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End-of-life cost and its determinants for cancer patients in urban China: a population-based retrospective study

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ABSTRACT

Objective This study aimed to define the end-of-life (EOL) healthcare utilisation and its cost and determinants for cancer patients and to proactively inform related strategies in mainland China.

Design A population-based retrospective study.

Setting and participants Data from 894 cancer patients were collected in urban Yichang, China from 01 July 2015 to 30 June 2017.

Outcome measures Emergency department (ED) visits, outpatient and inpatient hospitalisation services, intensive care unit (ICU) admission and total costs were used as the main outcomes.

Results In this study, 66.8% of the 894 patients were male, and the average age was 60.4 years. Among these patients, 37.6% died at home, and patients had an average of 4.86 outpatient services, 2.23 inpatient hospitalisation services and 1.44 ED visits. Additionally, 5.9% of these patients visited the ICU at least once. During the EOL periods, the costs in the last 6 months, 3 months, 1 month and 1 week were US$18 234, US$13 043, US$6349 and US$2085, respectively. The cost increased dramatically as death approached. The estimation results of generalised linear regression models showed that aggressive care substantially affected expenditure. Patients with Urban Employee Basic Medical Insurance spent more than those with Urban Resident-based Basic Medical Insurance or the New Rural Cooperative Medical Scheme. The place of death and the survival time are also risk factors for increased EOL cost.

Conclusion The findings suggested that the EOL cost for cancer patients is associated with aggressive care, insurance type and survival time. Timing palliative care is urgently needed to address ineffective and irrational healthcare utilisation and to reduce costs.

Ethics and dissemination This study was approved by the Ethics Committee of the Tongji Medical College, Huazhong University of Science and Technology (IORG No.: IORG0003571). All the data used in this study were de-identified.

Strengths and limitations

- This population-based study was the first to systematically estimate the end-of-life (EOL) health expenditure for cancer patients in mainland China. It is important to estimate the palliative care demand and guide its system building.
- This study introduced EOL healthcare utilisation and cost in China and quantified the relationship between them.
- This study will guide health policy regarding the delivery of high-quality, cost-effective cancer care systems.
- Given the anonymity of the data, we cannot obtain the health records from primary care facilities and healthcare utilisation outside Yichang. Thus, the EOL healthcare cost might have been underestimated.
- The unique socioeconomic status of the selected population may reduce the generalisability of our findings. Further studies on the provincial or national levels are essential to provide systematic evidence.

INTRODUCTION

Cancer is the leading cause of mortality and accounted for 14.1 million new cancer cases, 32.6 million individuals living with cancer, and 8.2 million deaths worldwide in 2012.[1] Cancer greatly affects low-income and middle-income countries and is expected to account for 70% of the newly reported cancer cases worldwide by 2030.[2] Given the considerable share of the total health expenditure on cancer (approximately, 6.0% in European countries[3] and 9.2% in Taiwan[4 5]) and the great gap in the cancer healthcare delivery system between developed and developing countries,[2] evaluating the end-of-life (EOL) cost and identifying its key determinants have been a worldwide concern.[6]

Several systematic reviews have noted that in-home EOL care can improve patient satisfaction, as well as reducing inpatient hospitalisation utilisation and hospital death.[7 8] These reviews also indicated that aggressive procedures do not improve the quality of life.[9 10] However, health expenditure and utilisation show large geographic variations among patients in the USA with high medical care intensity during the EOL period, thereby producing poor outcomes and confusing the patients' preference.[11–13]

EOL hospitalisation relatively lacks value worldwide with its unsustainable expenditure,[14 15] whereas palliative care is relatively underutilised, though it is proven to save costs.[16] These phenomena thereby aggravated inequality among patients with different socioeconomic statuses and decrease overall efficacy.[17–19]

According to the Fifth Chinese National Health Services Survey in 2013, the incidences of malignant neoplasms in China reached 0.35% and 0.23% in the urban and rural areas, respectively, higher than those in 2008.[20] The most common cancer types in China are lung and stomach cancers, accounting for 22% of new global cancer cases and deaths, and liver and oesophageal cancers, accounting for 27% of new global cancer cases and deaths.[21] Although the age-standardised 5-year relative survival rate has increased from 30.9% (2003–2005) to 40.5% (2012–2015), geographical differences in cancer survival still remain.[22] The Program of Cancer Prevention and Control in China (2004–2010) reported that the decreased mortality rates and the substantial geographic variation in the survival rates have become a burden to the health system, especially with the high out-of-pocket (OOP) expenditure.[21 23] The Economist Intelligence Unit noted that China ranked 71 among 80 countries in a survey on the quality of death.[24] A cross-sectional study in China found that OOP expenditures for cancer patients accounted for 57.5% of the annual household income.[25] This percentage is higher than that (23.7%) in the USA.[26] Given the limitations of medical insurance coverage and reimbursement rate, cancer patients and their families face extremely high health expenditures.[27 28] Hospital type, education, insurance type and household income can also predict the expenditure of cancer care.[25] Research on the EOL healthcare cost in mainland China has received considerable interest in terms of policy. Studies have noted that some treatments for cancer patients in tertiary hospitals are unnecessary, especially during the patients' last days.[21 29 30] However, cross-sectional studies mainly focus on the total healthcare cost limited to the single-institutional level; thus, underestimating the actual expenditure.[31] A population-based study examining EOL healthcare expenditure and its determinants is not explored, especially in terms of the real-world data of the regional health system in China. Therefore, in this study, we aimed (1) to define the EOL healthcare utilisation and its cost among cancer patients, (2) to investigate the determinants of EOL healthcare cost and (3) to inform related policy making and implementation in China.

METHODS

Data collection

On the basis of the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10), and the WHO version for 2016,[32] the present study selected patients diagnosed with C00–C97 in urban Yichang, China. Residents who died from cancer from 01 July 2015 to 30 June 2017 were continuously enrolled in this study. The demographic information of cancer patients, data on the place of death and cancer type were collected from the National Population Death Registration and Management System established in 2013. All healthcare utilisation and cost data were provided by the Yichang Health Management Center affiliated with the Yichang Center for Disease Control and Prevention integrating hospital information system, health insurance database and population information database with the identification card number.

Variables

Patients were divided into three groups: younger than 65 years, 65–80 years old and 80 years or older when diagnosed.[21] Survival was divided into four types,[33] namely, education, marital status, cancer type and medical insurance type. The place of death was routinely coded as a binary variable. The recommended benchmark measures for terminal cancer care were used to identify the aggressive and palliative procedures.[34–38] The main outcome was healthcare utilisation, including outpatient and inpatient hospitalisation services, emergency department (ED) visits and intensive care unit (ICU) admission, and the EOL expenditures. To compare the results, we converted the cost data to the international purchasing power parities using the rate for Chinese Yuan to US$ (¥2.03=US$1) in health from the International Comparison Program 2011.[39]

Patient and public involvement

All the data were provided by the Yichang Health Management Center affiliated with the Yichang Center for Disease Control and Prevention and de-identified before statistical analysis. Therefore, identifiable cancer patients were not involved in the recruitment or implementation of this study.

Statistical analysis

Descriptive analysis was used to describe the detailed information about the enrolled population. Generalised linear models were used to evaluate the mechanism of the effect of independent variables on the EOL cost because the EOL data were severely positively skewed.[40 41] Four regression models were conducted for patients with different lengths of survival, the EOL costs were the outcome variables, and the independent variables were as follows: (1) age (<65, 65–80 and ≥80 years), (2) gender (male/female), (3) education level, (4) marital status, (5) first cancer type, (6) medical insurance type, (7) number of outpatient services, (8) number of ED visits, (9) number of inpatient hospitalisation services, (10) number of ICU admissions and (11) survival. All the above-mentioned data were calculated with Stata V.14.0. Differences at $p<0.05$ were considered statistically significant.

Table 1 Basic characteristics of the enrolled patients

Demographic characteristics	Patients (n=894)	%
Age (year), median (range)	69 (25 to 102)	
<65	315	35.2
65–80	440	49.2
>80	139	15.6
Gender		
Male	597	66.8
Female	297	33.2
Marital status		
Unmarried	9	1.0
Married	742	83.0
Widow	126	14.2
Divorced	17	1.9
Insurance type		
Urban Employee Basic Medical Insurance	518	57.9
Urban Resident-based Basic Medical Insurance	181	20.3
New Rural Cooperative Medical Scheme	195	21.8
Education		
≤Junior school	675	75.5
Senior school	141	15.8
≥College	78	8.7
Place of death		
Health institution	558	62.4
Home	336	37.6
Survival time from cancer diagnosis*		
<3 months	260	29.3
3–6 months	231	26.0
7–12 months	219	24.6
>12 months	179	20.1

RESULTS

Characteristics of the patients and ICD-10 code

As shown in table 1, 894 patients were included in this study. The median age of enrolled patients was 69 (range, 25–102) years, 35.2% of which were younger than 65 years, and 15.6% were older than 80 years. Two-thirds (66.8%) of these patients were male, and 83% of the 894 patients were married. A total of 57.9%, 20.3% and 21.8% of the patients were enrolled in Urban Employee Basic Medical Insurance (UEBMI), Urban Resident-based Basic Medical Insurance (URBMI) and the New Rural Cooperative Medical Scheme (NRCMS), respectively. About 75.5% of the patients finished junior school or below, and 44.7% survived for at least 6 months. A total of 62.4% of the patients died in hospitals. As shown in table 2, the most common cancer types were lung cancer (34.7%), liver cancer (14.0%) and colorectal cancer (9.5%).

Healthcare utilisation and cost

As shown in table 3, the average numbers of outpatient and inpatient hospitalisation services were 4.86 and 2.23 times per capita, respectively. The ED and ICU visits were 1.44 and 0.06 times per capita, respectively. A total of 5.9% (53/894) of the patients were admitted once into the ICU, and 49.7% (444/894) visited the ED only once. The average expenditures per capita during the last 1 week, 1 month, 3 months and 6 months were US$2085, US$6349, US$13 043 and US$18 235, respectively. The population-level costs in the last 1 week, 1 month and 3 months were, on average, 11.4%, 34.8% and 71.5%, respectively, of the last 6 months.

Determinants of EOL healthcare cost

As shown in table 4, all the results revealed proportionate changes in health expenditures among the different groups. In the four generalised linear models, gender, marital status and education levels of the patients showed statistically insignificant differences in the costs during the four different EOL periods. High EOL healthcare expenditure was associated with the age of first diagnosis, insurance type, place of death, survival after diagnosis and aggressive care services.

For age, we can see that patients aged between 65 and 80 years spent 66.8% and 34.7% more than the oldest groups (OR=1.322, p=0.033, 95% CI=1.022 to 1.710) and younger patients (OR=1.347, p=0.036, 95% CI=1.02 to 1.779) on the cost during the last 6 months and 3 months, respectively. Patients with UEBMI spent more than those with URBMI and the NRCMS in the last 6 months (OR=1.79, p<0.001, 95% CI=1.313 to 2.44; OR=1.480, p=0.002, 95% CI=1.160 to 1.887), 3 months (OR=2.172, p<0.001, 95% CI=1.464 to 3.222; OR=1.668, p=0.002, 95% CI=1.206 to 2.305) and 1 month (OR=2.132, p<0.001, 95% CI=1.46 to 3.113; OR=1.581, p=0.004, 95% CI=1.161 to 2.152). Patients with the NRCMS spent between 98.2% (OR=1.982, p=0.005, 95% CI=1.228 to 3.2) and 153.2% (OR=2.532, p<0.001, 95% CI=1.548 to 4.139) higher than the URBMI group during the last week. Patients who died in the hospitals spent 1.488-fold (p=0.002, 95% CI=1.187 to 1.864), 2.323-fold (p<0.001, 95% CI=1.712 to 3.151), 3.481-fold (p<0.001, 95% CI=2.585 to 4.688) and 3.246-fold higher (p<0.001, 95% CI=2.427 to 4.341) than those who died at home during the four EOL periods.

For the survival time, the difference between the patients who survived for 7–12 months and those who survived for longer than 12 months was not statistically significant (OR=1.026, p=0.787, 95% CI=0.854 to 1.231). The cost during the last 3 months for patients who survived longer than 12 months was 31.7% (OR=0.682, p=0.032, 95% CI=0.482 to 0.968) less than that of the reference group (<3–6 months). Differences between the four groups were also observed on the cost during the last 1 week. The

Table 2 The ICD-10 codes of first cancer type when diagnosed

First cancer type	Codes	Patients (n=894)	%
Lung	C34.x	310	34.7
Stomach	C16.x	60	6.7
Colorectum	C18.x, C19.x and C20.x	85	9.5
Liver	C22.x	125	14.0
Pancreas	C25.xl	39	4.4
Biliary tract	C23.x and C24.x	19	2.1
Blood	C81.x-C86.x and C91.x-C95.x	0	0
Prostate	C61.x	15	1.7
Breast	C50.x	28	3.1
Others	C00.x-C15.x, C17.x, C21.x, C26.x, C30.x-C33.x, C37.x-C41.x, C43.x-C49.x, C51.x-C58.x, C60.x, C62.x, C80.x, C88.x, C90.x, C96.x and C97.x	213	23.8

ICD-10, International Statistical Classification of Diseases and Related Health Problems, 10th Revision.

mean costs estimated during the last 1 week of the groups who survived for 3–6 months (OR=0.624, p=0.023, 95% CI=0.416 to 0.937), 7–12 months (OR=0.54, p=0.007, 95% CI=0.346 to 0.845) and longer than 12 months (OR=0.346, p<0.001, 95% CI=0.199 to 0.599) were less than patients who survived less than 3 months. Moreover, patients with 7–12 months (OR=0.554, p=0.017, 95% CI=0.341 to 0.900) and longer survival spent less than patients surviving between 3 and 6 months (OR=1.602, p=0.023, 95% CI=1.067 to 2.405). Patients with more than 12 months of survival also spent (OR=0.640, p=0.048, 95% CI=0.411 to 0.997) less than those who survived 7–12 months. For the inpatient hospitalisation and ICU services, once the inpatient hospitalisation and ICU services increased by one time, the cost with the four periods increased 30.5% (p<0.001, 95% CI=1.25 to 1.362) and 83.5% (p<0.001, 95% CI=1.292 to 2.606), 35.3% (p<0.001, 95% CI=1.187 to 1.864) and 113.7% (p<0.001, 95% CI=1.253 to 1.461), 35.7% (p<0.001, 95% CI=1.248 to 1.477) and 202.5% (p<0.001, 95% CI=1.994 to 5.152), and 35.3% (p<0.001, 95% CI=1.245 to 1.471) and 222.9% (p<0.001, 95% CI=2.07 to 5.038), respectively.

DISCUSSION

Many studies have noted that aggressive treatment during the EOL of a patient can lead to higher costs.[17 18] In this study, patients with end-stage cancer had high rates of hospitalisation and an average admission of 2.23 times in the last 6 months of life. A total of 5.9% of the cancer patients had used ICU services during the EOL period. A comparative study in seven developed countries showed that 40.3% of patients were admitted to the ICU in the USA and approximately 18% of patients were admitted to the ICU in the six other countries.[42] The mean cost is US$18 234 per capita, which is lower than those of developed countries, such as Canada (US$21 840), Norway (US$19 783), the USA (US$18 500),[42] South Korea, Japan and Taiwan (annual cost of US$68 773 in 2010).[43] The cost increased dramatically as death approached, similar to the results that SEER-Medicare costs revealed.[44] We

Table 3 Healthcare services utilisation and cost of the enrolled patients*

Variable	Mean	Standard error	Median	Range
Outpatient services	4.86	7.67	2	59
Inpatient hospitalisation services	2.23	2.16	2	39
Emergency department visit	1.44	2.91	1	13
Intensive care unit admission	0.06	0.25	0	2
Cost during the last 1 week	2085	6829	1195	66 437
Cost during the last 1 month	6349	18 469	6640	195 182
Cost during the last 3 months	13 043	37 434	13 901	431 158
Cost during the last 6 months	18 234	34 583	19 276	723 144

*The international purchasing power parities using rate for Chinese Yuan to US$ (¥2.03=US$1) in health from International Comparison Program 2011.

Table 4 Results of the four generalised linear models

		Model 1			Model 2			Model 3			Model 4		
Variables	**Group**	**OR**	**P values**	**95% CI**	**OR**	**P values**	**95% CI**	**OR**	**P values**	**95% CI**	**OR**	**P values**	**95% CI**
Gender(e)	Female	0.906	0.305	(0.751 to 1.094)	1.016	0.903	(0.789 to 1.308)	0.824	0.127	(0.643 to 1.056)	0.946	0.722	(0.694 to 1.288)
Age(f)	65–80 (2)	1.098	0.369	(0.895 to 1.347)	**1.347**	**0.036**	(1.02 to 1.779)	1.017	0.901	(0.779 to 1.329)	1.241	0.212	(0.885 to 1.74)
	>80 (3)	0.831	0.224	(0.616 to 1.12)	1.043	0.834	(0.702 to 1.551)	0.767	0.156	(0.531 to 1.107)	0.932	0.778	(0.568 to 1.527)
Insurance type(g)	NRCMS (2)	1.21	**0.230**	(0.886 to 1.652)	1.302	0.215	(0.858 to 1.977)	1.349	0.117	(0.928 to 1.961)	1.982	**0.005**	(1.228 to 3.2)
	UEBMI (3)	1.79	**<0.001**	(1.313 to 2.44)	2.172	**<0.001**	(1.464 to 3.222)	2.132	**<0.001**	(1.46 to 3.113)	2.532	**<0.001**	(1.548 to 4.139)
Marital status(h)	Married (1)	2.457	0.069	(0.933 to 6.468)	1.205	0.757	(0.371 to 3.919)	1.07	0.906	(0.349 to 3.276)	1.239	0.764	(0.305 to 5.031)
	Widow (2)	2.163	0.132	(0.792 to 5.905)	0.893	0.855	(0.264 to 3.017)	1.27	0.687	(0.397 to 4.064)	1.004	0.996	(0.231 to 4.355)
	Divorced (3)	2.504	0.112	(0.808 to 7.763)	1.074	0.922	(0.257 to 4.489)	1.248	0.746	(0.327 to 4.772)	1.572	0.607	(0.28 to 8.824)
Education(i)	Senior (2)	1.143	0.242	(0.913 to 1.431)	1.004	0.978	(0.73 to 1.382)	1.043	0.791	(0.767 to 1.418)	0.921	0.702	(0.605 to 1.403)
	≥College (3)	0.996	0.981	(0.737 to 1.346)	1.227	0.358	(0.794 to 1.897)	1.255	0.277	(0.833 to 1.891)	1.244	0.406	(0.743 to 2.086)
POD(j)	Hospital	1.488	**0.001**	(1.187 to 1.864)	2.323	**<0.001**	(1.712 to 3.151)	3.481	**<0.001**	(2.585 to 4.688)	5.371	**<0.001**	(3.653 to 7.897)
Survival(k)	3–6 months (2)							0.648	**0.008**	(0.47 to 0.893)	0.624	**0.023**	(0.416 to 0.937)
	7–12 months (3)				0.827	0.186	(0.623 to 0.096)	0.661	**0.02**	(0.466 to 0.937)	0.54	**0.007**	(0.346 to 0.845)
	>12 months (4)	1.026	**0.787**	(0.854 to 1.231)	0.683	**0.032**	(0.482 to 0.968)	0.507	**0.002**	(0.333 to 0.771)	0.346	**<0.001**	(0.199 to 0.599)
OS		1.007	0.13	(0.998 to 1.016)	0.998	0.842	(0.981 to 1.015)	0.993	0.441	(0.974 to 1.011)	1.005	0.679	(0.98 to 1.031)
ED		0.997	0.824	(0.975 to 1.02)	0.98	0.267	(0.945 to 1.016)	0.98	0.343	(0.941 to 1.022)	0.971	0.273	(0.922 to 1.023)
IHS		1.305	**<0.001**	(1.25 to 1.362)	1.353	**0.001**	(1.253 to 1.461)	1.357	**<0.001**	(1.248 to 1.477)	1.369	**<0.001**	(1.229 to 1.526)
ICU		1.835	**0.001**	(1.292 to 2.606)	2.378	**<0.001**	(1.438 to 3.932)	3.205	**<0.001**	(1.994 to 5.152)	3.456	**<0.001**	(3.456 to 6.299)
No		398			629			**807**			868		

Model 1: cost during the last 6 months; Model 2: cost during the last 3 months; Model 3: cost during the last 1 month and Model 4: cost during the last 1 week. #Reference: (e) Male; (f) <65; (g) URBMI; (h) Unmarried; (i) Junior or below; (j) Home; (k) <3 months in Model 1 and 2, we took the patients survived 7–12 months and 3–6 months as reference, respectively. Results of additional models: Model 1: Age-group: two versus three (OR=1.322, p=0.033, 95% CI=1.022 to 1.710) and Insurance type: three versus two (OR=1.480, p=0.002, 95% CI=1.160 to 1.887); Model 2: Insurance type: three versus two (OR=1.668, p=0.002, 95% CI=1.206 to 2.305); Model 3: Insurance type: three versus two (OR=1.581, p=0.004, 95% CI=1.161 to 2.152) and Model 4: Survival: four versus two (OR=0.554, p=0.017, 95% CI=0.341 to 0.900); five versus two (OR=1.602, p=0.023, 95% CI=1.067 to 2.405) and four versus three (OR=0.640, p=0.048, 95% CI=0.411 to 0.997).

ED, Emergency Department visits, ICU, intensive care unit; IHS, inpatient hospitalisation services; No, number of observation; NRCMS, New Rural Cooperative Medical Scheme; OS, outpatient services; POD, place of death; UEBMI, Urban Employee Basic Medical Insurance; URBMI, Urban Resident-based Basic Medical Insurance.

also found that cost increased rapidly in the last 1 month, indicating excessive treatment and ineffective medical expenses. Considering the current status of EOL healthcare utilisation and the expenditures trajectory, the risk factors of the high EOL cost must be investigated.

In this study, several determinants were identified that were associated with the higher EOL cost. First, high EOL healthcare expenditure was associated with young age due to high hospital care intensity. This result is consistent with those of previous studies.[44–46] Many studies indicated that gender[46 47] and marital status[48] were not facilitative determinants of the increased EOL healthcare cost. Second, striking disparities were also observed among the different medical insurances, which is consistent with the study of Zeng *et al*.[49] Patients enrolled in the NRCMS spent more than those enrolled in URBMI during the last week. This phenomenon may be related to the traditional Chinese concept of death and suggests ineffective and irrational utilisation and low-value service provision.[50] However, this finding is inconsistent with the conclusion that patients prefer to receive relatively passive care in Taiwan.[43] Third, cost also depends on the place of death, and cost increased rapidly as death approached. The percentage (62.42%) of patients who died in hospitals in China was higher than patients in the USA (29.5%) and Canada (52%).[42] However, in the USA, 74% of non-hospice beneficiaries died in hospitals or skilled nursing facilities compared with the 14% who died receiving hospice care.[51] Fourth, the effect of survival on EOL cost differed among patients with different survival periods suggesting that the patients with poor cancer prognosis in the present study may have high rates of aggressive care at the EOL period. Moreover, inpatient hospitalisation and ICU services were risk factors for high EOL cost. An ED visit in China is not a risk factor for the increase in cost, which may be due to the current operation process wherein patients are usually hospitalised once admitted during ED visits.[52] One study by Obermeyer *et al*[53] revealed that Medicare fee-for-service beneficiaries with poor-prognosis cancer, which were enrolled in the hospice care programme, used less hospitalisation, ICU admissions and invasive procedures with a lower total cost than the non-hospice group. Hence, there is great potential for the development of hospice care programmes in China.

The abovementioned results indicated that numerous health resources in China might be ineffectively used, similar to other countries.[54] Patients receiving hospice care or early palliative care intervention could experience better management of pain and symptom[55] and an improved likelihood of dying at home if that was preferred.[12 52] Given the potential benefits of hospice care and early palliative care intervention, the timely initiation of hospice or home care may reduce low-value cancer healthcare services in China. The overuse of aggressive care during the EOL period can be harmful from the perspective of the patients, including additional care-related financial strain,[14] no reduction in the bereavement of their families.[18 56] Given the potential benefits of hospice care and early palliative care intervention, the healthcare need of patients should be satisfied. The timely initiation of hospice or home care may reduce the low-value cancer healthcare services in China.

CONCLUSION

According to real-world data, this study provides comprehensive evidence on healthcare utilisation and expenditure for cancer patients during the EOL period in China. This study revealed the potentially ineffective and irrational utilisation of medical resources and the urgency to improve hospice care systems in China. Overall, this study may aid in formulating specific measures to optimise the current cancer care delivery system, especially at the developing stages of the hospice care system. Future studies should focus on the evaluation of the current system on the provincial or national levels.

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Contributors ZL, ZP, PZ, LZ and BL designed this study; ZL, ZP, CX and FL collected and analyzed the data; ZL drafted the manuscript; RH, SJ, BL and LZ modified the manuscript. All authors read and approved the final manuscript.

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Competing interests None declared.

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