

Current status of and barriers to liver cancer treatment in China: a questionnaire-based study from the perspective of doctors

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Abstract

Background : Liver cancer is a severe public health problem worldwide, and it creates a relatively higher disease burden in China than in the Western world. Despite achieving notable progress in China, potential imbalances in some aspects of medical services for liver cancer may persist across different regions and hospitals. This warrants serious consideration of the actual status of and barriers to liver cancer treatment. We intended to explore the present status of and obstacles in liver cancer treatment.

Methods: In February 2021, a national multicenter cross-sectional study was conducted among 1,500 doctors from 31 provinces of mainland China using a self-administered online questionnaire. All doctors completed the questionnaire about their general information, perspectives on the current status of liver cancer treatment, and expectations for future treatment. Chi-square and logistic regression analyses were performed to explore the differences caused by the regions, professional titles, and hospital levels of the doctors.

Results: Treatment conditions, medications, and treatment strategies were inconsistent across different economic regions and hospitals of varied levels. With respect to obstacles in treatment, 76.59% of the doctors were unsatisfied with the current treatment for liver cancer. Important factors that influenced their satisfaction with the treatment for liver cancer included early diagnosis and the disclosure of true conditions to patients.

Conclusions: There persists unevenness in the treatment of liver cancer in China, besides barriers to treatment. Researchers should pay attention to the detection and treatment of liver cancer and the propagation of novel progress among doctors in underdeveloped areas.

1. Introduction

As a major public health issue, liver cancer is the sixth most diagnosed cancer and the second leading cause of cancer-related deaths worldwide (1). The incidence of liver cancer in China is higher than that in other countries (1, 2). Approximately 4,292,000 people in China are newly diagnosed with liver cancer each year, and approximately 2,814,000 patients die from the disease annually (3). The condition is often detected at an advanced stage, making the treatment extremely difficult, and the therapeutic effects are far from expectations (4). Therefore, liver cancer is a serious threat to the lives and health of the Chinese population.

With advances in the understanding of steps leading to liver cancer worldwide, researchers have proposed novel treatment strategies, including immunotherapy and targeted therapy (5). The constant development of novel techniques and drugs provides hope for further advances (6). The survival rates of patients with liver cancer have improved in certain countries (7). The Oncology Branch of the Chinese Medical Association revised and updated existing guidelines and issued the “Guidelines for diagnosis and treatment of primary liver cancer in China” to further standardize the diagnosis and treatment (8). In the recent two decades, China's overall medical and health services supply level has shown a significant

upward trend. The difference between the developed and underdeveloped regions has decreased. However, regional differences still clearly exist among different regions across the nation, with the overall pattern being that the medical resources are distributed more in the East than in the West. Potential unevenness of knowledge, therapeutic concepts, and economic status across different regions, hospitals, and individual doctors may exist in the Chinese society, which could create difficulties in the treatment of liver cancer. However, there are no reports on the actual status of liver cancer treatment in mainland China. Therefore, we aimed to conduct this national, multicenter study to investigate the present status of and obstacles in liver cancer treatment.

2. Methods

2.1 Study population

This research was conducted in 31 provinces in Mainland China. Participants were mainly liver disease-related physicians from departments, such as the liver disease and infection departments, at hospitals that were county-level and above. From each hospital, a maximum of six people could participate in the research. Table 1 summarizes the sociodemographic characteristics of the participants. Doctors were excluded from participation if they were unable to cooperate with the investigator or were unwilling to participate in the survey.

Table 1
Respondent characteristics

Demographic variables	No (n = 1021)	%
Gender		
Male	588	57.6
Female	433	42.4
Regions		
East	321	31.4
Central	351	34.4
West	255	25.0
Northeast	94	9.2
Work experience		
1–5 years	35	3.4
6–15 years	179	17.5
16–25 years	322	31.5
> 25 years	485	47.5
Title		
Resident	27	2.6
Attending physician	136	13.3
Deputy chief physician	356	34.9
Chief physician	502	49.2
Hospital level		
Secondary and lower hospital	265	26.0
Tertiary hospital	185	18.1
Tertiary first-class hospital	571	55.9

2.2 Questionnaire design

The questionnaire consisted of three sections (Appendix). The first section collected general information about the respondents, such as their gender, age, region, title, and hospitals (Table 1). The second section explored the current status of the diagnosis and treatment for liver cancer in China from the following three dimensions: economic status of the regions, levels of hospitals, and titles of doctors. We analyzed the treatment conditions (the equipment to determine the nature of the liver masses, the price and

adequacy of drugs, and the percentage of advanced cancer), medications (preferred immunotherapy and targeted drugs, methods to deal with adverse effects of targeted therapy, and attitude towards traditional Chinese medicine (TCM)), and treatment strategies (major considerations for prescribing, disclosure of the patients' true conditions, recommended hospitals for vague diagnosis, and individuals who will make the final decisions on treatment) for liver cancer. The last section comprised multiple-choice questions to collect information on expectations for future treatment.

2.3 Data collection

The survey was conducted via questionnaires. A total of 1,500 questionnaires were sent out through e-mail, and 1,021 of these were considered valid, which meant that participants completed the questionnaire within 10 minutes and answered all the questions in the questionnaire. Each subject signed the informed consent at the beginning of the study. Participants were able to withdraw at any stage of the survey, and privacy and confidentiality were ensured.

2.4 Data analysis

We used IBM SPSS Statistics for Windows, version 26.0, (IBM Corp, Armonk, NY) to process the research data. The variables are presented as frequency and ratio. To study the current status of liver cancer treatment, the participants were grouped according to their regions, professional titles, and the level of hospitals. We performed chi-square and logistic regression analyses to explore the differences caused by the above-mentioned factors. To investigate the barriers in liver cancer treatment, we grouped the doctors according to their satisfaction with the current treatment. The positive results of the chi-square analysis and other potential influencing factors were included in the multivariate logistic regression analysis to identify obstacles in the treatment of liver cancer. For all tests and analyses, a P-value < .05 was considered statistically significant.

3. Result

3.1 Treatment status

3.1.1 Differences in liver cancer treatment among different regions with different economic status

We identified statistical differences in the proportion of advanced liver cancer, attitude towards drug price, and major considerations for prescribing in different regions (Table 2).

Table 2

Differences in treatment conditions, medications, and treatment strategies among varied economic regions

		East China	Central China	West China	Northeast China	P-value
Treatment conditions						
Is the price of medication acceptable?	Yes	112 (34.9%)	84 (23.9%)	67 (26.3%)	24 (25.5%)	.011 *
	No	209 (65.1%)	267 (76.1%)	188 (73.7%)	70 (74.5%)	
Are drugs sufficient?	Yes	73 (22.7%)	87 (24.8%)	57 (22.4%)	33 (35.1%)	.075
	No	248 (77.3%)	264 (75.2%)	198 (77.6%)	61 (64.9%)	
What is your major drug source?	Imported	89 (27.7%)	118 (33.6%)	88 (34.5%)	43 (45.7%)	.011 *
	Domestic	188 (58.6%)	169 (48.1%)	132 (51.8%)	40 (42.6%)	
	Available	44 (13.7%)	64 (18.2%)	35 (13.7%)	11 (11.7%)	
What is the percentage of the advanced stage cancer?	< 40%	100 (31.2%)	85 (24.2%)	76 (29.8%)	39 (41.5%)	.012 *
	40–60%	129 (40.2%)	134 (38.2%)	90 (35.3%)	33 (35.1%)	
	> 60%	92 (28.7%)	132 (37.6%)	89 (34.9%)	22 (23.4%)	
What is the percentage of the first diagnosis?	< 20%	163 (50.8%)	183 (52.1%)	142 (55.7%)	52 (55.3%)	.621
	20–40%	94 (29.3%)	109 (31.1%)	66 (25.9%)	22 (23.4%)	
	> 40%	64 (19.9%)	59 (16.8%)	47 (18.4%)	20 (21.3%)	
Is the method of diagnosis enough?	Yes	166 (51.7%)	183 (52.1%)	117 (45.9%)	47 (50.0%)	.436
	No	155 (48.3%)	168 (47.9%)	138 (54.1%)	47 (50.0%)	
Is your hospital equipped to determine the nature of the liver masses?	Yes	312 (97.2%)	341 (97.2%)	244 (95.7%)	84 (89.4%)	.004*
Notes: * indicates statistical significance (P < 0.05).						

		East China	Central China	West China	Northeast China	P-value
	No	9 (2.8%)	10 (2.8%)	11 (4.3%)	10 (10.6%)	
Medication methods						
Do you advocate traditional Chinese medicine?	Yes	194 (60.4%)	243 (69.2%)	146 (57.3%)	51 (54.3%)	.005 *
	No	127 (39.6%)	108 (30.8%)	109 (42.7%)	43 (45.7%)	
What is your preferred immunotherapy drug?	PD-1	246 (76.6%)	273 (77.8%)	179 (70.2%)	75 (79.8%)	.054
	PD-L1	70 (21.8%)	62 (17.7%)	62 (24.3%)	16 (17.0%)	
	CTLA4	5 (1.6%)	16 (4.6%)	14 (5.5%)	3 (3.2%)	
How do you deal with adverse effects of targeted therapy?	Keeping the dosage and frequency	108 (33.6%)	116 (33.0%)	97 (38.0%)	35 (37.2%)	.844
	Reducing the dosage	174 (54.2%)	186 (53.0%)	125 (49.0%)	48 (51.1%)	
	Intermittent medication	39 (12.1%)	49 (14.0%)	33 (12.9%)	11 (11.7%)	
What is your preferred targeted drug?	Sorafenib	151 (47.0%)	200 (57.0%)	162 (63.5%)	59 (62.8%)	< .001 *
	Lenvatinib	145 (45.2%)	109 (31.1%)	65 (25.5%)	25 (26.6%)	
	Second-line drugs	25 (7.8%)	42 (12.0%)	28 (11.0%)	10 (10.6%)	
Treatment strategies						
What are your major considerations for prescribing?	Cost or insurance	95 (29.6%)	127 (36.2%)	97 (38.0%)	41 (43.6%)	.008 *
	Effectiveness	174 (54.2%)	174 (49.6%)	106 (41.6%)	40 (42.6%)	
	Availability	52 (16.2%)	50 (14.2%)	52 (20.4%)	13 (13.8%)	
What is your preferred treatment regimen?	Targeted therapy	36 (11.2%)	39 (11.1%)	28 (11.0%)	11 (11.7%)	.962
Notes: * indicates statistical significance (P < 0.05).						

		East China	Central China	West China	Northeast China	P-value
	Immunotherapy	5 (1.6%)	4 (1.1%)	3 (1.2%)	0 (0.0%)	
	Target therapy & Immunotherapy	272 (84.7%)	301 (85.8%)	217 (85.1%)	81 (86.2%)	
	Chemotherapy	8 (2.5%)	7 (2.0%)	7 (2.7%)	2 (2.1%)	
Do you support the disclosure of the patients' true conditions?	Yes	225 (70.1%)	205 (58.4%)	147 (57.6%)	55 (58.5%)	.004 *
	No	96 (29.9%)	146 (41.6%)	108 (42.4%)	39 (41.5%)	
Who will make the final decisions on treatment?	Doctors	37 (11.5%)	40 (11.4%)	46 (18.0%)	18 (19.1%)	.113
	Patients	75 (23.4%)	88 (25.1%)	61 (23.9%)	18 (19.1%)	
	Patients' family	209 (65.1%)	223 (63.5%)	148 (58.0%)	58 (61.7%)	
Is the pathological diagnosis important?	Yes	159 (49.5%)	172 (49.0%)	148 (58.0%)	40 (42.6%)	.036 *
	No	162 (50.5%)	179 (51.0%)	107 (42.0%)	54 (57.4%)	
What is your recommendation when the diagnosis is vague?	Local hospitals	83 (25.9%)	31 (8.8%)	23 (9.0%)	16 (17.0%)	< .001*
	Provincial capital hospitals	86 (26.8%)	206 (58.7%)	136 (53.3%)	34 (36.2%)	
	Renowned hospitals	152 (47.4%)	114 (32.5%)	96 (37.6%)	44 (46.8%)	
Notes: * indicates statistical significance (P < 0.05).						

In terms of treatment conditions, equipment to determine the nature of the liver masses was more complete in East China than in Northeast China (odds ratio, OR = 4.127, P = .003). Compared with those in East China, more doctors in Central and West China considered the drugs expensive (OR = .587 for Central China, P = .002; OR = .665 for West China, P = .027). In addition, the patients were at a higher risk of developing advanced cancer in central China than in East China (OR = 1.688, P = .009).

Regarding the medications for liver cancer, doctors in East China were more likely to select lenvatinib as the targeted drug, whereas those in other regions tended to opt for sorafenib (OR = .568 for Central China,

P = .001; OR = .418 for West China, P < .001; and OR = .441 for Northeast China, P = .002). TCM was less likely to be recommended in East China than in Central China (OR = .679, P = .017).

With regard to treatment strategies, recommendations to provincial capital hospitals were less preferred in East China than in other regions (OR = 6.413 for Central China P < .001; OR = 5.707 for West China, P < .001; and OR = 2.051 for Northeast China, P = .035). The recommendation for treatment in well-known hospitals across the country was more preferred in Central and West China than in East China (OR = 2.008 for Central China, P = .004; OR = 2.279 for West China, P = .002). Doctors in West China prioritized pathological examinations more than those in East China (OR = .710, P = .042). Informing patients of their true conditions was more supported in East China than in other regions. In addition, doctors in West and Northeast China paid more attention to cost or insurance than those in East China while prescribing drugs. Instead, they considered curative effects less important (OR = .597 for West China, P = .007; OR = .533 for Northeast China, P = .014).

3.1.2 Differences in liver cancer treatment among different levels of hospitals

The preferred targeted drugs and attitude towards TCM and informing patients of their true conditions were significantly different among different hospital levels (Table 3).

Table 3

Differences in treatment conditions, medications, and treatment strategies among different levels of hospitals

		Tertiary first-class hospital	Tertiary hospital	Secondary and lower hospital	P-value
Treatment conditions					
Is the price of medication acceptable?	Yes	398(69.7%)	148(80.0%)	188(70.9%)	.024*
	No	173(30.3%)	37(20.0%)	77(29.1%)	
Are drugs sufficient?	Yes	146(25.6%)	32(17.3%)	72(27.2%)	.038*
	No	425(74.4%)	153(82.7%)	193(72.8%)	
What is your major drug source?	Imported	188(32.9%)	66(35.7%)	84(31.7%)	.240
	Domestic	306(53.6%)	93(50.3%)	130(49.1%)	
	Available	77(13.5%)	26(14.1%)	51(19.2%)	
What is the percentage of the advanced stage cancer?	< 40%	165(28.9%)	48(25.9%)	87(32.8%)	.315
	40–60%	222(38.9%)	77(41.6%)	87(32.8%)	
	> 60%	184(32.2%)	60(32.4%)	91(34.3%)	
What is the percentage of first diagnosis?	< 20%	289(50.6%)	94(50.8%)	157(59.2%)	.058
	20–40%	161(28.2%)	58(31.4%)	72(27.2%)	
	> 40%	121(21.2%)	33(17.8%)	36(13.6%)	
Is the method of diagnosis enough?	Yes	290(50.8%)	81(43.8%)	142(53.6%)	.114
	No	281(49.2%)	104(56.2%)	123(46.4%)	
Is your hospital equipped to determine the nature of the liver masses?	Yes	564(98.8%)	180(97.3%)	237(89.4%)	< .001*
	No	7(1.2%)	5(2.7%)	28(10.6%)	
Medication methods					
Do you advocate traditional Chinese medicine?	Yes	330(57.8%)	115(62.2%)	189(71.3%)	< .001*
	No	241(42.2%)	70(37.8%)	76(28.7%)	
What is your preferred immunotherapy drug?	PD-1	445(77.9%)	134(72.4%)	194(73.2%)	.253
	PD-L1	106(18.6%)	41(22.2%)	63(23.8%)	
	CTLA4	20(3.5%)	10(5.4%)	8(3.0%)	

Notes: * indicates statistical significance ($P < 0.05$).

		Tertiary first-class hospital	Tertiary hospital	Secondary and lower hospital	P-value
How do you deal with adverse effects of targeted therapy?	Keeping the dosage and frequency	197(34.5%)	72(38.9%)	87(32.8%)	.020*
	Reducing the dosage	307(53.8%)	97(52.4%)	129(48.7%)	
	Intermittent medication	67(11.7%)	16(8.6%)	49(18.5%)	
What is your preferred targeted drug?	Sorafenib	326(57.1%)	102(55.1%)	144(54.3%)	< .001*
	Lenvatinib	209(36.6%)	56(30.3%)	79(29.8%)	
	Second-line drugs	36(6.3%)	27(14.6%)	42(15.8%)	
Treatment strategies					
What are your major considerations for prescribing?	Cost or insurance	199(34.9%)	68(36.8%)	93(35.1%)	.766
	Effectiveness	285(49.9%)	84(45.4%)	125(47.2%)	
	Availability	87(15.2%)	33(17.8%)	47(17.7%)	
What is your preferred treatment regimen?	Targeted therapy	58(10.2%)	20(10.8%)	36(13.6%)	.400
	Immunotherapy	8(1.4%)	3(1.6%)	1(0.4%)	
	Target therapy & Immunotherapy	489(85.6%)	157(84.9%)	225(84.9%)	
	Chemotherapy	16(2.8%)	5(2.7%)	3(1.1%)	
Do you support the disclosure of the patients' true conditions?	Yes	382(66.9%)	110(59.5%)	140(52.8%)	< .001*
	No	189(33.1%)	75(40.5%)	125(47.2%)	
Who will make the final decisions on treatment?	Doctors	84(14.7%)	22(11.9%)	35(13.2%)	.555
	Patients	129(22.6%)	52(28.1%)	61(23.0%)	
	Patients' family	358(62.7%)	111(60.0%)	169(63.8%)	
Is the pathological diagnosis important?	Yes	285(49.9%)	100(54.1%)	134(50.6%)	.616
	No	286(50.1%)	85(45.9%)	131(49.4%)	
What is your recommendation when the notes indicate it?	Local hospitals	65(11.4%)	27(14.6%)	61(23.0%)	< .001*

Notes: * indicates statistical significance (P < 0.05).

		Tertiary first-class hospital	Tertiary hospital	Secondary and lower hospital	P-value
	Provincial capital hospitals	199(34.9%)	109(58.9%)	154(58.1%)	
	Renowned hospitals	307(53.8%)	49(26.5%)	50(18.9%)	
Notes: * indicates statistical significance (P < 0.05).					

With regard to treatment conditions, the drugs were considered insufficient (OR = 1.642, P = .022) as well as costly (OR = .575, P = .007) in tertiary hospitals compared with tertiary first-class hospitals.

Regarding medications, upon encountering adverse effects of the targeted therapy, doctors in secondary and lower hospitals tended to recommend intermittent medications, whereas maintaining the dosage and frequency was more likely to be suggested in tertiary first-class hospitals (OR = 1.656, P = .027). Doctors in secondary and lower hospitals valued TCM more than those in tertiary first-class hospitals (OR = .551, P < .001).

Regarding treatment strategies, informing patients of their true conditions was more approved in tertiary first-class hospitals than in secondary and lower hospitals (OR = 1.805, P < .001). Compared with recommending patients to other local hospitals, doctors in lower-level hospitals were less inclined to recommend patients to renowned hospitals nationwide (OR = .384 for tertiary hospitals, P = .001; OR = .174 for secondary and lower hospitals, P < .001).

3.1.3 Differences in liver cancer treatment among doctors with different titles

We identified significant differences in the attitude towards informing patients of their true conditions, the importance of pathological diagnosis, and other factors (Table 4).

Table 4

Differences in treatment conditions, medications, and treatment strategies among doctors with varied titles

		Chief physicians	Deputy chief physicians	Attending physicians and residents	P-value
Treatment conditions					
Is the price of medication acceptable?	Yes	353(70.3%)	258(72.5%)	123(75.5%)	.427
	No	149(29.7%)	98(27.5%)	40(24.5%)	
Are drugs sufficient?	Yes	133(26.5%)	79(22.2%)	38(23.3)	.328
	No	369(73.5%)	277(77.8%)	125(76.7%)	
What is your major drug source?	Imported	156(31.1%)	132(37.1%)	50(30.7%)	.048*
	Domestic	274(54.6%)	177(49.7%)	78(47.9%)	
	Available	72(14.3%)	47(13.2%)	35(21.5%)	
What is the percentage of the advanced stage cancer?	< 40%	275(54.8%)	205(57.6%)	92(56.4%)	.302
	40–60%	182(36.3%)	113(31.7%)	49(30.1%)	
	> 60%	45(9.0%)	38(10.7%)	22(13.5%)	
What is the percentage of the first diagnosis?	< 20%	63(12.5%)	31(8.7%)	20(12.3%)	.264
	20–40%	5(1.0%)	3(0.8%)	4(2.5%)	
	> 40%	421(83.9%)	316(88.8%)	134(82.2%)	
Is the method of diagnosis enough?	Yes	239(47.6%)	180(50.6%)	94(57.7%)	.082
	No	263(52.4%)	176(49.4%)	69(42.3%)	
Is your hospital equipped to determine the nature of the liver masses?	Yes	488(97.2%)	344(96.6%)	149(91.4%)	.003*
	No	14(2.8%)	12(3.4%)	14(8.6%)	
Medication methods					
Do you advocate traditional Chinese medicine?	Yes	314(62.5%)	217(61.0%)	103(63.2%)	.851
	No	188(37.5%)	139(39.0%)	60(36.8%)	
What is your preferred immunotherapy drug?	PD-1	383(76.3%)	279(78.4%)	111(68.1%)	.011*
	PD-L1	100(19.9%)	61(17.1%)	49(30.1%)	
	CTLA4	19(3.8%)	16(4.5%)	3(1.8%)	
Notes: * indicates statistical significance (P < 0.05).					

		Chief physicians	Deputy chief physicians	Attending physicians and residents	P-value
How do you deal with adverse effects of targeted therapy?	Keeping the dosage and frequency	177(35.3%)	124(34.8%)	55(33.7%)	.688
	Reducing the dosage	268(53.4%)	181(50.8%)	84(51.5%)	
	Intermittent medication	57(11.4%)	51(14.3%)	24(14.7%)	
What is your preferred targeted drug?	Sorafenib	275(54.8%)	205(57.6%)	92(56.4%)	.302
	Lenvatinib	182(36.3%)	113(31.7%)	49(30.1%)	
	Second-line drugs	45(9.0%)	38(10.7%)	22(13.5%)	
Treatment strategies					
What are your major considerations for prescribing?	Cost or insurance	178(35.5%)	126(35.4%)	56(34.4%)	.794
	Effectiveness	249(49.6%)	166(46.6%)	79(48.5%)	
	Availability	75(14.9%)	64(18.0%)	28(17.2%)	
What is your preferred treatment regimen?	Targeted therapy	63(12.5%)	31(8.7%)	20(12.3%)	.264
	Immunotherapy	5(1.0%)	3(0.8%)	4(2.5%)	
	Target therapy & Immunotherapy	421(83.9%)	316(88.8%)	134(82.2%)	
	Chemotherapy	13(2.6%)	6(1.7%)	5(3.1%)	
Do you support the disclosure of the patients' true conditions?	Yes	336(66.9%)	215(60.4%)	81(49.7%)	< .001*
	No	166(33.1%)	141(39.6%)	82(50.3%)	
Who will make the final decisions on treatment?	Doctors	89(17.7%)	39(11.0%)	13(8.0%)	.004*
	Patients	121(24.1%)	86(24.2)	35(21.5%)	
	Patients' family	292(58.2%)	231(64.9%)	115(70.6%)	
Is the pathological diagnosis important?	Yes	230(45.8%)	191(53.7%)	98(60.1%)	.003*
	No	272(54.2%)	165(46.3%)	65(39.9%)	

Notes: * indicates statistical significance (P < 0.05).

		Chief physicians	Deputy chief physicians	Attending physicians and residents	P-value
What is your recommendation when the diagnosis is vague?	Local hospitals	61(12.2%)	64(18.0%)	28(17.2%)	< .001*
	Provincial capital hospitals	197(39.2%)	170(47.8%)	95(58.3%)	
	Renowned hospitals	244(48.6%)	122(34.3%)	40(24.5%)	
Notes: * indicates statistical significance (P < 0.05).					

Doctors with different professional titles did not display significant differences in the treatment conditions for liver cancer.

Regarding the medications, programmed death-ligand 1 (PD-L1) was more likely to be opted for immunotherapy by the attending physicians and residents than chief physicians than programmed cell death protein 1 (PD-1) (OR = 1.691, P = .010).

In terms of treatment strategies, doctors with higher professional titles preferred informing patients of their true conditions (OR = 1.327 for deputy chief physicians, P = .049; OR = 2.049 for attending physicians and residents, P < .001). The pathological diagnosis was prioritized more by those with lower professional titles (OR = 1.805 for deputy chief physicians, P = .005; OR = 1.805 for attending physicians and residents, P = .005). Chief physicians tended to select treatment solutions for the patients, whereas deputy chief physicians tended to let the patients select the treatment plan by themselves.

3.2 Obstacles in treatment

Physicians involved in this study were divided into two groups according to their response to the question regarding whether the current treatment for liver cancer was satisfactory. Figure 1 outlines the correlation between their satisfaction with the current treatment and other attitudes or considerations. Most doctors considered the treatment unsatisfactory; however, the percentage of doctors who were optimistic about the treatment varied across different regions (P = .015). A high percentage of patients diagnosed with advanced-stage disease was strongly associated with pessimistic attitudes of their doctors towards the current treatment for liver cancer (P < .001). The unsatisfied group was also correlated with pessimistic attitudes towards current diagnostic methods and medicine being sufficient for clinical needs (both P < .001). The doctors of both groups demonstrated significantly different methods to deal with adverse effects caused by the targeted drugs (P = .003), with more doctors in the satisfied group displaying a tendency to maintain the therapeutic dosage. In addition, those who supported informing the patients of their true conditions tended to be satisfied with the current treatment (P = .032).

The above-mentioned statistically significant correlations were included in the multivariate logistic regression analysis for further investigation. Moreover, we included the title of the doctors ($P = .696$), the hospital level ($P = .240$), and the preferred choice of targeted drugs ($P = .065$) as factors that potentially influenced doctors' attitude towards the current treatment, despite not reaching statistical significance in the χ^2 analysis.

The regions ($P = .015$), percentages of advanced stage ($P < .001$), preferred choice of targeted drugs ($P = .036$), methods to deal with adverse effects of targeted drugs ($P = .014$), informing patients of their real conditions ($P = .040$), and attitudes towards the current medicine ($P < .001$) were independently associated with the satisfaction of doctors with the current treatment for liver cancer, whereas the title of doctors ($P = .410$), hospital level ($P = .237$), and attitude towards the methods of diagnosis ($P = .087$) failed to display a correlation (Fig. 1). Compared with those from East China, doctors from other regions tended to be satisfied with the current treatment (OR = 1.548 for Middle China, $P = .037$; OR = 1.901 for West China, and $P = .004$; OR = 2.004 for Northeast China, $P = .016$). A higher percentage of advanced stage patients suggested that their doctors were less likely to be satisfied ($< 40\%$ as the reference, OR = .583 for 40%-60%, $P = .004$; OR = .325 for $> 60\%$, $P < .001$). A pessimistic attitude towards the current medicine was negatively related to their satisfaction with the treatment for liver cancer (OR = .274, $P < .001$). The preferred choice of second-line targeted drugs rather sorafenib and lenvatinib impaired the satisfaction of doctors (OR = .535, $P = .036$). Regarding the methods to deal with adverse effects caused by the targeted drugs, dosage reduction displayed a negative correlation with doctors' satisfaction (OR = .608, $P = .004$) than dosage maintenance. However, there was no significant difference in intermittent medications (OR = .693, $P = .172$). Interestingly, the willingness to inform patients of their true conditions was a protective indicator of the optimistic attitude towards the current treatment for liver cancer (OR = 1.425, $P = .040$).

3.3 Future expectations of doctors and patients

Nearly 90% of the doctors agreed with two treatment modes for liver cancer, as follows: (i) long-term treatment, in which the patients lived with tumors and the disease progressed slowly; (ii) to minimize the suffering of patients and improve their quality of lives. However, a complete cure was approved by approximately half of the doctors, and only one-fifth of the doctors agreed on not implementing any painful and risky treatment (Fig. 2A). More than 90% of the doctors displayed strong expectations for obtaining updated knowledge about the progress of liver cancer diagnosis and treatment by participating in academic conferences, accessing journal literature, and attending video lectures on professional websites (Fig. 2B). Moreover, approximately 90% of the doctors believed that patients with liver cancer were in demand of increased early diagnosis rate, more novel medications, the relief of economic burden, an improvement in the quality of life, and psychological counseling (Fig. 2C).

4. Discussion

This article used 1021 qualified questionnaires to analyze the current status of and obstacles in the treatment of liver cancer treatment in China. We identified unevenness in the treatment of liver cancer in

China, particularly across diverse economic regions. While most doctors are unhappy with the present treatment for liver cancer, early diagnosis and the revelation of true conditions to patients were recognized as the contributing factors.

In 2015, the incidence of liver cancer in the economically developed eastern region of China was 24.46/100,000, compared with 27.41/100,000 and 29.56/100,000 in the relatively underdeveloped central and western regions, respectively. Liver cancer-related mortality was highest in the western region, at 2.545/100,000, followed by 24.18/100,000 and 21.98/100,000 in the central and eastern regions, respectively (9). High mortality due to liver cancer in economically undeveloped areas was closely related to its high incidence, and relatively incomplete treatment conditions for liver cancer were likely an important influencing factor. With a non-negligible imbalance in the distribution of health resources across different regions of China, which is a developing country with economic diversity (10, 11), major cancer treatments and health service use were more concentrated in rich patients than in poor patients (12). In the present survey, we reported on significant differences in treatment conditions for liver cancer among different regions. Equipment to determine the nature of the liver masses, drug price, and tumor staging were more positive in economically developed regions. In addition, doctors paid more attention to cost or insurance, which were realistic considerations in the treatment for liver cancer, compared with curative effects, in less developed regions. Therefore, more attention should be paid to alleviating the imbalance in the treatment of liver cancer among different regions in China.

The vague symptoms of liver cancer at an early stage lead to the diagnosis at an advanced stage in most patients, which excludes the possibility of local treatments, such as curative hepatic resection, tumor ablation, or trans-arterial therapy. Therefore, the systemic treatment of advanced liver cancer has attracted much attention. The current first-line treatment includes sorafenib, introduced in 2007 (13), and lenvatinib (14), introduced in 2017. Furthermore, second-line treatments, such as regorafenib and cabozantinib, (14) are available. In addition, PD-1 and PD-L1 are available for liver cancer immunotherapy (15). With remarkable advancements in targeted therapy and immunotherapy for advanced liver cancer, selecting the most suitable medication for patients has become a new concern. Most doctors preferred lenvatinib, particularly in tertiary first-class hospitals. A phase III randomized, multicenter, open-label, non-inferiority trial on first-line targeted therapy drugs demonstrated that lenvatinib achieved better overall survival benefits and longer median progression-free survival than sorafenib (16). Moreover, lenvatinib is less costly than sorafenib. In this study, lenvatinib was more preferred in East China than in other regions, compared with the conventional first-line targeted therapy drug sorafenib. This may be attributed to limited availability of updated knowledge about liver cancer treatment to doctors in Central, West, and Northeast China than to those in East China.

Targeted therapies, such as sorafenib, lenvatinib, regorafenib, and cabozantinib, are associated with adverse events that negatively impact the quality of life of patients (17). Severe drug resistance to targeted therapy is maintained during long-term application (18). Low-cost TCM can be used for comprehensive treatment with fewer adverse events and multitarget regulation characteristics. In the early stages of tumor development, TCM can be used as a therapeutic regimen to alleviate protumor

factors. Meanwhile, it can work as an adjuvant therapy to improve the survival, alleviate drug-related adverse effects, and improve quality of life in the intermediate and terminal stages. Therefore, the application of Chinese medicine has been advocated in different stages of liver cancer development (19). As reported by the World Health Organization, traditional medicines principally derived from plants serve as a fundamental part of the primary health care of the major population in developing countries (20). China is the origin of TCM and is the largest developing country with a population of 1.4 billion. In this study, two-third of the doctors approved the use of TCM in the treatment of liver cancer. However, clinicians of tertiary first-class hospitals, which were the highest-ranked hospitals, were inclined to disapprove of the application of TCM. This was possibly attributed to the availability of adequate medications to doctors from tertiary first-class hospitals.

Informing patients with cancer about the exact diagnoses and poor prognoses remains debatable, without a consensus on this issue (21). In this study, 60% of the doctors believed that patients with liver cancer should be informed of their true condition. Further analysis demonstrated that telling the truth was more supported by doctors who were satisfied with the treatment results. In addition, doctors from economically developed areas and high-level hospitals and those with higher professional titles were more likely to disclose the diagnosis. Furthermore, the negative consequences of non-disclosure are not limited to the neglect of patients' natural rights. Poor physical conditions (22), increased mental illnesses, and decreased trust in family members and doctors (23) have been reported in patients during the process of seeking out the truth. Thus, disclosing the truth about the diagnosis and prognosis of patients seems beneficial. Nonetheless, further research is warranted to confirm the internal link between disclosure and the treatment for liver cancer.

The prognosis of liver cancer is considerably driven by the tumor stage (24). The 5-year survival rate in patients detected at an early stage approaches 70% (25), whereas those with advanced tumors have much poorer prognoses, with a median survival of 1–2 years (26). A higher percentage of advanced-stage cancer suggested that the doctors were less likely to be satisfied in our research. The implementation of primary preventive measures for liver cancer in China is an important way to reduce its disease burden; however, clinicians should consider its secondary prevention, which involves detecting the lesions timely, thus improving the treatment efficacy and reducing the mortality (9).

In this study, hospital levels and doctor titles were not associated with the satisfaction of doctors with the treatment effect. Compared with doctors from East China, those from other regions tended to be satisfied with the current treatment for liver cancer, thereby suggesting possible higher expectations for treatment efficacy in East China.

This study had some limitations. First, this questionnaire-based study was based on a cross-sectional survey, which could not reflect the dynamic changes in the doctors' perspectives on the treatment of liver cancer. In addition, doctors invited to complete the questionnaire were not randomly sampled, which could compromise their worldwide representativeness. Despite a small proportion of patients being suitable for surgery, we barely discussed surgical treatment, with the questionnaire focusing on the

systemic treatment for liver cancer. However, this nationwide study with a relatively large sample provided valuable references for unraveling the current status of and obstacles in the treatment of liver cancer.

5. Conclusion

This is the first questionnaire-based study to investigate the current status of and obstacles in the diagnosis and treatment of liver cancer from doctors' perspectives in China. Our findings highlighted the need to pay attention to improving the subpar level of detection and treatment for liver cancer in underdeveloped areas. In addition, early diagnosis, disclosure of true conditions to the patients, choice of system therapy drugs, and application of Chinese medicine were positively correlated with the doctors' satisfaction with liver cancer treatment. This necessitates efforts to promote the current status of liver cancer treatment and achieve better medical services for patients with liver cancer.

Abbreviations

OR odds ratio

PD-L1 programmed death-ligand 1

PD-1 programmed cell death protein 1

TCM traditional Chinese medicine

Declarations

1. Ethics approval and consent to participate

This study was performed in accordance with the 1964 Helsinki Declaration, and was approved by the Ethics Committee of Beijing You'an Hospital. Informed consent was obtained from all individual participants included in the study.

2. Consent for publication

Not applicable.

3. Availability of data and materials

All data generated or analyzed during this study are presented in the article and appendix materials.

4. Competing interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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6. Authors' contributions

Q W and H Z analyzed the data and wrote the manuscript that led to submission; X H and X L collected the data; S C, X H and Y C revised the manuscript; M L and Z D designed this study and provided financial support for this study. All authors read and approved the manuscript.

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References

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA: a cancer journal for clinicians*. 2015;65(2):87–108.
2. Allemani C, Weir HK, Carreira H, Harewood R, Spika D, Wang XS, et al. Global surveillance of cancer survival 1995–2009: analysis of individual data for 25,676,887 patients from 279 population-based registries in 67 countries (CONCORD-2). *Lancet (London, England)*. 2015;385(9972):977–1010.
3. Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, et al. Cancer statistics in China, 2015. *CA: a cancer journal for clinicians*. 2016;66(2):115–32.
4. Fu J, Wang H. Precision diagnosis and treatment of liver cancer in China. *Cancer Lett*. 2018;412:283–8.
5. Liu CY, Chen KF, Chen PJ. Treatment of Liver Cancer. *Cold Spring Harb Perspect Med*. 2015;5(9):a021535.
6. Anwanwan D, Singh SK, Singh S, Saikam V, Singh R. Challenges in liver cancer and possible treatment approaches. *Biochim Biophys Acta Rev Cancer*. 2020;1873(1):188314.
7. Kudo M. Surveillance, diagnosis, treatment, and outcome of liver cancer in Japan. *Liver cancer*. 2015;4(1):39–50.
8. Zhou J, Sun H, Wang Z, Cong W, Wang J, Zeng M, et al. Guidelines for the Diagnosis and Treatment of Hepatocellular Carcinoma (2019 Edition). *Liver cancer*. 2020;9(6):682–720.
9. An L, Zeng HM, Zheng RS, Zhang SW, Sun KX, Zou XN, et al. [Liver cancer epidemiology in China, 2015]. *Zhonghua zhong liu za zhi [Chinese journal of oncology]*. 2019;41(10):721–7.

10. Wang Y, Li Y, Qin S, Kong Y, Yu X, Guo K, et al. The disequilibrium in the distribution of the primary health workforce among eight economic regions and between rural and urban areas in China. *Int J Equity Health*. 2020;19(1):28.
11. Zhang L, Wang F, Wang L, Wang W, Liu B, Liu J, et al. Prevalence of chronic kidney disease in China: a cross-sectional survey. *The Lancet*. 2012;379(9818):815–22.
12. Zhao Y, Zhang L, Fu Y, Wang M, Zhang L. Socioeconomic Disparities in Cancer Treatment, Service Utilization and Catastrophic Health Expenditure in China: A Cross-Sectional Analysis. *Int J Environ Res Public Health*. 2020;17(4).
13. Kudo M. Targeted and immune therapies for hepatocellular carcinoma: Predictions for 2019 and beyond. *World journal of gastroenterology*. 2019;25(7):789–807.
14. Kudo M. Systemic Therapy for Hepatocellular Carcinoma: Latest Advances. *Cancers*. 2018;10(11).
15. Chang Lee R, Tebbutt N. Systemic treatment of advanced hepatocellular cancer: new hope on the horizon. *Expert review of anticancer therapy*. 2019;19(4):343–53.
16. Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *Lancet (London, England)*. 2018;391(10126):1163–73.
17. Rimassa L, Danesi R, Pressiani T, Merle P. Management of adverse events associated with tyrosine kinase inhibitors: Improving outcomes for patients with hepatocellular carcinoma. *Cancer Treat Rev*. 2019;77:20–8.
18. Ranieri G, Marech I, Lorusso V, Goffredo V, Paradiso A, Ribatti D, et al. Molecular targeting agents associated with transarterial chemoembolization or radiofrequency ablation in hepatocarcinoma treatment. *World journal of gastroenterology*. 2014;20(2):486–97.
19. Jia W, Wang L. Using Traditional Chinese Medicine to Treat Hepatocellular Carcinoma by Targeting Tumor Immunity. *Evid Based Complement Alternat Med*. 2020;2020:9843486.
20. Liu C, Yang S, Wang K, Bao X, Liu Y, Zhou S, et al. Alkaloids from Traditional Chinese Medicine against hepatocellular carcinoma. *Biomed Pharmacother*. 2019;120:109543.
21. Kendall S. Being asked not to tell: nurses' experiences of caring for cancer patients not told their diagnosis. *Journal of clinical nursing*. 2006;15(9):1149–57.
22. Pasipanodya EC, Parrish BP, Laurenceau JP, Cohen LH, Siegel SD, Graber EC, et al. Social constraints on disclosure predict daily well-being in couples coping with early-stage breast cancer. *Journal of family psychology: JFP : journal of the Division of Family Psychology of the American Psychological Association (Division 43)*. 2012;26(4):661–7.
23. Shahidi J. Not telling the truth: circumstances leading to concealment of diagnosis and prognosis from cancer patients. *European journal of cancer care*. 2010;19(5):589–93.
24. El-Serag HB. Epidemiology of viral hepatitis and hepatocellular carcinoma. *Gastroenterology*. 2012;142(6):1264-73.e1.

25. Llovet JM, Fuster J, Bruix J. Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma: resection versus transplantation. *Hepatology* (Baltimore, Md). 1999;30(6):1434–40.
26. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. Sorafenib in advanced hepatocellular carcinoma. *The New England journal of medicine*. 2008;359(4):378–90.

Figures

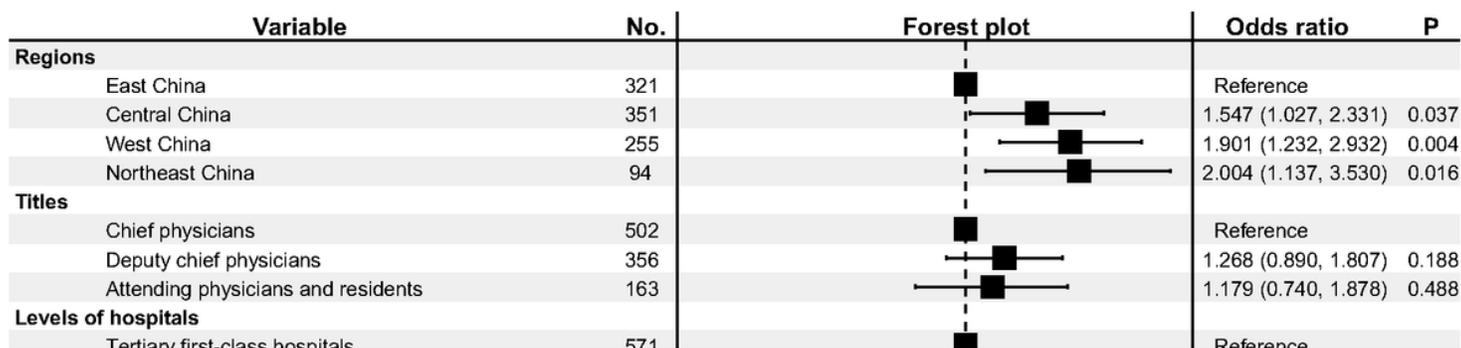


Figure 1

Differences in baseline demographics and treatments between satisfied and dissatisfied physicians.

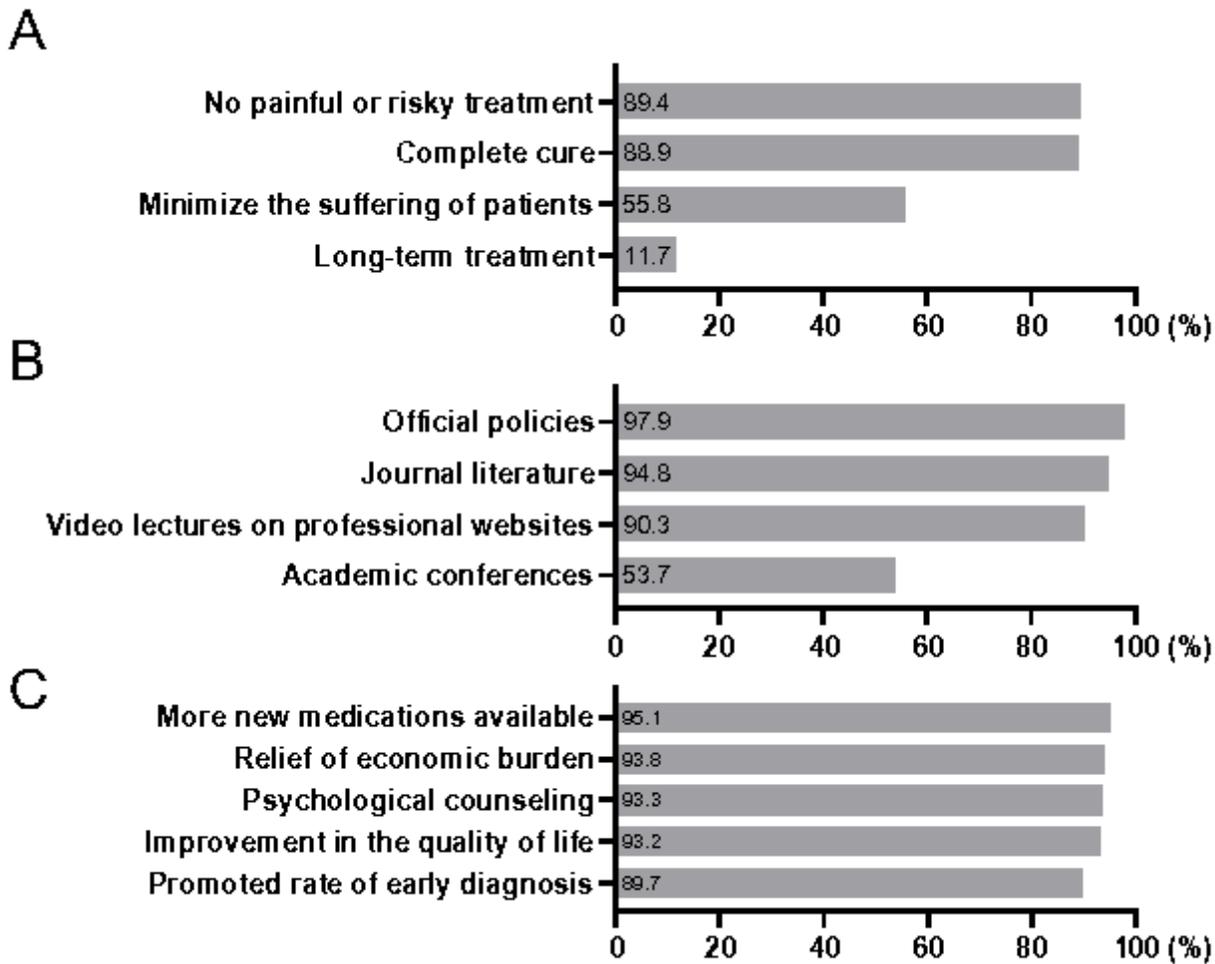


Figure 2

Future expectations of doctors and patients

(A) Which of the following treatment models do you approve for liver cancer?

(B) How would you like to get access to the updated knowledge on the progress of liver cancer diagnosis and treatment?

(C) What do patients with liver cancer need?

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Appendix220312.docx](#)