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Economic effects of childhood acute lymphoblastic leukemia on families: evidence from China

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Abstract:

Objectives: To estimate the economic burden in families of children with acute lymphoblastic leukemia (ALL) in China.

Design: A single-site, cross-sectional survey of primary caretakers of patients with childhood ALL was performed.

Setting and participants: We analyzed the total cost incurred upon the completion of the first three-phase treatment (induction, consolidation, and intensification), which require intensive hospitalization. Eligible patients were: a) diagnosed with ALL between 2010 and 2012 at Shanghai Children's Medical Center, b) 0-14 years at diagnosis, and c) completed the first three phases of treatment at SCMC. The data was collected between October 2014 and December 2014.

Outcome measures: We decomposed the estimate of the total cost into three categories (a) direct medical cost, which was further divided into outpatient and inpatient costs; (b) direct non-medical cost, which referred to expenses incurred in relation to the illness; and (c) indirect cost due to productivity loss.

Results: Total of 161 patients were included in the study. Among three cost categories, direct medical cost accounted for about 51.7% of the overall cost, and the rest of 48.3% of the total cost was attributed to direct non-medical cost and indirect cost. Regarding families with different household registration type (rural versus urban), the distributions of costs among the three categories were different. Productivity loss contributed a much higher weight in total cost for the urban families than for the rural families. In addition, rural families spent most of their money on the treatment of ALL.

Conclusions: Families of children with ALL experience a wide range of costs. Ongoing investigation of families' costs will yield a rich understanding of the disease costs, formulate the basis of cost assessments, and lend insight into practice and policy changes aimed at lessening the economic impact of this burden.

Strengths and limitations of this study

- Research on determining the costs associated with a childhood acute lymphoblastic leukemia is rare and the nature of these costs is poorly understood in developing countries.
- We filled the gap by estimating the economic burden in families with a child with acute lymphoblastic leukemia in China.
- We decomposed the estimate of the total cost into three categories: direct medical cost, direct non-medical cost and indirect cost due to productivity loss.
- Our findings help yield a rich understanding of the disease costs, formulate the basis of cost assessments, and lend insight into practice and policy changes aimed at lessening the economic impact of this burden.
- Majority cost measures were based on parents' self-report and there might exist recall bias for some measures.

Key words: Economic burden; Child; Acute lymphoblastic leukemia; Family; China

Introduction

Acute lymphoblastic leukemia (ALL) is the most common malignant disease among children, accounting for about 25% of all childhood cancers[1]. It not only seriously endangers the physical and mental health of child and their parents, but also imposes enormous financial risks to the family[2-7]. On the one hand, the costs of treatment of ALL and illness-related expenses are immense, on the other hand, parents may have to reduce their work hours, or give up paid work to care for their child resulting in loss of income.

Various studies have been conducted in developed countries to determine the costs associated with a childhood cancer from a family perspective[8]. In these studies, the economic and financial impact of childhood cancer on families was examined across two primary categories: direct costs including the actual monetary expenditures related to the illness such as those associated with transport, food, accommodation, *etc.*[3, 4, 9, 10], and indirect costs including the value of productivity loss such as cut on work time, take unpaid leave and loss of job[4-7, 11-13]. Although it is hard to make a precise comparison on the magnitudes of financial costs to families due to variations in study design, all studies reported substantial family financial burden due to childhood cancer treatment. Specifically, two Canadian studies found that income loss due to work disruption and out-of-pocket expenses were estimated at over 30% of after-tax family income[2, 6], and one American study reported that over 50% of the poorest families experienced annual income losses of more than 40%[11].

While childhood cancer was shown to have huge adverse economic consequences on

households in developed countries, it is likely to have even more severe effect on households in developing countries, which are usually characterized by poorly developed health care system. In developing countries, such as China, although the government has realized the importance of reforming the current system, the process is far from perfect. On the one hand, there are huge differences in the allocation of medical resources between rural and urban areas, and among different provinces. High quality medical resources are mainly distributed in large central cities such as Beijing, Shanghai, Guangzhou, *etc*. Therefore, families with seriously ill child have to go to these cities to receive treatment for better chance of survival. As a result, the corresponding non-medical out-of-pocket expenses may increase dramatically due to extra expenditure on transport, accommodation and others. In addition, it is also hard for the parents of sick child to keep their jobs if they have to leave their places of residence. On the other hand, the health insurance system in China is segmented, different programs for different population groups and independently implemented in different provinces, even in cities[14]. As a result, patients who seek treatment in other cities may not be able to get reimbursement even they have insurance at their hometowns. Therefore, these families may have to bear most of the medical cost. As can be seen, under current health care system, the economic burden on the families of children with ALL could be devastated. Lacking financial aids from various sources may cause these families to fall from above to below the poverty line, or even give up treatment.

However, research on determining the costs associated with a childhood ALL is rare and the nature of these costs is poorly understood in developing countries[15-18]. It makes policy planning in the context of essential medicines, national fiscal policy towards childhood ALL and donor

policy difficult without any reliable estimates of costs. The purpose of this paper was to fill the gap by estimating the economic burden in families of children with ALL. Specifically, we decomposed the estimates of costs into three categories (a) direct medical costs, which was further divided into outpatient and inpatient costs; (b) direct non-medical costs, which referred to expenses incurred in relation to the illness; and (c) indirect costs due to productivity loss.

Methods

Data and study population

The treatment of childhood ALL usually has four phases: induction, consolidation, intensification, and maintenance and lasts 2 to 3 years[19]. In the present paper, we estimated total cost incurred upon the completion of the first three-phase treatment (induction, consolidation, and intensification), which require intensive hospitalization. Therefore, eligible patients were: a) diagnosed with ALL between 2010 and 2012 at Shanghai Children's Medical Center (SCMC), b) 0-14 years at diagnosis, and c) completed the first three phases of treatment at SCMC. The data was collected between October 2014 and December 2014. The time between diagnosis and completion of the questionnaire was required to be greater than two years in order to capture parents' employment experiences throughout the treatment. Since quite a lot of the families were not living in Shanghai, face-to-face interviews were difficult to conduct. As an alternative, we conducted telephone interviews on the parents. Only one parent of the child, who self-identified as the major responsibility for daily care of the child answered the questionnaire. The interview lasted about 30-45 minutes. We obtained approval from the Institutional Review Board of Shanghai Children's Medical Center to conduct the study.

Pre-testing

In order to ensure the rationality and accuracy of the questionnaire, we pre-tested the questionnaire with 15 parents of children with ALL who were randomly picked during their follow-up visits to the center. During this period, we revised the questionnaire many times to make sure that parents understood the questions, did not feel uncomfortable, and were aware of their costs reflecting the costs incurred during the induction, consolidation and intensification phases, not the costs associated with the maintenance therapy.

Measures

The questionnaire included three modules. The first module asked questions about socio-demographic characteristics of parents and their child. The second module included direct non-medical cost questions. The last module focused on the indirect cost questions. More specifically, the details of these modules were shown as follows:

Demographic and socio-economic variables: child age at diagnosis, child gender and whether child had health insurance, parent's age at diagnosis, the highest degree of parental education (elementary or lower, high/vocational school or lower, or college and above), family monthly income, family size, household registration type (Hukou types: rural versus urban), place of residence (Shanghai versus other provinces).

Direct non-medical cost variables: direct non-medical costs included expenses related to illness during the period of the first three stages of treatment. Specifically, parent was asked to provide

information on: a) expenses on accommodation per month including rent and utility fee; b) expenses on transportation; c) increased expenses on food and nutritional supplements per month; d) expenses on hygiene cleaning products and auxiliary treatment equipment, such as ultraviolet disinfection lamp, air purifier, humidifier, *etc.*; e) expenses on gifts and treats including electrical devices (e.g. computer, TV, video games *etc.*) and network fee.

Indirect cost variables: indirect costs were the costs associated with the lost productivity due to illness. In the present paper, parent was asked to provide information on employment status at diagnosis and during the treatment period, changes in role or hours worked since diagnosis and absence from work. Informants were also asked to complete this section for their partner. The indirect costs were measured by lost earnings using the human capital approach.

Direct medical cost variables: The computerized database of medical costs at SCMC was established in 1998. The database strictly adheres to medical administration regulations. All outpatient and hospitalization costs were recorded according to their names/case numbers. In the present paper, overall outpatient and inpatient costs for each child with ALL between the confirmation of diagnosis at SCMC and the completion of the intensification therapy were collected. In addition, the database also contained information on inpatient expenses paid by insurance for local patients.

Patient and public involvement

No patients were involved in the development of research question, the outcome measures, the

design or implementation of the study. There are no plans about dissemination of the results.

Statistical Analysis

All data were reviewed for completeness and relevance. Data were entered into Microsoft Excel and imported into the STATA 13 statistical package (Stata Corporation, College Station, TX, USA) for analysis. Descriptive statistics were used to describe the sample characteristics and to categorize the type and value of cost categories and items. The amounts of all cost categories were projected to the estimates that incurred during the treatment. Total cost was then computed as the sum of all cost categories for the sample.

Results

Medical expenses and parental contact information of a total of 171 patients were extracted from SCMC database. We contacted the 171 parents using the telephone numbers provided in the database and 161 parents gave the consents before we conducted the interview. The 10 failed calls were due to either loss of contact or refuse to participate.

Table 1 presents the child, parent, and family characteristics. Mean patient age at diagnosis was 4.9 years (standard deviation (SD) = 3.3 years; range: 0-14 years), the majority were male (58.4%). Average length of therapy (induction, consolidation, and intensification) was 13.8 months (SD = 9.9 months). In terms of health insurance at the time of diagnosis, 103 children (63.9%) had at least one type of health insurance, however, 56 (34.8%) had no insurance at all. The mean age of parents at diagnosis was 32.6 years (SD = 4.28 years), 41.9% of the parents'

highest education level was middle school or below, 20% was high/vocational school or below and 38.1% was college or above. In terms of household characteristics, the average family size was 4.1 (SD = 1.1), 71 households (44.1%) had rural registration and only 45 households (28.0%) were local residences (Shanghai). The average household monthly income at diagnosis was RMB8341.72 (USD1218.04)[1].

Table 2 describes the parents' employment statuses at the time of diagnosis and during the treatment period. On diagnosis, 35(22%) fathers worked in government, state-owned enterprise (SOE) or public sector, 109(68.6%) worked in private sector or self-employed, 11(6.9%) were farmers and 4(2.5%) were unemployed. During the treatment, 47 working fathers managed to keep their employment status unchanged, 13 completely stopped working, and 97 reported to take extended absences from work. The average length of absences was 14.4 months (SD = 11.1). Regarding mothers, on diagnosis, 32(20.1%) worked in government, SOE or public sector, 73(45.9) worked in private sector or self-employed, 16(10.1%) were farmers and 38(23.9%) were unemployed or doing housework. Among those who had a job, 14.8% did not change their employment status, 6.6% stopped working, and the majority of working mothers (78.7%) took extended absences from work. The average length of absences was 18.1 months (SD = 10.8).

The costs of direct medical expenses during the treatment are given in Table 3 (Panel A). The average total medical expenses between diagnosis and completion of the intensification

[1] The average exchange rate between RMB and USD in 2010 is 6.8485.

treatment per person was RMB115768.90 (USD16904.27). Medical expenses were then divided into two subcategories: outpatient and inpatient costs. The average total expense at clinic per patient was RMB38506.89 (USD5622.68), and the average total in-hospital expense per patient was RMB77262.05 (USD11281.60).

Panel B of Table 3 presents the costs of direct non-medical expenses incurred during the treatment for the whole sample and for the urban and rural households separately. Specifically, the average cost for the whole sample was RMB45896.16 (USD6701.63) with the largest expenditure on accommodation, followed by those on food and nutritional supplements, on gifts and treats, on hygiene cleaning products and auxiliary treatment equipment, and the smallest portion was on transportation. Regarding the expenditures on rural and urban households respectively, the average direct non-medical cost was RMB50993.63 (USD7445.96) for the urban sample, whereas the amount was RMB39434.57 (USD5758.13) for the rural counterparts. The urban households spent the largest proportion of expenses on accommodation (50.0%), whereas the largest proportion was on food and nutritional supplements (38.5%) for the rural households.

The indirect cost incurred during the treatment is shown in Panel C of Table 3. The average productivity loss due to a childhood ALL for the whole sample was RMB62403.41 (USD9111.98). In addition, we found that the urban households incurred much higher productivity loss than the rural households (RMB88457.34 versus RMB29377.31 or USD12916.31 versus USD4289.60).

Table 4 summarizes the total cost incurred during the treatment and the proportion of each component. On average, the total cost for the whole sample was RMB224068.47 (USD32717.89). The direct medical cost accounted for more than half of the total cost (51.7%), followed by the indirect cost (27.9%) and direct non-medical cost (20.5%). For the urban households, direct medical cost contributed 46.5% of total costs, whereas the number became 61.3% for the rural households. In addition, the indirect cost for the urban households accounted for 33.9% of total cost, however, it only made up 16.5% of total cost for the rural households.

Discussion

A cancer diagnosis in childhood can substantially affect the physical, psychosocial, and socioeconomic well-being of patients and their families. Yet, research on determining the costs associated with a childhood ALL is rare and the nature of these costs is poorly understood, especially in developing countries. The present study provides a breakdown of families' costs and resource use and an in-depth understanding of families' financial burden. We found that the financial burden faced by the Chinese families of children with ALL was tremendous. Among three cost categories, direct medical cost accounted for about 51.7% of the overall cost, and the rest of 48.3% of the total cost was attributed to direct non-medical cost and indirect cost. Regarding families with different household registration type (rural versus urban), the distributions of costs among the three categories were different. Productivity loss contributed a much higher weight in total cost for the urban families than for the rural families. In addition, rural families spent most of their money on the treatment of ALL.

Unlike most of developed countries where cost of treatment is borne mainly by the public sector and by health insurance[4, 13], patients in developing countries have to bear a big portion of direct medical cost[16, 17]. Shanghai is one of the most economically developed regions in China, and has relatively well developed health insurance system and the most generous reimbursement system compared to other provinces of China. However, based on the insurance reimbursement data extracted from the SCMC database, the reimbursement rate for hospitalization expenses was just 49.8%. For those who were not eligible for the local health insurance policy (79.5% of the total sample), they had to fund the treatment on their own and tried to get the reimbursement at their hometown later. According to the health insurance regulations of China, if the patients choose to receive treatment in other provinces or cities, or in non-designated hospitals, the reimbursement rate could be very low or none at all. Although we were unable to determine this from our study directly, one report did have shown that the actual reimbursement rate is less than 50% for most of the rural families of children with leukemia, of which around 27% of children can only get 30% of reimbursement[19]. In addition, in the questionnaire we asked the parents "any comments or suggestions on current insurance reimbursement policy", more than half of the non-local parents (57.8%) mentioned that reimbursement rate was too low. Specifically, the low reimbursement was mainly due to the following reasons: there existed a big gap on reimbursement rate between local and non-local residents; outpatient and imported medicines were not covered by the insurance; and the reimbursement procedure across provinces was tedious and time consuming, and the actual reimbursement rate was low, so some parents chose to forgo reimbursement.

In addition to direct medical cost, direct non-medical cost accounted for 20.5% of the total cost. Around 45% of the total direct non-medical expenses were spent on accommodation. Although the very poor families can receive 30 days of accommodation at the center at very low price[15], the space is limited and the 30-day rental period is far from enough. Most non-local families had to rent a room or an apartment near the hospital for about RMB1000-RMB5000 (USD146.02-USD730.09) per month for average 12 months. Food and nutritional supplements accounted for about 35% of the total direct non-medical cost. As described by Tsimicalis et al., increased expenses on food were to accommodate the child's fluctuating weight, satisfy food cravings, taste alterations, *etc.*[10]. In contrast to the previous literature which found that transport took a significant portion of family financial cost[9, 10, 20], we found that transport only contributed to 2.7% of the total direct non-medical cost. That was because most of non-local families chose to rent near the hospital, which saved travel cost. Although the local families needed to travel "back and forth" constantly from home to the hospital, the amount was much less than those on accommodation and food.

Following diagnosis, 85% of working mothers and 70% of working fathers gave up all paid employment or took unpaid extended leaves in our sample. These numbers were much higher than those reported in the previous studies[4, 6, 12, 13]. The possible explanation was that in our sample, the majority families were from other provinces (72%), and it was hard for only one parent to handle all the issues related to treatment, accommodation, food, *etc.*, therefore, both parents had to quit their jobs or took unpaid leaves during the treatment. In addition, although

indirect cost only accounted for about 28% of the total cost, the patient families might experience long-term negative effects of the illness on their financial situation. Specifically, consistent with previous literature[3, 21], most of the families in our sample (59%) had to borrow during the treatment. In addition, Wakefeild *et al.* (2014) found that it was quite challenge for parents to return to work after their child's cancer treatment due to familial, psychological and practical factors[22]. As a result, the two factors may make the affected families more difficult to recover from economic hardship.

Our data indicated that the families with high socio-economic status were more likely to receive treatment in high quality medical facilities. Specifically, according to data from National Bureau of Statistics of China, in 2010, the annual urban per capita income was RMB19109.4, and the amount was RMB5919.0 in the rural areas[23]. However, our data indicated that the sample urban per capita income was 1.7 times that of the national urban average and the ratio became 2.7 times for the rural per capita income. In addition, our data showed that the total cost was 2.12 times of the sample urban family's annual income, and was 2.49 times of the sample rural family's annual income. This finding indicated that even for these high socio-economic families, the economic burden of child ALL was huge, especially for the rural families.

Our findings have very important policy implications. First, policy makers should make effort on simplifying the reimbursement procedure across provinces and eliminating the huge disparities in reimbursement ratio across regions; second, our sample indicated 35% of patients did not have any insurance at diagnosis, although we did not have direct data on why these

parents chose not to purchase insurance for their child, previous study has shown that lack of knowledge or the concept of insurance could be a major barrier for people from participating the insurance program[24], therefore, the government should work hard on educating people regarding the different programs; third, patients with cancer and their families may need ongoing financial management with a designated financial advisor well beyond the initial treatment phase to help them manage debt, access resources to cope with direct and indirect costs of cancer treatment and maintain patients' and families' financial capacity later in life.

There are limitations in this study. First, majority measures were based on parents' self-report, and there may exist recall bias for some measures. However, to minimize recall bias, before conducting formal interview, we contacted them one week in advance and asked parents to recall and list out the details of all the expenses during the treatment. After the interview, we double checked data. If there was inconsistency in the data, we called back to clarify. Second, while the generalizability of this study may be somewhat limited as we focused on one hospital, SCMC, as one of the primary pediatric tertiary care centers in China, it provides treatment of severe disease in children around China (Our data showed that 72% of patients were non-local residents). Therefore, our results are likely applicable to other geographic areas. Third, our sample included the families who were relatively rich compare with national average, which limited our ability to assess the financial impact among the families with low socio-economic status.

Families of children with ALL experience a wide range of costs. Ongoing investigation of

families' costs will yield a rich understanding of the disease costs, formulate the basis of cost assessments, and lend insight into practice and policy changes aimed at lessening the economic impact of this burden.

Contribution Statement

YR and XL designed the study, developed data analysis plan and equally contributed to this study. XL performed statistical analysis of the data. All authors made significant contributions to the interpretation of results and participated in drafting and revising the manuscript. All authors have approved the final version.

Competing Interests

None.

Ethics approval

This study was approved by the Institutional Review Board of Shanghai Children's Medical Center.

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Data Sharing Statement

No additional data are available.

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Table 1. Child, parent, and family characteristics (n=161)

Characteristics	N	%
Child characteristics		
Age at diagnosis, years (mean, SD)	4.9	(3.3)
Average treatment period, months (mean, SD)	13.8	(9.9)
Gender		
Male	94	58.4
Female	67	41.6
No Health insurance	56	34.8
Parent characteristics		
Age at diagnosis, years (mean, SD)	32.6	(4.28)
Education (the highest degree of parental education)		
Middle school or lower	67	41.9
High/vocational school	32	20.0
College or above	61	38.1
Household characteristics		
Family size (mean, SD)	4.1	(1.1)
Household monthly income, RMB (mean, SD)	8341.72	(11942.80)
Hukou (Registered residence type)		
Rural	71	44.1
Urban	90	56.0
Area of residence		
Shanghai	45	28.0
Other provinces	116	72.0

Table 2. Employment status of parents

Characteristics	N	%	N	%
Employment at diagnosis	Father		Mother	
Government, SOE, or Public sector	35	22.0	32	20.1
Private sector or self-employed	109	68.6	73	45.9
Agriculture	11	6.9	16	10.1
Unemployed or doing housework	4	2.5	38	23.9
Change of employment status (conditional on employed at diagnosis)	Father		Mother	
No change	47	29.9	18	14.8
Completely stop working	13	8.3	8	6.6
Extended leave	97	61.7	96	78.7
Average length of absence, months (mean, SD)	14.4	11.1	18.1	10.8

Table 3. Costs of different categories during the treatment

	Total sample (n = 161)			Urban sample (n =90)			Rural sample (n = 71)		
	Mean(RMB)	SD	%	Mean(RMB)	SD	%	Mean(RMB)	SD	%
Panel A: Total direct medical costs	115768.90	102733.40		121232.00	126696.70		108843.90	60230.74	
Inpatient cost	77262.05	89289.19	66.7	82257.79	11043.20	70.3	67126.61	50313.70	61.7
Outpatient cost	38506.89	21393.90	33.3	35974.21	24217.62	29.7	41717.34	16786.42	38.3
Panel B: Total direct non-medical costs	45896.16	36451.59		50993.63	40194.46		39434.57	30119.78	
Accommodation	20754.26	24462.92	45.2	25599.94	25216.43	50.0	14611.85	22156.97	37.1
Transportation	1238.21	1519.98	2.7	1327.32	1636.24	2.6	1125.25	1361.48	2.9
Food and nutritional supplements	16232.70	19562.25	35.4	17048.43	21022.11	33.4	15198.67	17631.77	38.5
Hygiene cleaning products and auxiliary treatment equipment	3063.38	4620.81	6.7	2726.92	4433.65	5.3	3489.87	4845.77	8.8
Gifts and treats including electrical devices	4607.61	6310.41	10.0	4291.01	35151.27	8.4	5008.93	7549.15	12.7
Panel C: Total indirect costs	62403.41	174086.24		88457.34	226401.38		29377.31	46059.62	

Table 4. Total cost and its components

	Total sample (n = 161)			Urban sample (n =90)			Rural sample (n = 71)		
	Mean(RMB)	SD	%	Mean(RMB)	SD	%	Mean(RMB)	SD	%
Total costs	224068.47	229637.26		260682.96			177655.82		
Direct medical cost	115768.90	102733.40	51.7	121231.99	126696.69	46.5	108843.94	60230.74	61.3
Direct non-medical cost	45896.16	36451.59	20.5	50993.63	40194.46	19.6	39434.57	30119.78	22.2
Indirect cost	62403.41	174086.24	27.9	88457.34	226401.38	33.9	29377.31	46059.62	16.5
Total household monthly income, RMB	8341.72	11942.80		10246.43	12814.06		5953.73	10356.65	
Family size	4.1	1.1		3.8	1.0		4.5	1.1	

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Direct and indirect costs of families with a child with acute lymphoblastic leukemia in an academic hospital in China: a cross-sectional survey

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Abstract:

Objectives: To estimate the direct and indirect costs in families with a child with acute lymphoblastic leukemia (ALL) in China.

Design: A single-site, cross-sectional survey of primary caregiver of a child with ALL was performed.

Setting and participants: We analyzed the total costs incurred upon the completion of the first three-phase treatment (induction, consolidation, and intensification), which requires intensive hospitalization. Eligible patients were: a) diagnosed with ALL between 2010 and 2012 at Shanghai Children's Medical Center (SCMC), b) 0-14 years at diagnosis, and c) completed the first three-phase treatment at SCMC. The data was collected between October 2014 and December 2014.

Outcome measures: We decomposed the total costs into three categories (a) direct medical costs, which were further divided into outpatient and inpatient costs; (b) direct non-medical costs, which referred to expenses incurred in relation to the illness; and (c) indirect costs due to productivity loss.

Results: A total of 161 patients were included in the study. Direct medical costs accounted for about 51.7% of the overall costs, and the rest of 48.3% of the total costs were attributed to direct non-medical costs and indirect costs. Regarding families with different household registration type (rural versus urban), the total costs were significantly different between the two groups (USD36125 vs. USD 25593; P = 0.021). Specifically, urban families incurred significantly larger indirect costs than rural families (USD 12343 vs. USD 4157; P = 0.018). Although the direct non-medical costs were not significantly different, urban families spent more money on hygiene cleaning products and auxiliary treatment equipment (P = 0.041) and gifts and treats (P = 0.034) than rural families.

Conclusions: The financial burden faced by the Chinese families with a child with ALL was tremendous, and the distributions of costs among the three categories were different between urban and rural families.

Strengths and limitations of this study

- We estimated the direct and indirect costs in families with a child with acute lymphoblastic leukemia in China.
- We decomposed the estimates of the total costs into three categories: direct medical costs, direct non-medical costs and indirect costs due to productivity loss.
- Majority cost measures were based on parents' self-report and there might exist recall bias for some measures.

Keywords: Direct and indirect costs; Child; Acute lymphoblastic leukemia; Family; China

Introduction

In China, the incidence of childhood cancer was 87.1 per million and the mortality was 36.3 per million in 2010[1]. Acute lymphoblastic leukemia (ALL) is the most common malignant disease among children, accounting for about 40% of all newly diagnosed childhood cancers[1]. The 5-year survival rate in childhood ALL has greatly increased over time and is now about 70% in China[1]. Regardless of better survival, life-saving therapy is costly and may result in a financial burden for these patients' families[2-7]. On the one hand, the costs of treatment of ALL and illness-related expenses are immense, on the other hand, parents may have to reduce their work hours, or give up paid work to care for their child resulting in loss of income.

Various studies have been conducted in developed countries to determine the costs associated with childhood cancer from a family perspective[8]. In these studies, the economic and financial impact of childhood cancer on families was examined on two primary cost categories: direct costs including the actual monetary expenditure related to the illness such as those associated with transport, food, accommodation, *etc.*[3, 4, 9, 10], and indirect costs including the value of productivity loss such as cutting on work time, taking unpaid leave or quitting job[4-7, 11-13]. Although it is hard to make a precise comparison of the magnitude of the financial costs of families due to variation in study design, all studies reported substantial family financial burden associated with childhood cancer treatment. Specifically, two Canadian studies found that income loss due to work disruption and out-of-pocket expenses were estimated at over 30% of after-tax family income[2, 6], and one American study reported that over 50% of the poorest families experienced annual income loss of more than 40%[11].

While childhood cancer was shown to have an adverse economic consequence on families in developed countries, it is likely to have even more severe effects in developing countries. In

China, average treatment costs for childhood ALL were estimated to be between USD 15,128 and USD 45,386[14], whereas per capita income was USD 4270 in 2018. Although the Chinese government has made great efforts to provide universal health coverage by the year 2010, the coverage is typically shallow. 65.1% of childhood ALL patients' insurance covered less than 50% of overall medical costs[14].

Unfortunately, medical costs are not the only financial burden faced by the Chinese families, the families with a child with ALL may also incur substantial additional costs associated with the illness. Specifically, there are huge differences in the allocation of medical resources between rural and urban areas, and among different provinces. High-quality medical resources are mainly distributed in large central cities such as Beijing, Shanghai, Guangzhou, *etc*. Therefore, families with a seriously ill child have to go to these cities to receive treatment for a better chance of survival. As a result, the corresponding non-medical out-of-pocket expenses may increase dramatically due to extra expenditures on transport, accommodation, *etc*. In addition, it is also hard for the parents to keep their jobs while taking care of the sick child, therefore resulting in loss of income.

In addition to unequal distribution of medical resources, there are significant differences between urban and rural areas in terms of income and social security system in China. In 2018, urban per capita income was more than 2.5 times of rural per capita income (USD 5938 vs. USD 2211). Regarding the social security system, rural and urban populations are entitled to enroll in different health insurance schemes with different coverage plans, and unemployment and retirement insurances are only available to the urban working population. As a result, the economic burden is very likely to be different between rural and urban families.

As can be seen, the economic burden on Chinese families with a child with ALL could be devastated. Lacking financial aids from various sources may cause these families to fall from above to below the poverty line, or even give up treatment[14]. However, research on determining the costs associated with a childhood ALL is rare and the nature of these costs is poorly understood in developing countries[15-18]. It makes policy planning in the context of essential medicines, national fiscal policy towards childhood ALL and donor policy difficult without any reliable estimates of costs. The purpose of this paper was to estimate the economic burden in families with a child with ALL in China. In addition, we also reported the total costs and its three components for rural and urban families separately.

Methods

Data and study population

The treatment of childhood ALL usually has four phases: induction, consolidation, intensification, and maintenance and lasts 2 to 3 years[19]. In the present paper, we estimated total costs incurred upon the completion of the first three-phase treatment (induction, consolidation, and intensification), which requires intensive hospitalization. Therefore, eligible patients were: a) diagnosed with ALL between 2010 and 2012 at Shanghai Children's Medical Center (SCMC), b) 0-14 years old at diagnosis, and c) completed the first three-phase treatment at SCMC. The data was collected between October 2014 and December 2014. The time between diagnosis and completion of the questionnaire was required to be greater than two years in order to capture parents' employment experiences throughout the treatment. Since quite a lot of the families were not living in Shanghai, face-to-face interviews were difficult to conduct. As an alternative, we conducted telephone interviews on the parents. Only one parent of the child, who self-identified as the major caregiver of the child answered the questionnaire. The interview lasted about 30-45 minutes. We obtained approval from the Institutional Review

Board of Shanghai Children's Medical Center to conduct the study.

Pre-testing

In order to ensure the rationality and accuracy of the questionnaire, we pre-tested the questionnaire with 15 parents with a child with ALL who were randomly picked during their follow-up visits to the center. During this period, we revised the questionnaire many times to make sure that parents understood the questions, did not feel uncomfortable, and were aware of their costs reflecting the costs incurred during the induction, consolidation and intensification phases, not the costs associated with the maintenance therapy.

Measures

We decomposed the costs into three categories (a) direct medical costs, which were further divided into outpatient and inpatient costs; (b) direct non-medical costs, which referred to expenses incurred in relation to the illness; and (c) indirect costs due to productivity loss.

The questionnaire included three modules. The first module asked questions about socio-demographic characteristics of parents and their child. The second module included direct non-medical cost questions. The last module focused on indirect cost questions. More specifically, the details of these modules were shown as follows:

Demographic and socioeconomic variables: child age at diagnosis, child gender and whether child had health insurance, parent's age at diagnosis, the highest degree of parental education (elementary or lower, high/vocational school or lower, or college and above), family monthly income, family size, household registration type (Hukou types: rural versus urban), place of residence (Shanghai versus other provinces).

Direct non-medical cost variables: direct non-medical costs included expenses related to illness during the period of the first three stages of treatment. Specifically, parent was asked to provide information on: a) expenses on accommodation per month including rent and utility fee; b) expenses on transportation; c) increased expenses on food and nutritional supplements per month; d) expenses on hygiene cleaning products and auxiliary treatment equipment, such as ultraviolet disinfection lamp, air purifier, humidifier, *etc.*; e) expenses on gifts and treats including electrical devices (e.g. computer, TV, video games *etc.*) and network fee.

Indirect cost variables: indirect costs were the costs associated with lost productivity due to illness. In the present paper, parent was asked to provide information on employment status at diagnosis and during the treatment period, changes in role or hours worked since diagnosis and length of absence from work. Informant was also asked to complete this section for his or her partner. The indirect costs were measured by lost earnings using the human capital approach.

Direct medical cost variables: The computerized database of medical costs at SCMC was established in 1998. The database strictly adheres to medical administration regulations. According to the administration system, all medicines and blood products should be supplied by the department of pharmacy and blood bank at SCMC. All lab tests and non-lab tests (including EEG, EKG, and various diagnostic imaging) should be done at SCMC as well. All outpatient and hospitalization costs were recorded according to their names/case numbers. In the present paper, overall outpatient and inpatient costs for each child with ALL between the confirmation of diagnosis at SCMC and the completion of the intensification therapy were collected from the database. The components of costs included costs for western medicine, Chinese medicine, blood products, lab tests, non-lab tests, hospital bed/daycare, consultant fees, using the nursing injection facility and consumption of materials and oxygen. In addition, the

database also contained information on inpatient expenses paid by insurance for local patients.

Patient and public involvement

No patients were involved in the development of the research question, the outcome measures, the design or implementation of the study. There are no plans about the dissemination of the results.

Statistical Analysis

All data were reviewed for completeness and relevance. Data were entered into Microsoft Excel and imported into the STATA 13 statistical package (Stata Corporation, College Station, TX, USA) for analysis. Descriptive statistics were used to describe the sample characteristics and categorize the types and values of cost categories and items. The Chi-square tests and the *t* tests were used for bivariate comparisons of categorical and continuous variables for the urban and rural families, respectively. The amounts of all cost categories were projected to the estimates that incurred during the treatment. We expressed all cost estimates in 2010 RMB by using the Consumer Price Index and then converted in USD by using the average exchange rate between RMB and USD in 2010 (USD 1.00 = RMB 6.7695). Total costs were then computed as the sum of all cost categories for the sample. *T*-tests were used to examine the rural vs. urban differences in all cost estimates.

Results

Medical expenses and parental contact information of a total of 171 patients were extracted from the SCMC database. We contacted the 171 parents using the telephone numbers provided in the database and 161 parents gave the consent before we conducted the interview. The 10 failed calls were due to either loss of contact or refuse to participate.

Table 1 presents the child, parent, and family characteristics for the whole sample and for the urban and rural subsamples. The mean patient age at diagnosis was 4.9 years (standard deviation (SD) = 3.3 years; range: 0-14 years), the majority were male (58.4%). The average length of therapy (induction, consolidation, and intensification) was 11.6 months (SD = 9.6 months). 52 patients (33.1%) did not have any insurance at the time of diagnosis. The mean age of parents at diagnosis was 33.2 years (SD = 4.3 years), the majority of the parents' highest education level was high/vocational school or below (61.9%). In terms of household characteristics, the average family size was 4.1 (SD = 1.1), 71 households (44.1%) had rural registration and only 33 households (20.6 %) were local residents (Shanghai). The average household monthly income at diagnosis was USD1232.25. Regarding urban and rural families, the highest education for parents in an urban area was significantly higher than that of parents from a rural area (P<0.001). In addition, urban families had smaller family size (P<0.001), higher monthly income (P=0.02) and were more likely to be local residents (P < 0.001) than their rural counterparts.

Table 2 describes the parents' employment statuses at the time of diagnosis and during the treatment period. On diagnosis, 35(22%) fathers worked in government, state-owned enterprise (SOE) or public sector, 109(68.6%) worked in private sector or self-employed, 11(6.9%) were farmers and 4(2.5%) were unemployed. During the treatment, 47 working fathers managed to keep their employment status unchanged, 13 completely stopped working, and 97 reported to take extended absences from work. The average length of absences was 14.4 months (SD = 11.1 months). Regarding mothers, on diagnosis, 32(20.1%) worked in government, SOE or public sector, 73(45.9) worked in private sector or self-employed, 16(10.1%) were farmers and 38(23.9%) were unemployed or doing housework. Among those who had a job, 14.8% did not

change their employment status, 6.6% stopped working, and the majority of working mothers (78.7%) took extended absences from work. The average length of absences was 18.1 months (SD = 10.8 months).

The three categories of the total costs and their components for the whole sample are given in Table 3. Panel A reported that the average total medical costs during the treatment were USD 16307 (SD = 14488; interquartile range (IQR) 9441–18120). Medical costs were then divided into two subcategories: outpatient and inpatient costs. The inpatient costs accounted for the majority of the total medical costs (66.9%). Panel B of Table 3 presents the direct non-medical costs incurred during the treatment. The average direct non-medical costs were USD 6441 (SD = 5038; IQR 3013-8543) with the largest expenditure on accommodation. The average indirect costs incurred during the treatment (Panel C of Table 3) were estimated to be USD 8733 (SD = 24321; IQR 0-6727). On average, the total costs for the whole sample were USD 31480 (SD = 31847; IQR 15518-33177). The direct medical costs accounted for more than half of the total costs (51.8%), followed by indirect costs (27.7%) and direct non-medical costs (20.5%).

Table 4 reports the total costs and their components for rural and urban families, respectively. The total costs were significantly different between the two groups (mean: USD 36125 vs. USD 25592; P = 0.021). Regarding to the three cost categories, the urban families incurred significantly larger indirect costs than the rural families (mean: USD 12343 vs. USD 4157; P = 0.018). Although the direct non-medical costs were not significantly different, the urban families spent more money on hygiene cleaning products and auxiliary treatment equipment (P = 0.041) and gifts and treats (P = 0.034) than the rural families.

Discussion

A cancer diagnosis in childhood can substantially affect the physical, psychosocial, and socioeconomic well-being of patients and their families. Yet, research on determining the costs associated with a childhood ALL is rare and the nature of these costs is poorly understood, especially in developing countries. The present study provides a breakdown of families' costs and resource use and an in-depth understanding of families' financial burden. We found that the financial burden faced by Chinese families with a child with ALL was tremendous. Among the three cost categories, direct medical costs accounted for about 51.8% of the overall costs, and the rest of 48.2% of the total costs were attributed to direct non-medical costs and indirect costs. Regarding families with different household registration type (rural versus urban), the distributions of costs among the three categories were different. Productivity loss contributed a much higher weight in total costs for urban families than for rural families. In addition, rural families spent most of their money on the treatment of ALL.

Our results showed that the average medical costs were approximately USD 16307, which were comparable to the findings from previous studies using data of developing countries[14, 15, 20]. Unlike most developed countries where costs of treatment are borne mainly by the public sector and health insurance[4, 13], patients in developing countries have to bear a significant portion of direct medical costs[16, 17]. According to the health insurance regulations of China, if patient chooses to receive treatment in other province or city, or in non-designated hospital, the reimbursement rate could be very low or none at all. Although we were unable to determine this from our study directly, one report did have shown that the actual reimbursement rate was less than 50% for most of the rural families with a child with leukemia, of which around 27% of children only got 30% of reimbursement[14]. In addition, in the questionnaire we asked “any comments or suggestions on current insurance reimbursement policy?” more than half of the non-local parents (57.8%; data not shown) mentioned that the reimbursement rate was too low.

Specifically, they identified the low reimbursement mainly due to the following reasons: there existed a big gap on reimbursement rate between local and non-local residents; outpatient and imported medicines were not covered by the insurance, and the reimbursement procedure across provinces was tedious and time-consuming, and the actual reimbursement rate was low, so some parents chose to forgo reimbursement.

In contrast to the previous literature which found that transport took a significant portion of family financial cost[9, 10, 21], our results showed that transport only contributed to 2.7% of the total direct non-medical costs, whereas around 45% of the total direct non-medical expenses were spent on accommodation. That was because most of the non-local families chose to rent near the hospital, which saved travel costs. Although the very poor families can receive 30 days of accommodation at the center at very low price[15], space is limited and the 30-day rental period is far from enough. Most non-local families had to rent a room or an apartment near the hospital for about USD146.02-USD730.09 per month for an average 12 months. Food and nutritional supplements accounted for about 35% of the total direct non-medical cost. As described by Tsimicalis et al. (2013), increased expenses on food were to accommodate the child's fluctuating weight, satisfy food cravings, taste alterations, *etc.*[10].

Following diagnosis, 85% of working mothers and 70% of working fathers gave up all paid employment or took unpaid extended leaves in our sample. These numbers were much higher than those reported in the previous studies[4, 6, 12, 13]. The possible explanation was that in our sample, the majority families were from other provinces (79%), and it was hard for only one parent to handle all the issues related to treatment, accommodation, food, *etc.*, therefore, both parents had to quit their jobs or took unpaid leaves during the treatment.

Our data indicated that families with high socio-economic status were more likely to receive treatment in high-quality medical facilities. Specifically, according to data from the National Bureau of Statistics of China, in 2010, the annual urban per capita income was USD 2822.87, and the amount was RMB874.36 in the rural areas[22]. However, our data indicated that the sample urban per capita income was 1.9* times that of the national urban average and the ratio became 2.4 times for the rural per capita income. In addition, our data showed that the total costs were 1.79 times of the sample urban family's annual income, and were 2.72 times of the sample rural family's annual income. This finding indicated that even for these high socio-economic families, the economic burden of childhood ALL was huge, especially for rural families.

Our findings have very important policy implications. First, policymakers should make effort on simplifying the reimbursement procedure across provinces and eliminating the huge disparities in reimbursement ratio across regions; second, our sample indicated 33% of patients did not have any insurance at diagnosis, although we did not have direct data on why these parents chose not to purchase insurance for their child, previous study has shown that lack of knowledge or the concept of insurance could be a major barrier for people from participating the insurance program[23], therefore, the government should work hard on educating people regarding the different programs; third, patients with cancer and their families may need ongoing financial management with a designated financial advisor well beyond the initial treatment phase to help them manage debt, access resources to cope with direct and indirect costs of cancer treatment and maintain patients' and families' financial capacity later in life.

*Sample annual urban per capita income was calculated as: urban household monthly income*12/family size, using the data from Table 1.

There are limitations to this study. First, majority measures were based on parents' self-report, and there may exist recall bias for some measures. However, to minimize recall bias, before conducting a formal interview, we contacted them one week in advance and asked parents to recall and list out the details of all the expenses during the treatment. After the interview, we double checked data. If there was inconsistency in the data, we called back to clarify. Second, while the generalizability of this study may be somewhat limited as we focused on one hospital, SCMC, as one of the primary pediatric tertiary care centers in China, it provides treatment of severe disease in children around China (Our data showed that 79% of patients were non-local residents). Therefore, our results are likely applicable to other geographic areas. Third, our sample included the families who were relatively rich compare with the national average, which limited our ability to assess the financial impact among the families with low socio-economic status.

Families of children with ALL experience a wide range of costs. An ongoing investigation of families' costs will yield a rich understanding of the disease costs, formulate the basis of cost assessments, and lend insight into practice and policy changes aimed at lessening the economic impact of this burden.

Contribution Statement

YR and XL designed the study, developed a data analysis plan and equally contributed to this study. XL performed a statistical analysis of the data. All authors made significant contributions to the interpretation of results and participated in drafting and revising the manuscript. All authors have approved the final version.

Competing Interests

None.

Ethics approval

This study was approved by the Institutional Review Board of Shanghai Children's Medical Center.

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Data Sharing Statement

Data are not available because the authors promised the SCMC that the information was only used for research, and it would not be disclosed.

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Table 1. Child, parent, and family characteristics (n=161)

	Total (N=161)		Urban (N=90)		Rural (N=71)		P-value
Characteristics	N	%	N	%	N	%	
Child characteristics							
Age at diagnosis, years (mean, SD)	4.9	(3.3)	4.7	(3.2)	5.1	(3.3)	0.48
Average treatment period, months (mean, SD)	11.6	(9.6)	12.4	(10.4)	10.6	(8.5)	0.25
Gender							
Male	94	58.4	54	60.0	40	56.3	0.64
Female	67	41.6	36	40.0	31	43.7	
No Health insurance	52	33.1	32	35.5	20	28.1	0.33
Parent characteristics							
Age at diagnosis, years (mean, SD)	33.2	(4.3)	33.6	(4.4)	32.8	(4.7)	0.34
Education (the highest degree of parental education)							
Middle school or lower	67	41.9	18	20.0	50	70.4	<0.001
High/vocational school	32	20.0	17	18.9	15	21.1	
College or above	61	38.1	55	61.1	6	8.5	
Household characteristics							
Family size (mean, SD)	4.1	(1.1)	3.8	(0.9)	4.5	(1.1)	<0.001
Household monthly income, USD (mean, SD)	1287.31	(2518.36)	1681.56	(3082.12)	783.35	(1379.65)	0.02
Area of residence							
Shanghai	33	20.6	30	33.3	3	4.2	<0.001
Other provinces	128	79.4	60	66.7	68	95.8	

Table 2. Employment status of parents

Characteristics	N	%	N	%
Employment at diagnosis	Father		Mother	
Government, SOE, or Public sector	35	22.0	32	20.1
Private sector or self-employed	109	68.6	73	45.9
Agriculture	11	6.9	16	10.1
Unemployed or doing housework	4	2.5	38	23.9
Change of employment status (conditional on employed at diagnosis)	Father		Mother	
No change	47	29.9	18	14.8
Completely stop working	13	8.3	8	6.6
Extended leave	97	61.7	96	78.7
Average length of absence, months (mean, SD)	14.4	11.1	18.1	10.8

Table 3. Total cost and its components (in 2010 US$)*

	Total sample (n = 161)				
	Median	IQR	Mean	SD	%
Panel A: Total direct medical costs	12562	9441 - 18120	16307	14488	
Inpatient cost	7064	5097 - 11786	7622	18645	66.9
Outpatient cost	5272	3391 - 6712	7031	6843	33.1
Panel B: Total direct non-medical costs	5220	3013 - 8543	6441	5038	
Accommodation	2158	280 - 3700	2898	3357	45.0
Transportation	112	44 - 219	175	219	2.7
Food and nutritional supplements	1682	392 - 2864	2289	2743	35.5
Hygiene cleaning products and auxiliary treatment equipment	177	59 - 505	429	651	6.7
Gifts and treats including electrical devices	428	123 - 841	651	888	10.1
Panel C: Total indirect costs	1677	0 - 6727	8733	24321	
Total costs	22702	15518-33177	31480	31847	

*The average exchange rate between RMB and USD in 2010 is 6.7695.

Table 4. Costs of different categories during the treatment (in 2010 USD)*

	Urban sample (n =90)					Rural sample (n = 71)					P-Value**
	Median	IQR	Mean	SD	%	Median	IQR	Mean	SD	%	
Panel A: Total direct medical costs	11820	8680 - 17158	17075	17854		12857	9939 - 18660	15332	8531		0.393
Inpatient cost	7064	5018 - 11458	12048	15571	70.6	6894	5157 - 11786	9475	7176	61.7	0.155
Outpatient cost	4735	2803 - 6375	5027	3383	29.4	5634	4495 - 6843	5858	2321	38.3	0.074
Panel B: Total direct non-medical costs	5343	2873 - 9447	6707	5535		5204	3443 - 7265	6104	4342		0.468
Accommodation	1752	0 - 3900	2830	3880	42.2	2568	1430 - 3676	2983	2569	48.9	0.727
Transportation	137	30 - 280	189	207	2.8	109	56 - 178	156	233	2.6	0.376
Food and nutritional supplements	1773	221 - 3418	2392	2849	35.7	1472	463 - 2482	2158	2618	35.4	0.597
Hygiene cleaning products and auxiliary treatment equipment	281	74 - 675	520	706	7.8	103	36 - 278	313	556	5.1	0.041
Gifts and treats including electrical devices	519	147 - 981	774	1067	11.5	328	70 - 701	494	558	8.1	0.034
Panel C: Total indirect costs	463	0 - 7379	12343	31598		1822	44 - 6391	4157	6677		0.018
Total costs	22154	14036 - 41289	36125	40487		22860	16065 - 30601	25593	13088		0.021

* The average exchange rate between RMB and USD in 2010 is 6.7695.
** P value for *t* test comparing means between rural and urban samples.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Section and page number (P)
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title page (P1) Abstract (P2)
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract (P2–3)
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Introduction (P4-6)
Objectives	3	State specific objectives, including any prespecified hypotheses	Introduction (P7)
Methods			
Study design	4	Present key elements of study design early in the paper	Methods (P7)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods (P7-8)
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Methods (P7-8)
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Methods (P8)
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Methods (P8-10)
Bias	9	Describe any efforts to address potential sources of bias	Methods (P8) Discussion (P16)
Study size	10	Explain how the study size was arrived at	Results (P10-11)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Methods (P10)
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Methods (P10)
		(*b*) Describe any methods used to examine subgroups and interactions	Methods (P10)
		(*c*) Explain how missing data were addressed	N/A
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Results (P10-12)
		(b) Give reasons for non-participation at each stage	N/A

		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Tables 1, 2 Results (P10-11)
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) Summarise follow-up time (eg, average and total amount)	N/A
Outcome data	15*	Report numbers of outcome events or summary measures over time	Tables 3, 4
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Tables 3 Results (P12)
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Table 4 Results (P12-13)
Discussion			
Key results	18	Summarise key results with reference to study objectives	Discussion (P13)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Discussion (P16)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Discussion (P13-16)
Generalisability	21	Discuss the generalisability (external validity) of the study results	Discussion (P16)
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Funding information (P17)

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Direct and indirect costs of families with a child with acute lymphoblastic leukemia in an academic hospital in China: a cross-sectional survey

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Direct and indirect costs of families with a child with acute lymphoblastic leukemia in an academic hospital in China: a cross-sectional survey

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Word count: 3518

Abstract:

Objectives: To estimate the direct and indirect costs in families with a child with acute lymphoblastic leukemia (ALL) in China.

Design: A single-site, cross-sectional survey of primary caregiver of a child with ALL was performed.

Setting and participants: We analyzed the total costs incurred upon the completion of the first three-phase treatment (induction, consolidation, and intensification), which requires intensive hospitalization. Eligible patients were: a) diagnosed with ALL between 2010 and 2012 at Shanghai Children's Medical Center (SCMC), b) 0-14 years at diagnosis, and c) completed the first three-phase treatment at SCMC. The data was collected between October 2014 and December 2014.

Outcome measures: We decomposed the total costs into three categories (a) direct medical costs, which were further divided into outpatient and inpatient costs; (b) direct non-medical costs, which referred to expenses incurred in relation to the illness; and (c) indirect costs due to productivity loss.

Results: A total of 161 patients were included in the study. Direct medical costs accounted for about 51.7% of the overall costs, and the rest of 48.3% of the total costs were attributed to direct non-medical costs and indirect costs. Regarding families with different household registration type (rural versus urban), the total costs were significantly different between the two groups (USD36125 vs. USD 25593; P = 0.021). Specifically, urban families incurred significantly larger indirect costs than rural families (USD 12343 vs. USD 4157; P = 0.018). Although the direct non-medical costs were not significantly different, urban families spent more money on hygiene cleaning products and auxiliary treatment equipment (P = 0.041) and gifts and treats (P = 0.034) than rural families.

Conclusions: The financial burden faced by the Chinese families with a child with ALL was tremendous, and the distributions of costs among the three categories were different between urban and rural families.

Strengths and limitations of this study

- We estimated the direct and indirect costs in families with a child with acute lymphoblastic leukemia in China.
- We decomposed the estimates of the total costs into three categories: direct medical costs, direct non-medical costs and indirect costs due to productivity loss.
- Majority cost measures were based on parents' self-report and there might exist recall bias for some measures.

Keywords: Direct and indirect costs; Child; Acute lymphoblastic leukemia; Family; China

Introduction

In China, the incidence of childhood cancer was 87.1 per million and the mortality was 36.3 per million in 2010[1]. Acute lymphoblastic leukemia (ALL) is the most common malignant disease among children, accounting for about 40% of all newly diagnosed childhood cancers[1]. The 5-year survival rate in childhood ALL has greatly increased over time and is now about 70% in China[1]. Regardless of better survival, life-saving therapy is costly and may result in a financial burden for these patients' families[2-7]. On the one hand, the costs of treatment of ALL and illness-related expenses are immense, on the other hand, parents may have to reduce their work hours, or give up paid work to care for their child resulting in loss of income.

Various studies have been conducted in developed countries to determine the costs associated with childhood cancer from a family perspective[8]. In these studies, the economic and financial impact of childhood cancer on families was examined on two primary cost categories: direct costs including the actual monetary expenditure related to the illness such as those associated with transport, food, accommodation, *etc.*[3, 4, 9, 10], and indirect costs including the value of productivity loss such as cutting on work time, taking unpaid leave or quitting job[4-7, 11-13]. Although it is hard to make a precise comparison of the magnitude of the financial costs of families due to variation in study design, all studies reported substantial family financial burden associated with childhood cancer treatment. Specifically, two Canadian studies found that income loss due to work disruption and out-of-pocket expenses were estimated at over 30% of after-tax family income[2, 6], and one American study reported that over 50% of the poorest families experienced annual income loss of more than 40%[11].

While childhood cancer was shown to have an adverse economic consequence on families in developed countries, it is likely to have even more severe effects in developing countries. In

China, average treatment costs for childhood ALL were estimated to be between USD 15,128 and USD 45,386[14], whereas per capita income was USD 4270 in 2018. Although the Chinese government has made great efforts to provide universal health coverage by the year 2010, the coverage is typically shallow. 65.1% of childhood ALL patients' insurance covered less than 50% of overall medical costs[14].

Unfortunately, medical costs are not the only financial burden faced by the Chinese families, the families with a child with ALL may also incur substantial additional costs associated with the illness. Specifically, there are huge differences in the allocation of medical resources between rural and urban areas, and among different provinces. High-quality medical resources are mainly distributed in large central cities such as Beijing, Shanghai, Guangzhou, *etc*. Therefore, families with a seriously ill child have to go to these cities to receive treatment for a better chance of survival. As a result, the corresponding non-medical out-of-pocket expenses may increase dramatically due to extra expenditures on transport, accommodation, *etc*. In addition, it is also hard for the parents to keep their jobs while taking care of the sick child, therefore resulting in loss of income.

In addition to unequal distribution of medical resources, there are significant differences between urban and rural areas in terms of income and social security system in China. In 2018, urban per capita income was more than 2.5 times of rural per capita income (USD 5938 vs. USD 2211). Regarding the social security system, rural and urban populations are entitled to enroll in different health insurance schemes with different coverage plans, and unemployment and retirement insurances are only available to the urban working population. As a result, the economic burden is very likely to be different between rural and urban families.

As can be seen, the economic burden on Chinese families with a child with ALL could be devastated. Lacking financial aids from various sources may cause these families to fall from above to below the poverty line, or even give up treatment[14]. However, research on determining the costs associated with a childhood ALL is rare and the nature of these costs is poorly understood in developing countries[15-18]. It makes policy planning in the context of essential medicines, national fiscal policy towards childhood ALL and donor policy difficult without any reliable estimates of costs. The purpose of this paper was to estimate the economic burden in families with a child with ALL in China. In addition, we also reported the total costs and its three components for rural and urban families separately.

Methods

Data and study population

The treatment of childhood ALL usually has four phases: induction, consolidation, intensification, and maintenance and lasts 2 to 3 years[19]. In the present paper, we estimated total costs incurred upon the completion of the first three-phase treatment (induction, consolidation, and intensification), which requires intensive hospitalization. Therefore, eligible patients were: a) diagnosed with ALL between 2010 and 2012 at Shanghai Children's Medical Center (SCMC), b) 0-14 years old at diagnosis, and c) completed the first three-phase treatment at SCMC. The data was collected between October 2014 and December 2014. The time between diagnosis and completion of the questionnaire was required to be greater than two years in order to capture parents' employment experiences throughout the treatment. Since quite a lot of the families were not living in Shanghai, face-to-face interviews were difficult to conduct. As an alternative, we conducted telephone interviews on the parents. Only one parent of the child, who self-identified as the major caregiver of the child answered the questionnaire. The interview lasted about 30-45 minutes. We obtained approval from the Institutional Review

Board of Shanghai Children's Medical Center to conduct the study.

Pre-testing

In order to ensure the rationality and accuracy of the questionnaire, we pre-tested the questionnaire with 15 parents with a child with ALL who were randomly picked during their follow-up visits to the center. During this period, we revised the questionnaire many times to make sure that parents understood the questions, did not feel uncomfortable, and were aware of their costs reflecting the costs incurred during the induction, consolidation and intensification phases, not the costs associated with the maintenance therapy.

Measures

We decomposed the costs into three categories (a) direct medical costs, which were further divided into outpatient and inpatient costs; (b) direct non-medical costs, which referred to expenses incurred in relation to the illness; and (c) indirect costs due to productivity loss.

The questionnaire included three modules. The first module asked questions about socio-demographic characteristics of parents and their child. The second module included direct non-medical cost questions. The last module focused on indirect cost questions. More specifically, the details of these modules were shown as follows:

Demographic and socioeconomic variables: child age at diagnosis, child gender and whether child had health insurance, parent's age at diagnosis, the highest degree of parental education (elementary or lower, high/vocational school or lower, or college and above), family monthly income, family size, household registration type (Hukou types: rural versus urban), place of residence (Shanghai versus other provinces).

Direct non-medical cost variables: direct non-medical costs included expenses related to illness during the period of the first three stages of treatment. Specifically, parent was asked to provide information on: a) expenses on accommodation per month including rent and utility fee; b) expenses on transportation; c) increased expenses on food and nutritional supplements per month; d) expenses on hygiene cleaning products and auxiliary treatment equipment, such as ultraviolet disinfection lamp, air purifier, humidifier, *etc.*; e) expenses on gifts and treats including electrical devices (e.g. computer, TV, video games *etc.*) and network fee.

Indirect cost variables: indirect costs were the costs associated with lost productivity due to illness. In the present paper, parent was asked to provide information on employment status at diagnosis and during the treatment period, changes in role or hours worked since diagnosis and length of absence from work. Informant was also asked to complete this section for his or her partner. The indirect costs were measured by lost earnings using the human capital approach.

Direct medical cost variables: The computerized database of medical costs at SCMC was established in 1998. The database strictly adheres to medical administration regulations. According to the administration system, all medicines and blood products should be supplied by the department of pharmacy and blood bank at SCMC. All lab tests and non-lab tests (including EEG, EKG, and various diagnostic imaging) should be done at SCMC as well. All outpatient and hospitalization costs were recorded according to their names/case numbers. In the present paper, overall outpatient and inpatient costs for each child with ALL between the confirmation of diagnosis at SCMC and the completion of the intensification therapy were collected from the database. The components of costs included costs for western medicine, Chinese medicine, blood products, lab tests, non-lab tests, hospital bed/daycare, consultant fees, using the nursing injection facility and consumption of materials and oxygen. In addition, the

database also contained information on inpatient expenses paid by insurance for local patients.

Patient and public involvement

No patients were involved in the development of the research question, the outcome measures, the design or implementation of the study. There are no plans about the dissemination of the results.

Statistical Analysis

All data were reviewed for completeness and relevance. Data were entered into Microsoft Excel and imported into the STATA 13 statistical package (Stata Corporation, College Station, TX, USA) for analysis. Descriptive statistics were used to describe the sample characteristics and categorize the types and values of cost categories and items. The Chi-square tests and the *t* tests were used for bivariate comparisons of categorical and continuous variables for the urban and rural families, respectively. The amounts of all cost categories were projected to the estimates that incurred during the treatment. We expressed all cost estimates in 2010 RMB by using the Consumer Price Index and then converted in USD by using the average exchange rate between RMB and USD in 2010 (USD 1.00 = RMB 6.7695). Total costs were then computed as the sum of all cost categories for the sample. *T*-tests were used to examine the rural vs. urban differences in all cost estimates. A two-tailed p value of 0.05 was considered statistically significant.

Results

Medical expenses and parental contact information of a total of 171 patients were extracted from the SCMC database. We contacted the 171 parents using the telephone numbers provided in the database and 161 parents gave the consent before we conducted the interview. The 10 failed calls were due to either loss of contact or refuse to participate.

Table 1 presents the child, parent, and family characteristics for the whole sample and for the urban and rural subsamples. The mean patient age at diagnosis was 4.9 years (standard deviation (SD) = 3.3 years; range: 0-14 years), the majority were male (58.4%). The average length of therapy (induction, consolidation, and intensification) was 11.6 months (SD = 9.6 months). 52 patients (33.1%) did not have any insurance at the time of diagnosis. The mean age of parents at diagnosis was 33.2 years (SD = 4.3 years), the majority of the parents' highest education level was high/vocational school or below (61.9%). In terms of household characteristics, the average family size was 4.1 (SD = 1.1), 71 households (44.1%) had rural registration and only 33 households (20.6 %) were local residents (Shanghai). The average household monthly income at diagnosis was USD1232.25. Regarding urban and rural families, the highest education for parents in an urban area was significantly higher than that of parents from a rural area (P<0.001). In addition, urban families had smaller family size (P<0.001), higher monthly income (P=0.02) and were more likely to be local residents (P < 0.001) than their rural counterparts.

Table 2 describes the parents' employment statuses at the time of diagnosis and during the treatment period. On diagnosis, 35(22%) fathers worked in government, state-owned enterprise (SOE) or public sector, 109(68.6%) worked in private sector or self-employed, 11(6.9%) were farmers and 4(2.5%) were unemployed. During the treatment, 47 working fathers managed to keep their employment status unchanged, 13 completely stopped working, and 97 reported to take extended absences from work. The average length of absences was 14.4 months (SD = 11.1 months). Regarding mothers, on diagnosis, 32(20.1%) worked in government, SOE or public sector, 73(45.9) worked in private sector or self-employed, 16(10.1%) were farmers and 38(23.9%) were unemployed or doing housework. Among those who had a job, 14.8% did not

change their employment status, 6.6% stopped working, and the majority of working mothers (78.7%) took extended absences from work. The average length of absences was 18.1 months (SD = 10.8 months).

The three categories of the total costs and their components for the whole sample are given in Table 3. Panel A reported that the average total medical costs during the treatment were USD 16307 (SD = 14488; interquartile range (IQR) 9441–18120). Medical costs were then divided into two subcategories: outpatient and inpatient costs. The inpatient costs accounted for the majority of the total medical costs (66.9%). Panel B of Table 3 presents the direct non-medical costs incurred during the treatment. The average direct non-medical costs were USD 6441 (SD = 5038; IQR 3013-8543) with the largest expenditure on accommodation. The average indirect costs incurred during the treatment (Panel C of Table 3) were estimated to be USD 8733 (SD = 24321; IQR 0-6727). On average, the total costs for the whole sample were USD 31480 (SD = 31847; IQR 15518-33177). The direct medical costs accounted for more than half of the total costs (51.8%), followed by indirect costs (27.7%) and direct non-medical costs (20.5%).

Table 4 reports the total costs and their components for rural and urban families, respectively. The total costs were significantly different between the two groups (mean: USD 36125 vs. USD 25592; P = 0.021). Regarding to the three cost categories, the urban families incurred significantly larger indirect costs than the rural families (mean: USD 12343 vs. USD 4157; P = 0.018). Although the direct non-medical costs were not significantly different, the urban families spent more money on hygiene cleaning products and auxiliary treatment equipment (P = 0.041) and gifts and treats (P = 0.034) than the rural families.

Discussion

A cancer diagnosis in childhood can substantially affect the physical, psychosocial, and socioeconomic well-being of patients and their families. Yet, research on determining the costs associated with a childhood ALL is rare and the nature of these costs is poorly understood, especially in developing countries. The present study provides a breakdown of families' costs and resource use and an in-depth understanding of families' financial burden. We found that the financial burden faced by Chinese families with a child with ALL was tremendous. Among the three cost categories, direct medical costs accounted for about 51.8% of the overall costs, and the rest of 48.2% of the total costs were attributed to direct non-medical costs and indirect costs. Regarding families with different household registration type (rural versus urban), the distributions of costs among the three categories were different. Productivity loss contributed a much higher weight in total costs for urban families than for rural families. In addition, rural families spent most of their money on the treatment of ALL.

Our results showed that the average medical costs were approximately USD 16307, which were comparable to the findings from previous studies using data of developing countries[14, 15, 20]. Unlike most developed countries where costs of treatment are borne mainly by the public sector and health insurance[4, 13], patients in developing countries have to bear a significant portion of direct medical costs[16, 17]. According to the health insurance regulations of China, if patient chooses to receive treatment in other province or city, or in non-designated hospital, the reimbursement rate could be very low or none at all. Although we were unable to determine this from our study directly, one report did have shown that the actual reimbursement rate was less than 50% for most of the rural families with a child with leukemia, of which around 27% of children only got 30% of reimbursement[14]. In addition, in the questionnaire we asked “any comments or suggestions on current insurance reimbursement policy?” more than half of the non-local parents (57.8%; data not shown) mentioned that the reimbursement rate was too low.

Specifically, they identified the low reimbursement mainly due to the following reasons: there existed a big gap on reimbursement rate between local and non-local residents; outpatient and imported medicines were not covered by the insurance, and the reimbursement procedure across provinces was tedious and time-consuming, and the actual reimbursement rate was low, so some parents chose to forgo reimbursement.

In contrast to the previous literature which found that transport took a significant portion of family financial cost[9, 10, 21], our results showed that transport only contributed to 2.7% of the total direct non-medical costs, whereas around 45% of the total direct non-medical expenses were spent on accommodation. That was because most of the non-local families chose to rent near the hospital, which saved travel costs. Although the very poor families can receive 30 days of accommodation at the center at very low price[15], space is limited and the 30-day rental period is far from enough. Most non-local families had to rent a room or an apartment near the hospital for about USD146.02-USD730.09 per month for an average 12 months. Food and nutritional supplements accounted for about 35% of the total direct non-medical cost. As described by Tsimicalis et al. (2013), increased expenses on food were to accommodate the child's fluctuating weight, satisfy food cravings, taste alterations, *etc.*[10].

Following diagnosis, 85% of working mothers and 70% of working fathers gave up all paid employment or took unpaid extended leaves in our sample. These numbers were much higher than those reported in the previous studies[4, 6, 12, 13]. The possible explanation was that in our sample, the majority families were from other provinces (79%), and it was hard for only one parent to handle all the issues related to treatment, accommodation, food, *etc.*, therefore, both parents had to quit their jobs or took unpaid leaves during the treatment.

Our data indicated that families with high socio-economic status were more likely to receive treatment in high-quality medical facilities. Specifically, according to data from the National Bureau of Statistics of China, in 2010, the annual urban per capita income was USD 2822.87, and the amount was RMB874.36 in the rural areas[22]. However, our data indicated that the sample urban per capita income was 1.9* times that of the national urban average and the ratio became 2.4 times for the rural per capita income. In addition, our data showed that the total costs were 1.79 times of the sample urban family's annual income, and were 2.72 times of the sample rural family's annual income. This finding indicated that even for these high socio-economic families, the economic burden of childhood ALL was huge, especially for rural families.

Our findings have very important policy implications. First, policymakers should make effort on simplifying the reimbursement procedure across provinces and eliminating the huge disparities in reimbursement ratio across regions; second, our sample indicated 33% of patients did not have any insurance at diagnosis, although we did not have direct data on why these parents chose not to purchase insurance for their child, previous study has shown that lack of knowledge or the concept of insurance could be a major barrier for people from participating the insurance program[23], therefore, the government should work hard on educating people regarding the different programs; third, patients with cancer and their families may need ongoing financial management with a designated financial advisor well beyond the initial treatment phase to help them manage debt, access resources to cope with direct and indirect costs of cancer treatment and maintain patients' and families' financial capacity later in life.

*Sample annual urban per capita income was calculated as: urban household monthly income*12/family size, using the data from Table 1.

There are limitations to this study. First, majority measures were based on parents' self-report, and there may exist recall bias for some measures. However, to minimize recall bias, before conducting a formal interview, we contacted them one week in advance and asked parents to recall and list out the details of all the expenses during the treatment. After the interview, we double checked data. If there was inconsistency in the data, we called back to clarify. Second, while the generalizability of this study may be somewhat limited as we focused on one hospital, SCMC, as one of the primary pediatric tertiary care centers in China, it provides treatment of severe disease in children around China (Our data showed that 79% of patients were non-local residents). Therefore, our results are likely applicable to other geographic areas. Third, our sample included the families who were relatively rich compare with the national average, which limited our ability to assess the financial impact among the families with low socio-economic status.

Families of children with ALL experience a wide range of costs. An ongoing investigation of families' costs will yield a rich understanding of the disease costs, formulate the basis of cost assessments, and lend insight into practice and policy changes aimed at lessening the economic impact of this burden.

Contribution Statement

YR and XL designed the study, developed a data analysis plan and equally contributed to this study. XL performed a statistical analysis of the data. All authors made significant contributions to the interpretation of results and participated in drafting and revising the manuscript. All authors have approved the final version.

Competing Interests

None.

Ethics approval

This study was approved by the Institutional Review Board of Shanghai Children's Medical Center.

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Data Sharing Statement

Data are not available because the authors promised the SCMC that the information was only used for research, and it would not be disclosed.

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Table 1. Child, parent, and family characteristics (n=161)

	Total (N=161)		Urban (N=90)		Rural (N=71)		P-value
Characteristics	N	%	N	%	N	%	
Child characteristics							
Age at diagnosis, years (mean, SD)	4.9	(3.3)	4.7	(3.2)	5.1	(3.3)	0.48
Average treatment period, months (mean, SD)	11.6	(9.6)	12.4	(10.4)	10.6	(8.5)	0.25
Gender							
Male	94	58.4	54	60.0	40	56.3	0.64
Female	67	41.6	36	40.0	31	43.7	
No Health insurance	52	33.1	32	35.5	20	28.1	0.33
Parent characteristics							
Age at diagnosis, years (mean, SD)	33.2	(4.3)	33.6	(4.4)	32.8	(4.7)	0.34
Education (the highest degree of parental education)							
Middle school or lower	67	41.9	18	20.0	50	70.4	<0.001
High/vocational school	32	20.0	17	18.9	15	21.1	
College or above	61	38.1	55	61.1	6	8.5	
Household characteristics							
Family size (mean, SD)	4.1	(1.1)	3.8	(0.9)	4.5	(1.1)	<0.001
Household monthly income, USD (mean, SD)	1287.31	(2518.36)	1681.56	(3082.12)	783.35	(1379.65)	0.02
Area of residence							
Shanghai	33	20.6	30	33.3	3	4.2	<0.001
Other provinces	128	79.4	60	66.7	68	95.8	

Table 2. Employment status of parents

Characteristics	N	%	N	%
Employment at diagnosis	Father		Mother	
Government, SOE, or Public sector	35	22.0	32	20.1
Private sector or self-employed	109	68.6	73	45.9
Agriculture	11	6.9	16	10.1
Unemployed or doing housework	4	2.5	38	23.9
Change of employment status (conditional on employed at diagnosis)	Father		Mother	
No change	47	29.9	18	14.8
Completely stop working	13	8.3	8	6.6
Extended leave	97	61.7	96	78.7
Average length of absence, months (mean, SD)	14.4	11.1	18.1	10.8

Table 3. Total cost and its components (in 2010 US$)*

	Total sample (n = 161)				
	Median	IQR	Mean	SD	%
Panel A: Total direct medical costs	12562	9441 - 18120	16307	14488	
Inpatient cost	7064	5097 - 11786	7622	18645	66.9
Outpatient cost	5272	3391 - 6712	7031	6843	33.1
Panel B: Total direct non-medical costs	5220	3013 - 8543	6441	5038	
Accommodation	2158	280 - 3700	2898	3357	45.0
Transportation	112	44 - 219	175	219	2.7
Food and nutritional supplements	1682	392 - 2864	2289	2743	35.5
Hygiene cleaning products and auxiliary treatment equipment	177	59 - 505	429	651	6.7
Gifts and treats including electrical devices	428	123 - 841	651	888	10.1
Panel C: Total indirect costs	1677	0 - 6727	8733	24321	
Total costs	22702	15518-33177	31480	31847	

*The average exchange rate between RMB and USD in 2010 is 6.7695.

Table 4. Costs of different categories during the treatment (in 2010 USD)*

	Urban sample (n =90)					Rural sample (n = 71)					P-Value**
	Median	IQR	Mean	SD	%	Median	IQR	Mean	SD	%	
Panel A: Total direct medical costs	11820	8680 - 17158	17075	17854		12857	9939 - 18660	15332	8531		0.393
Inpatient cost	7064	5018 - 11458	12048	15571	70.6	6894	5157 - 11786	9475	7176	61.7	0.155
Outpatient cost	4735	2803 - 6375	5027	3383	29.4	5634	4495 - 6843	5858	2321	38.3	0.074
Panel B: Total direct non-medical costs	5343	2873 - 9447	6707	5535		5204	3443 - 7265	6104	4342		0.468
Accommodation	1752	0 - 3900	2830	3880	42.2	2568	1430 - 3676	2983	2569	48.9	0.727
Transportation	137	30 - 280	189	207	2.8	109	56 - 178	156	233	2.6	0.376
Food and nutritional supplements	1773	221 - 3418	2392	2849	35.7	1472	463 - 2482	2158	2618	35.4	0.597
Hygiene cleaning products and auxiliary treatment equipment	281	74 - 675	520	706	7.8	103	36 - 278	313	556	5.1	0.041
Gifts and treats including electrical devices	519	147 - 981	774	1067	11.5	328	70 - 701	494	558	8.1	0.034
Panel C: Total indirect costs	463	0 - 7379	12343	31598		1822	44 - 6391	4157	6677		0.018
Total costs	22154	14036 - 41289	36125	40487		22860	16065 - 30601	25593	13088		0.021

* The average exchange rate between RMB and USD in 2010 is 6.7695.
** P value for *t* test comparing means between rural and urban samples.

Questionnaire on Family Financial Burden of Child with Acute Lymphoblastic Leukemia

A、Family Background Information

1. Your date of birth (solar calendar)：_____. You are the child's (a) father (b) mother.
2. Your place of residence (province)：_____，your current HuKou location：_____，your current Hukou status：(a) rural (b) urban
3. Date of birth of your spouse (solar calendar)：_____, your spouse's place of residence (province)：_____，your spouse's current Hukou location：_____, your spouse's current Hukou status：(a) rural (b) urban
4. Place of residence of your child（province）：_____, your child's current Hukou location：_____, your child's current Hukou status：(a) rural (b) urban
5. Does your child live with his or her parents? (a) Yes (b) No
6. Prior to the child illness, your child's education level was :(a) not in school (b) in kindergarten (c) in primary school (d) in junior high school
7. Prior to the child illness, your family had a total of _____ people, including___ people with income. After the child fell ill, did your family have new-born child? (a) Yes (b) No
8. Your education level: (a) no formal education (illiterate) (b) primary school or below (c) junior high school or below (d) the high school/technical school (e) college/university (f) master degree or above
9. Education level of your spouse: (a) no formal education (illiterate) (b) primary school or below (c) junior high school or below (d) the high school/technical school (e) college/university (f) master degree or above
10. Prior to the child illness, your average monthly income was_____RMB, your

spouse's average monthly income was_____RMB, and your family's average annual income was_____RMB.

11. Did you own your current residence prior to the child illness? (a) Yes (b) No
12. Did your family belong to low income family prior to the child illness? (a) Yes (b) No
13. Did you purchase social medical insurance for your child before his/her illness? (a) Yes (b) No

    If yes, the insurance purchased was: (a) Urban Resident Basic Medical Insurance (b) Children's Hospitalization Fund (c) New Rural Cooperative Medical Insurance (d) others

    If no, after the child fell ill, did you child enroll in social medical insurance? The enrolled social medical treatment insurance was _____(fill one list in Q13).
14. Did you receive medical assistance for your child after the child became ill? (a) Yes (b) No
15. Did you purchase commercial health insurance for your child before the child became ill? (a) Yes (b) No

    If yes, how many commercial health insurances you purchased for your child: (a)1 (b)2 (c) more than 2

B、Family Financial Burden

B.1 Direct Medical Costs

1. The date of your child's diagnosis at the Children's Medical Center was _____, The completion date of the first three-phase treatment in the Children's Medical Center was _____
2. During the first three-phase treatment, the total medical costs paid to the Children's Medical Center were_____ RMB, to other medical institutions were____RMB, including:

    (a) medical insurance paid: _____ RMB, among them, the commercial medical insurance paid: _____ RMB.

(b) medical assistance (including funded by the Children's Medical Center): _____ RMB.

3. During the first three-phase treatment, the costs that your family paid for purchasing the medicines from other medical institutions were about _____RMB.

B.2 Direct Non-medical Costs

4. During the treatment, your family's average monthly costs on food were_____RMB. Compared with the costs before child's illness, the increased average monthly costs on food were____ RMB.
5. Did your family purchase large electronic products (such as computer, video games, television, refrigerator, etc.) for your child during his or her treatment? (a)Yes (b) No

   If yes, the costs were____RMB. Among them, computer:_____RMB, video games: RMB, television:_____RMB, refrigerators:_____RMB, others：____RMB.
6. Did your family buy toys for your child during the treatment? (a)Yes (b) No

   If yes, the costs were____RMB. Compared with the costs before child illness, the new toy purchase expenses were_____RMB.
7. Your family spent an average of _____RMB on communications per month during the child's treatment. The increased average monthly communication fee was_____RMB, compared with fee before child illness. If you registered for online service for your child, the total costs of the Internet were_____RMB.
8. During the treatment of child, your average monthly costs on purchasing hygiene cleaning products and related materials were ____RMB. The costs of purchasing auxiliary treatment facilities (e.g., ultraviolet disinfection lamp, air purifier, humidifier, etc.) were _____RMB.

[If you do not live in Shanghai, please answer question 9. If you live in Shanghai, please answer question 10.]

9. If you do not live in Shanghai, what kind of transportation did you and your family usually take to and from the Children's Medical Center during your child's treatment? (a) train (b) coach (c) plane (d) others _____

You and your family traveled to Children's Medical Center altogether ___ times. The average costs per person on transportation were _____RMB. The total costs of transportation were_____RMB.

10. If you live in Shanghai, what kind of transportation did you and your family usually take to and from the Children's Medical Center during your child's treatment? (a) taxi (b) family car (c) others

    On average, you and your family commuted from home to Children's Medical Center ___ times each month. Every time the transportation costs were_____RMB. The total costs of transportation were _____RMB.（If using family car, please estimate the costs of fuel, tolls and parking fees, *etc.*）

11. Did you rent an apartment near the hospital for the convenience of your family during your child's hospitalization? (a) Yes (b) No.

    If yes, the agency fee was _____RMB. The average monthly rent was ____ RMB. The average monthly payment for utility was _____RMB. You rent for a total of _____ months.

12. Did you hire a day laborer while your child was hospitalized? (a) Yes (b) No

    If yes, you total hired_____ months. Day laborer worked_____ hours a day; hour salary was _____RMB; day laborer worked _____days per month.

B.3 Indirect Costs

13. Before the child fell ill, what was the type of your work unit：(a) government agency (b) State-owned enterprises (including state-owned holding enterprises) (c) Private enterprise (d) Overseas-invested enterprises, foreign-funded enterprises or foreign-invested enterprises (e) public institution (f) Individual household or freelancer (g) farmer (h) Unemployed

[If question 13 you chose (a)-(e), please answer question 14; If (f)-(h), please answer question 15.]

14. What change did your employment situation have during your child's treatment? (a) unchanged (b) discontinuation of work (c) short-term leave (d) long-term

leave (including irregular leave) (e) others_____

If (c), the average monthly salary or work income decreased by_____%.

If (d), the length of absence from work was_____months. The average monthly salary or work income decreased by_____%

15. What change did your employment situation have during your child's treatment?

(a) unchanged (b) discontinuation of work (c) reduction of workload (d) others__

If (b)，you stop working altogether _____months，the average yearly income decreased by_____%.

If (c)，due to the reduction of workload, the average yearly income decreased by_____%.

16. Before the child fell ill, what was the type of your spouse work unit：(a) government agency (b) State-owned enterprises (including state-owned holding enterprises) (c) Private enterprise (d) Overseas-invested enterprises, foreign-funded enterprises or foreign-invested enterprises (e) public institution (f) Individual household or freelancer (g) farmer (h) Unemployed

[If question 16 you chose (a)-(e), please answer question 17. If (f)-(h), please answer question 18.]

17. What change did your spouse's employment situation have during your child's treatment? (a) unchanged (b) discontinuation of work (c) short-term leave (d) long-term leave (including irregular leave) (e) others

If (c), the average monthly salary or work income decreased by_____%.

If (d), the length of absence from work was_____months. The average monthly salary or work income decreased by_____%

18. What change did your spouse's employment situation have during your child's treatment?

(a) unchanged (b) discontinuation of work (c) reduction of workload (d) others

If (b)，your spouse stop working altogether _____months，the average yearly income decreased by _____%.

If (c)，due to the reduction of workload, the average yearly income decreased by _____%_

19. During the first three-phase treatment, was there other relative besides you and your spouse caring for the child? (a) Yes (b) No
    If yes,_____(who) cared for the child, he or she cared for ____ months. His or her work unit was _____ (no work, please fill "no"). The average monthly income loss for caring child was_____RMB.
20. During the first three-phase treatment, did you hire a full-time staff besides your family to accompany your child? (a) Yes (b) No.
    If yes, she or he escorted for a total of _____months, earning _____RMB.
21. During the first three-phase treatment, other large non-medical expenses that your family incurred for your child included _____. The average expenditure increased _____RMB per month.

B.4 Other Information

1. (Just ask parents with rural Hukou) Before you decided to go to Children's Medical Center for treatment, were you and your spouse aware of the new policy announced by the National Ministry of Health in early 2011 concerning that children's leukemia would be reimbursed by the new rural cooperative medical system (NCMS) for 70%, and the Serious Disease Relief Fund would give 20% compensation according to the family situation? (a) Yes (b) No
2. In terms of medical expenses, reimbursement and concern and other aspects for children's leukemia, do you have any suggestions or appeals to hospital, Health Administrative Department, Medical Insurance Department and other relevant government departments?

_____

_____

3. If we still have questions regarding the questions in the questionnaire, or we want to know more about your family's financial burden and pressure in the future, can we contact you directly for further inquiry? (1) Yes (2) No

Your mobile phone number：_____ Signature of parents：_____

****

The researcher's comprehensive evaluation of the quality of this questionnaire is:

（1）high （2）medium （3）low

****

Signature of interviewer：_____

Date of signature ：_____

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Section and page number (P)
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title page (P1) Abstract (P2)
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract (P2–3)
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Introduction (P4-6)
Objectives	3	State specific objectives, including any prespecified hypotheses	Introduction (P7)
Methods			
Study design	4	Present key elements of study design early in the paper	Methods (P7)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods (P7-8)
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Methods (P7-8)
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Methods (P8)
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Methods (P8-10)
Bias	9	Describe any efforts to address potential sources of bias	Methods (P8) Discussion (P16)
Study size	10	Explain how the study size was arrived at	Results (P10-11)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Methods (P10)
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Methods (P10)
		(*b*) Describe any methods used to examine subgroups and interactions	Methods (P10)
		(*c*) Explain how missing data were addressed	N/A
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Results (P10-12)
		(b) Give reasons for non-participation at each stage	N/A

		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Tables 1, 2 Results (P10-11)
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) Summarise follow-up time (eg, average and total amount)	N/A
Outcome data	15*	Report numbers of outcome events or summary measures over time	Tables 3, 4
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Tables 3 Results (P12)
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Table 4 Results (P12-13)
Discussion			
Key results	18	Summarise key results with reference to study objectives	Discussion (P13)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Discussion (P16)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Discussion (P13-16)
Generalisability	21	Discuss the generalisability (external validity) of the study results	Discussion (P16)
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Funding information (P17)

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.