a greater extent, however, these trends reflect the current reality where most patients are diagnosed in the advanced stages when surgical treatment is no longer an option [12]. Further research, using databases with more detailed information on tumor size and liver function at diagnosis, is needed to better understand whether patients with HCC who are clinically eligible for surgical treatment are not receiving guideline-recommended care.

TCM was the most commonly used therapy, administered at approximately half of all hospitalizations. According to current guideline recommendations in China, TCM is considered to be a useful and relatively low-cost supplemental therapy to reduce discomfort from treatment-related adverse effects and HCC-related symptoms [8]. Use of TCM as the primary treatment is generally not recommended because of a lack of clinical trial evidence suggesting clinical effectiveness. Consistent with guideline recommendations, TCM was generally used as a supplemental therapy, primarily in combination with other systemic therapy or transarterial intervention therapy, and less commonly used alone (39%). Use of TCM in combination with other treatments had a relatively modest impact on average hospital costs.



**Fig. 1 – Average HCC-related hospital expenditures and BHI reimbursement ratios\* by year, city level, and insurance type, extrapolated to reflect HCC hospitalizations among the national population with urban BHI (N = 615,359). BHI, basic health insurance; HCC, hepatocellular carcinoma. \*Reflects the ratio of mean costs for each BHI reimbursement category over the mean total costs of hospitalization. †Insurance type was unspecified for n = 47 cases of HCC-related hospitalizations included in the study sample.**

The results of this study are largely consistent with those from previous studies estimating the clinical impact of HCC in China. As noted in population-based studies of HCC incidence in China [3], most of the HCC cases in the present study were men, older than 40 years, and clustered in the more populated regions of China. A previous study of inpatient treatment patterns among patients with HCC treated across 10 hospital sites in China from 1996 to 1998 also found that approximately 29% of the patients received local therapies during hospitalization and use of radiotherapy was limited (0.7%) [12]. However, the study found that more than 46% of the patients received surgical resection, compared with only 2% of the patients in the present study. In interpreting these results, however, it is important to note that most of the HCC cases were identified from three large provincial hospitals in Shanghai, Guangzhou, and Nanning ( $n = 2659$ , 82%) [12]. As a result, patients treated at these hospitals may have had greater access to surgical technologies than did the broader population of patients with HCC in China. Further research is needed to understand whether the current trends in HCC treatment approaches observed in this study can be replicated using other large-scale databases.

To our knowledge, no other studies have assessed hospital expenditures related to HCC treatment using a large and representative sample of HCC cases in China. One small database study assessed direct and indirect costs of HCC among individuals with chronic hepatitis B diagnosed with HCC in Beijing ( $n = 53$ ) and Guangzhou ( $n = 48$ ) [14]. The study found that average hospital expenditures in the period 2006 to 2007 for patients with HCC treated in a tier 3 hospital ranged from \$2,638 (~¥20,075; 7.61 ¥/US \$ for 2007 [17]) to \$3,370 (~¥25,646) in Beijing and Guangzhou, respectively. In the present study, average hospital expenditures for level 1 cities were generally similar (mean [95% CI] ¥17,119 [¥16,292–¥17,946]; \$2,506 [\$2,385–\$2,628]). The study further analyzed average annual outpatient treatment costs, which totaled \$1,251 (¥9,520) in Beijing and \$868 (¥6,605) in Guangzhou [14]. Unfortunately, the CHIRA database did not contain information on outpatient services; however, these costs are comparatively low, representing approximately 20% of the total annual direct costs associated with HCC management in China [14].

This study provides valuable insights into current treatment practices and associated hospital expenditures among the population with urban BHI in China, which currently covers more than 90% of China's population in urban areas nationwide [15]. Nonetheless, the study does not capture HCC treatment patterns among the rural population in China, which represent nearly half (49%) of the total population in China [16]. Even in urban areas, this study found substantial disparities in the use of HCC treatments across city levels and hospital tiers. Previous research suggests that health care inequities are even larger in rural areas [19]. In the present study, the urban BHI reimbursed approximately 75% to 80% of inpatient expenditures for each hospitalization related to HCC in the period 2008 to 2011, whereas previous research suggests that individuals from rural areas are generally either uninsured or underinsured [15,19]. Although research conducted in rural areas of Qidong has identified improvements in survival disparities in comparison to developed regions, there is still a need for improving earlier detection and access to curative treatments [18].

Recognizing the wide socioeconomic inequities in health care coverage and access, China has launched its health care reform plan to ensure universal and affordable health coverage by 2020 [15]. Initiated in April 2009, the plan aims to expand health care coverage to more than 90% of the population, establish a national essential medicines system, improve the primary care delivery system, expand public health services, and pilot public hospital reforms [15,20]. Already, the program has expanded the role of primary care providers, established national formulary lists to

curb drug spending, and has initiated pilot programs in 16 cities to reform hospital governance and improve quality and efficiency of care [15]. Since 2011, policies have also identified priority diseases, including cirrhosis and cancer, for further reductions in co-payments. With these remarkable systemwide improvements, the climate surrounding the clinical management of HCC will likely change in the near future. The results of this study highlight current disparities in access to active treatment approaches for HCC in China, particularly across city levels and hospital tiers, to help prioritize areas of improvement.

Although the results of this study provide valuable insights into current resource use and costs associated with HCC in China, it has certain limitations: 1) As previously mentioned, the study database exclusively captured services provided during each hospitalization among individuals with urban BHI for each year, and does not capture outpatient treatments or any services provided in rural areas. In particular, molecular targeted drugs, such as sorafenib, can be purchased outside the hospital; as a result, this study may underestimate the use of these drugs. 2) Although the annual CHIRA surveys are designed to be representative of the urban BHI population through both multistage stratified sampling and systematic sampling methods, the annual samples are small relative to the extrapolated population and, as yet, there is no validation or comparison between the sampled and nonsampled populations. 3) In addition, because of database profile and availability, the study is based on event-level data (i.e., hospitalization), not patient-level data. As a result, the database does not capture the entire treatment course for patients who are readmitted to the hospital for HCC treatment. 4) Because the study surveyed data from hospital charge lists, systematic misclassification of devices and procedures across surveyed hospital sites may have occurred. To minimize this possibility, hospital charge lists were reviewed on a case-by-case basis, using a comprehensive device/agent list of more than 50,000 items to facilitate treatment classification. 5) Last, the use of the *International Classification of Diseases, Tenth Revision, Clinical Modification* code of C22.9 (Malignant neoplasm of liver, not specified as primary or secondary) might overestimate the number of HCC-related hospitalizations because it includes other more rare cases of liver cancer unrelated to hepatocellular carcinoma.

In conclusion, among the population with urban BHI in China, approximately two-thirds of the patients diagnosed with HCC in the period 2008 to 2011 received active treatment during hospitalization and average inpatient expenditures were more than ¥13,000 (\$1900). Only 2% of all patients with HCC received curative surgical treatments during hospitalization, indicating that patients were generally diagnosed in the more advanced stages. TCM was the most commonly used therapy, administered at approximately half of all hospitalizations, and was mainly used in combination with other HCC treatments. There were substantial disparities in the use of HCC treatments across different city levels and hospital tiers in China. As a result, hospital expenditures were considerably higher in the more developed regions. With the recent launch of health care reform in China, the landscape surrounding HCC management will likely change in the near future. The results of this study provide valuable insights into current resource use and costs for HCC, as well as treatment disparities, to help prioritize areas of improvement.

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