

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Direct and indirect costs of families with a child with acute lymphoblastic leukemia in an academic hospital in China: a cross-sectional survey
AUTHORS	Ren, Yijiong; Li, Xin

VERSION 1 – REVIEW

REVIEWER	Mejbah Bhuiyan Telethon Kids Institute, Perth, Australia
REVIEW RETURNED	17-Apr-2019

GENERAL COMMENTS	<p>Abstract:</p> <ul style="list-style-type: none">• The result section is very poorly presented. The distribution of costs including indirect cost in rural vs urban families should be informed.• It is difficult to understand the authors conclusion from the results presented in the abstract. <p>Strengths and limitations:</p> <ul style="list-style-type: none">• The authors failed to convince the importance and present the strengths of the research. While the authors took credit the fill up gaps of data, but this is different from study strength.• The section's texts were very similar to abstract's text which should not be <p>Introduction:</p> <ul style="list-style-type: none">• The burden of ALL in China is not mentioned anywhere in the introduction, thus it remains a question whether the burden is significant enough for which cost estimation would be informative. Besides, what is the authors rationale for this study is not clear from the introduction section. Generating new information is important but it is more important to inform the readers why this is important.• The cost categories mentioned in the introduction should be part of methods. <p>Methods:</p> <ul style="list-style-type: none">• Methods on data collection process were well described. However, the statistical analysis used in this research seemed incomplete. The authors did not run any significance test or described 95% CI of the estimates to understand if there were differences between groups.• <p>Results</p> <ul style="list-style-type: none">• Texts in paragraphs of this section were mostly repetitive of the data presented in the tables.• The cost information in the tables should be presented in US\$ for international readers.• The authors provided no information on coping strategy in the result section but discussed about it in discussion section.
-------------------------	--

	<ul style="list-style-type: none"> • The section did not present any way to understand if the difference between rural vs urban were substantially different or not. <p>Discussion:</p> <ul style="list-style-type: none"> • The discussion section can be shorten. • The authors failed to discuss the findings in this section rather repeated the results in many occasions. • Some of the findings were mentioned in discussion section but not in results section. • The discussion section did not provide how the data of this study was comparable to other available data from other settings. There might be limited cost data on ALL developing settings, but author could argue how this data could be comparable to other type of childhood immunosuppressive conditions.
--	---

REVIEWER	Nickhill Bhakta St. Jude Children's Research Hospital
REVIEW RETURNED	18-Apr-2019

GENERAL COMMENTS	<p>This work represents an important contribution to the literature. The authors report the costs, both direct and indirect, associated with the first three phases of therapy at a cancer center in Shanghai. Overall, the data is well presented. However, I do have a few comments:</p> <p>Major:</p> <p>Additional methodological detail regarding the ascertainment of direct medical costs is needed. Right now the paper reads that all costs were recorded according to name/case numbers but without any detail to process. Ideally a microcosting spreadsheet of what inputs went into the direct cost totals should be included. Otherwise, a more detailed account and justification of why the authors think their total costs are complete is required or references (are the methods for the database published anywhere else in detail). Some of this can be placed in a supplement so as not to overwhelm a reader but referenced in the manuscript.</p> <p>What methods for exchange and inflation were incorporated in the analysis?</p> <p>Why were the tables dichotomized as urban vs rural? Why shanghai vs not? Or education status? Univariate analyses on total costs against demographic characteristics could help guide this decision. I presume the sample size is too small for multivariate analyses to identify predictors.</p> <p>The methods appropriately restrict the cohort analyzed to only those completing the first three phases of ALL therapy. How representative of the overall ALL population treated at SPMC is this subgroup? For example, the insurance mix may vary in which case out of pocket costs would be different. Also what impact does abandonment play in determining who was eligible (aka, should we assume the costs generally lower on an intention to treat basis, a finding that is much more relevant from a health services perspective).</p> <p>Building on the above, the data from the paper seems to be from 2014. If follow-up data were available beyond 2014 for the patients enrolled in maintenance, it would add substantially to see if there was an impact on out of pocket expenses/insurance and abandonment.</p>
-------------------------	---

	<p>Overall, the study would benefit from further copy-editing for grammar and clarity.</p> <p>Minor:</p> <p>Can boundaries be placed around each point estimate. For example, IQR for all costs.</p> <p>How are farmers and self-employed different?</p> <p>It is okay from my perspective to report all in USD if the methods for conversion are provided. This would make it easier to read and also provide IQR.</p> <p>A broader review in the discussion of the now growing costing literature in LMIC would be useful for the authors to include.</p>
--	---

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

Reviewer Name: Mejbah Bhuiyan

Institution and Country: Telethon Kids Institute, Perth, Australia

Please state any competing interests or state 'None declared': None

Please leave your comments for the authors below

Comments for the authors are in attached doc file.

Abstract:

The result section is very poorly understand. The distribution of costs including indirect cost in rural vs urban families should be informed.

Response: Sorry for the confusion. As per the suggestion, we have revised the Results section in Abstract.

It is difficult to understand the authors conclusion from the results presented in the abstract.

Response: Sorry for the confusion. We have revised the Conclusion section in Abstract.

Strengths and limitations:

The authors failed to convince the importance and present the strengths of the research. While the authors took credit the fill up gaps of data, but this is different from study strength.

Response: As per the suggestion, we have revised the 'Strengths and limitations' section.

The sections's texts were very similar to abstract's text which should not be

Response: As per the suggestion, we have revised the 'Strengths and limitations' section.

Introduction:

The burden of ALL in China is not mentioned anywhere in the introduction, thus it remains a question whether the burden is significant enough for which cost estimation would be informative. Besides,

what is the authors rationale for this study is not clear from the introduction section. Generating new information is important but it is more important to inform the readers why this is important.

Response: Thank you for the suggestion. We have added the information on the burden of childhood ALL in China and provided rationale of doing this study in the Introduction section. Please see pages 5-6.

The cost categories mentioned in the introduction should be part of methods

Response: As per the suggestion, we have moved the cost categories to the Methods section. Please see page 8.

Methods:

Methods on data collection process were well described. However, the statistical analysis used in this research seemed incomplete. The authors did not run any significance test or described 95%CI of the estimates to understand if there were differences between groups.

Response: As per the suggestion, we have provided p-value for t test comparing rural vs. urban cost estimates. Please see pages 10, 12-13 and Table 4.

Results:

Texts in paragraphs of this section were mostly repetitive of the data presented in the tables.

Response: We have rewritten the Results section to avoid the repetition with the data presented in the tables.

The cost information in the tables should be presented in US\$ for international readers.

Response: As per the suggestion, we have presented the costs in USD in tables 3 and 4. Specifically, to control for inflation, we expressed all cost estimates in 2010 RMB by using the Consumer Price Index, and then converted in USD by using average exchange rate between RMB and USD in 2010 (USD 1.00 = RMB 6.7695). We have added this information in the manuscript. Please see page 10.

The authors provided no information on coping strategy in the result section but discussed about in discussion section.

Response: Thank you for pointing out this issue. We have revised the Discussion section to make sure that all the discussions are based on the results derived from the Results section.

The section did not present any way to understand if the difference between rural vs. urban were substantially different or not.

Response: As per the suggestion, we have provided p-value for t test comparing rural vs. urban cost estimates. Please see pages 12-13 and Table 4.

Discussion:

The discussion section can be shorten.

Response: As per the suggestion, we have shortened the Discussion section.

The authors failed to discuss the findings in this section rather repeated the results in many occasions.

Response: As per the suggestion, we have added more discussions and removed repetition of the results in the Discussion section.

Some of the findings were mentioned in discussion section but not in results section.

Response: Thank you for pointing out this issue. We have revised the Discussion section to make sure that all the discussions are based on the results derived from the Results section.

The discussion section did not provide how the data of this study was comparable to other available data from other settings. There might be limited cost data on ALL developing settings, but author could argue how this data could be comparable to other type of childhood immunosuppressive conditions.

Response: As per the suggestion, we have provided more comparisons of findings of our study and those from previous studies.

Reviewer: 2

Reviewer Name: Nickhill Bhakta

Institution and Country: St. Jude Children's Research Hospital

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

This work represents an important contribution to the literature. The authors report the costs, both direct and indirect, associated with the first three phases of therapy at a cancer center in Shanghai.

Overall, the data is well presented. However, I do have a few comments:

Major:

Additional methodological detail regarding the ascertainment of direct medical costs is needed. Right now the paper reads that all costs were recorded according to name/case numbers but without any detail to process. Ideally a microcosting spreadsheet of what inputs went into the direct cost totals should be included. Otherwise, a more detailed account and justification of why the authors think their total costs are complete is required or references (are the methods for the database published anywhere else in detail). Some of this can be placed in a supplement so as not to overwhelm a reader but referenced in the manuscript.

Response: As per the suggestion, we have added a more detailed information on the components of direct medical costs. Please see pages 9-10.

What methods for exchange and inflation were incorporated in the analysis?

Response: Sorry for the confusion. In the present paper, We expressed all cost estimates in 2010 RMB by using the Consumer Price Index, and then converted in USD by using average exchange rate between RMB and USD in 2010 (USD 1.00 = RMB 6.7695). We have added this information in the manuscript. Please see page 10.

Why were the tables dichotomized as urban vs rural? Why shanghai vs not? Or education status? Univariate analyses on total costs against demographic characteristics could help guide this decision. I presume the sample size is too small for multivariate analyses to identify predictors.

Response: The reasons we chose to dichotomize as rural vs. urban groups are as follows: in China, there are huge differences in the allocation of medical resources between rural and urban areas. High quality medical resources are mainly distributed in large central cities such as Beijing, Shanghai, Guangzhou, etc. Therefore, families with a seriously ill child, especially rural families, have to go to 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 expenditures on transport, accommodation, etc. In addition, there are significant differences between urban and rural areas in terms of income and social security system. As a result, the economic burden is very likely to be different between rural and urban families. More detail explanations have been added in the manuscript. Please see page 6. In the revised manuscript, we added the Chi-square tests and the t tests for bivariate comparisons of categorical and continuous variables for the urban and rural families, respectively. We found that urban families have significantly higher education level, higher monthly income and were more likely to be local residents. The test results suggested that grouping

by household registration type can fully reflect the difference in socio-economic status of different groups. We have added the test results in the manuscript. Please see page11 and Table 1.

The methods appropriately restrict the cohort analyzed to only those completing the first three phases of ALL therapy. How representative of the overall ALL population treated at SPMC is this subgroup? For example, the insurance mix may vary in which case out of pocket costs would be different. Also what impact does abandonment play in determining who was eligible (aka, should we assume the costs generally lower on an intention to treat basis, a finding that is much more relevant from a health services perspective).

Response: According to the previous study, the 5-year survival rate in childhood ALL reaches 72% in China, which means the majority of patients who seek treatment at SCMC are able to complete the first three phases of ALL therapy successfully. Therefore, our study sample is quite representative. Regarding the insurance policy, urban child is eligible to Urban Resident Basic Medical Insurance (URBMI) and rural child is eligible to New Cooperative Medical Scheme (NCMS). Both insurance schemes do not cover outpatient expenses and imported medicine. In terms of inpatient costs, different insurance schemes have different coverage plans. However, within each insurance scheme, it has a uniform standard for the payment of various diseases, which means insurance coverage does not depend on the severity of the disease. Regarding how abandonment affects the cost estimates, the reviewer is right that the costs generally lower on an intention to treat basis. However, although we do not have data on treatment abandonment rate at SCMC, a previous study focusing on treatment abandonment in childhood ALL reported that the average treatment abandonment rate in China is 3.1% with the majority of abandonment cases residing in the low-income region. Our sample families are relatively wealthy compare with national average (we have mentioned this as one of our limitations in the manuscript), therefore, at least for our study sample, the impact of abandonment of treatment on cost estimates should be small.

Ref: Cai J, Yu J, Zhu X, et. al. Treatment abandonment in childhood acute lymphoblastic leukaemia in China: a retrospective cohort study of the Chinese Children's Cancer Group. Arch. Dis. Child 2019; 0: 1-8.

Building on the above, the data from the paper seems to be from 2014. If follow-up data were available beyond 2014 for the patients enrolled in maintenance, it would add substantially to see if there was an impact on out of pocket expenses/insurance and abandonment.

Response: Thank you for your valuable suggestion. Unfortunately the follow-up data were not available beyond 2014 for the patients enrolled in maintenance.

Overall, the study would benefit from further copy-editing for grammar and clarity.

Response: Thank you for the suggestion. We have revised the manuscript accordingly to improve grammar and clarity.

Minor:

Can boundaries be placed around each point estimate. For example, IQR for all costs.

Response: Thank you for the suggestion. We have presented Median and IQR for all costs. Please see Tables 3 and 4.

How are farmers and self-employed different?

Response: In China, farmer is defined as individual who has rural Hukou and is engaged in agricultural industry. Self-employed generally refers to individual who has either urban or rural Hukou, is not engaged in agricultural industry, earns his or her livelihood directly from one's own trade or business.

It is okay from my perspective to report all in USD if the methods for conversion are provided. This would make it easier to read and also provide IQR.

Response: Thank you for the suggestion. We have reported all costs in USD and provided corresponding IQR. Please see Tables 3 and 4.

A broader review in the discussion of the now growing costing literature in LMIC would be useful for the authors to include.

Response: Thank you for the suggestion. We have added information on the burden of childhood ALL and associated treatment costs in China. Please see pages 5-6.