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Determinants of Treatment Abandonment in Childhood Cancer: Results from a Global Survey

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Abstract

Background

Understanding and addressing treatment abandonment (TxA) is crucial for bridging the pediatric cancer survival gap between high-income (HIC) and low-and middle-income countries (LMC). In childhood cancer, TxA is defined as failure to start or complete curative cancer therapy and known to be a complex phenomenon. With rising interest on causes and consequences of TxA in LMC, this study aimed to establish the lay-of-the-land regarding determinants of TxA globally, perform and promote comparative research, and raise awareness on this subject.

Methods

Physicians (medical oncologists, surgeons, and radiation therapists), nurses, social workers, and psychologists involved in care of children with cancer were approached through an online survey February-May 2012. Queries addressed social, economic, and treatment-related determinants of TxA. Free-text comments were collected. Descriptive and qualitative analyses were performed. Appraisal of overall frequency, burden, and predictors of TxA has been reported separately.

Results

581 responses from 101 countries were obtained (contact rate = 26%, cooperation rate = 70%). Most respondents were physicians (86%), practicing pediatric hematology/oncology (86%) for >10 years (54%). Providers from LMC considered social/economic factors (families' low socioeconomic status, low education, and long travel time), as most influential in

analysis, decision to publish or preparation of the manuscript.

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increasing risk of TxA. Treatment-related considerations such as preference for complementary and alternative medicine and concerns about treatment adverse effects and toxicity, were perceived to play an important role in both LMC and HIC. Perceived prognosis seemed to mediate the role of other determinants such as diagnosis and treatment phase on TxA risk. For example, high-risk of TxA was most frequently reported when prognosis clearly worsened (i.e. lack of response to therapy, relapse), or conversely when the patient appeared improved (i.e. induction completed, mass removed), as well as before aggressive/mutilating surgery. Provider responses allowed development of an expanded conceptual model of determinants of TxA; one which illustrates established and emerging individual, family, center, and context specific factors to be considered in order to tackle this problem. Emerging factors included vulnerability, family dynamics, perceptions, center capacity, public awareness, and governmental healthcare financing, among others.

Conclusion

TxA is a complex and multifactorial phenomenon. With increased recognition of the role of TxA on global pediatric cancer outcomes, factors beyond social/economic status and beliefs have emerged. Our results provide insights regarding the role of established determinants of TxA in different geographical and economic contexts, allow probing of key determinants by deliberating their mechanisms, and allow building an expanded conceptual model of established and emerging determinants TxA.

Introduction

Treatment abandonment (TxA) is a leading cause of treatment failure for children with cancer in low- and middle-income countries (LMC).[1–5] TxA entails the failure to start or complete curative therapy (except when such treatment is contraindicated for medical reasons) and is defined by missed therapy for 4 or more consecutive weeks.[4] TxA should be distinguished from "lost to follow-up," which is intended to describe patients who have transferred care elsewhere or have missed follow-up after completing curative therapy. Although reports on TxA in children with cancer exist since early 2000s,[6, 7] a consensus definition for TxA was not available until 2011.[4] This lack of uniformity has limited aggregated and comparative research on determinants (causes) of this complex phenomenon.

This study aimed to establish the lay-of-the-land regarding determinants of TxA globally, perform and promote comparative research, and raise awareness on this subject by capturing data directly from healthcare providers taking care of children with cancer in a variety of regional and economic settings. This study complements efforts in the global pediatric oncology community to assess the global burden of TxA,[1] evaluate published data through systematic reviews and meta-analyses,[2, 3, 5] assess the role of treatment costs on TxA in resource-limited settings,[8] and pursue on-site projects to improve TxA tracking and prevention.[9, 10] We now present our results regarding healthcare providers' opinion on determinants of TxA and compare our results to published literature.

Methods

Strategy

An internet-based survey was conducted on a convenience sample in order to obtain up-to-date information from providers and centers globally. At the time this study was conducted,

Cure4Kids (www.cure4kids.org) offered the broadest representation of pediatric hematology and oncology clinicians globally. Cure4Kids is a free online education and collaboration resource with diverse international membership dedicated to supporting the care of children with cancer and other catastrophic diseases worldwide.[11] Quantitative analyses of frequency, burden, and predictors of TxA were performed and reported elsewhere.[1] This report focuses on descriptive, qualitative, and landscaping analyses of healthcare providers' opinion about causes of TxA in their setting. Queries for this study, therefore, predominantly addressed social, economic, and treatment-related factors that could influence TxA.

Survey

An online, self-administered survey was used (see S1 Text Survey Tool to review all questions as included in the survey). The survey was evaluated for content validity by members of the International Society of Pediatric Oncology (SIOP) committee on Developing Countries (PODC) Working Group on Treatment Abandonment and piloted for ease of use in a second SIOP PODC Working Group. The survey included close- and open-ended questions, was administered in English, and required about 10–15 minutes for completion.

Population

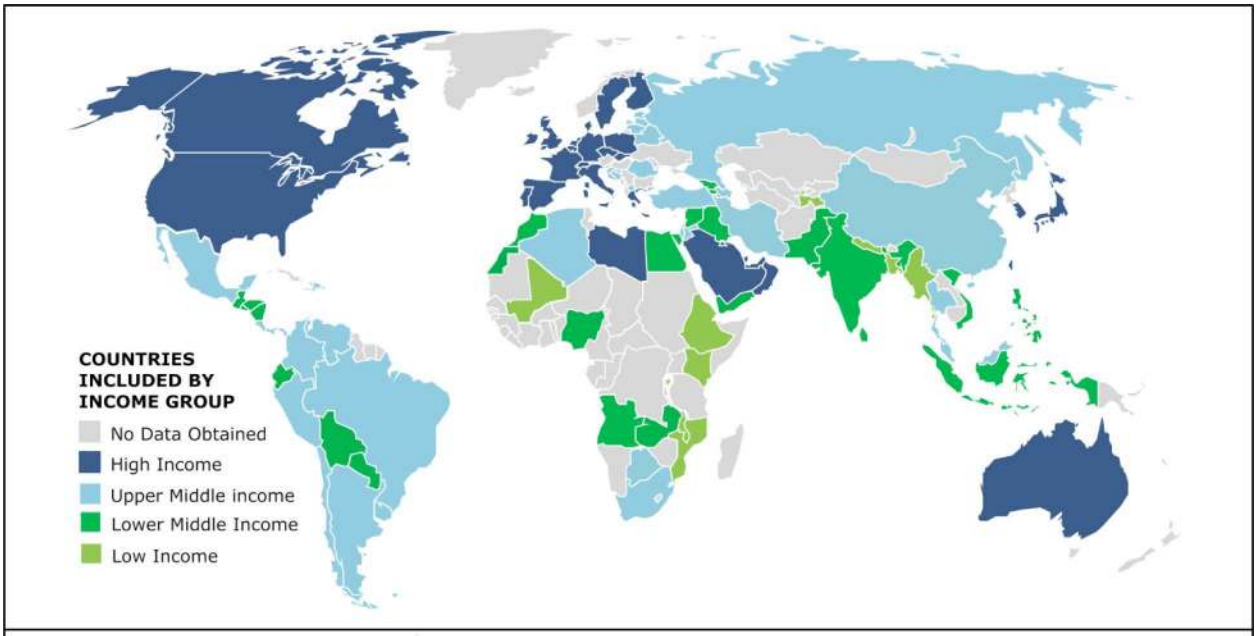
Physicians (including medical oncologists, surgeons, and radiation oncologists), nurses, social workers, and psychologists involved in the care of children with cancer were approached. Email addresses were obtained from the Cure4Kids member directory after ethics approval. Authors never had direct access to the master distribution list. Eligibility was confirmed through two screening questions. Students, data managers, parents and patients were excluded.

Conducting the survey

Subjects received an individualized email-specific link, four reminders, and details regarding research activity and purpose. The survey remained open from February 10 to May 10 of 2012. Patient-level data was not collected or analyzed.

Data Analysis

Survey data was analyzed using Excel and SAS 9.3. Countries were classified according to the World Bank Atlas Method[12] by reported gross national income per capita in 2010 into high-income country (HIC), upper-middle-income country (UMIC), lower-middle-income country (LMIC), or low-income country (LIC) for the univariable and mutlivariable analyses presented in the companion manuscript.[1] These four categories were then collapsed into two categories (HIC and LMC, where LMC stands for low-and-middle income countries and integrates LIC, LMIC, and UMIC) for the descriptive, qualitative, and landscaping analyses presented in this manuscript. Of note, some countries presented in Fig 1 (such as Chile and Russian Federation) have a higher income group and some countries (such as Libya) have lower income group classification as of 2016. Because economies and their classifications change over time, for the sake of consistency, all countries were classified based on the 2010 value, regardless of values in previous or later years. Countries were also classified into 10 geographical groups (Fig 1). Demographic binary variables were analyzed with Fisher's exact test, categorical variables with Chi-square test, ordinal variables with Spearman, and continuous variables with ANOVA or Wilcoxon Rank Test. No adjustments were made for missing data. A p-value <0.05 was considered significant. Open-ended data were independently reviewed and categorized by two investigators (P.F. and G.K.) and reviewed by a third (C.G.L.). Content analysis software was not used



North America: Canada and United States.
Central America and the Caribbean: Dominican Republic, Trinidad and Tobago, Belize, Costa Rica, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, and Panama.
South America: Argentina, Bolivia, Brazil, Chile, Colombia, Ecuador, Paraguay, Peru, Uruguay, and Venezuela.
Eastern Europe: Belarus, Bosnia and Herzegovina, Croatia, Czech Republic, Estonia, Greece, Latvia, Lithuania, Poland, Romania, Russian Federation, Slovak Republic, and Macedonia, FYR.
Western Europe: Belgium, Denmark, Finland, France, Germany, Ireland, Italy, Netherlands, Portugal, Spain, Sweden, Switzerland, and United Kingdom.
Northern Africa: Algeria, Egypt, Arab Rep, Libya, and Morocco.
Sub-Saharan Africa: Ethiopia, Kenya, Malawi, Mozambique, Rwanda, Zambia, Angola, Botswana, South Africa, Mali, and Nigeria.
Central and Eastern Asia: Kyrgyz Republic, China, Hong Kong SAR, China, Taiwan, Province of China, Korea, Rep, Indonesia, Malaysia, Myanmar, Philippines, Singapore, Thailand, Vietnam, Japan, Bangladesh, India, Iran, Islamic Rep, Nepal, Pakistan, and Sri Lanka.
Western Asia: Armenia, Azerbaijan, Bahrain, Georgia, Iraq, Israel, Jordan, Kuwait, Lebanon, West Bank and Gaza, Oman, Qatar, Saudi Arabia, Syrian Arab Republic, Turkey, United Arab Emirates, and Yemen.
Oceania: Micronesia, Fed. Sts, and Australia.

Fig 1. Countries included in study by World Bank income group classification in 2010 and geographical region. Country names listed are as they appear in World Bank. HIC, high-income countries; UMIC, upper-middle-income countries; LMIC, lower-middle-income countries; LIC, low-income countries. Some countries (such as Chile and Russian Federation) have a higher income group as of 2016.

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in the qualitative analysis. Spelling and grammar of responses were corrected only as needed for clarity; in effort to preserve respondents' original intent, translations and any changes in wording done for clarification purposes were noted outside of quotations.

Regulatory Requirements

This study was approved by the Institutional Review Board (IRB) at St. Jude Children's Research Hospital and Dana-Farber Cancer Institute.

Results

Response Rate

The survey was sent to 3,242 email addresses. It obtained an overall contact rate of 26% and a cooperation rate of 70% for the sections of interest for this study (based on definitions

established by the American Association for Public Opinion Research[13]). In particular, of 829 responses obtained (26% cooperation rate), 729 subjects met eligibility criteria, 667 provided demographic information, 581 completed domains on likelihood of TxA by diagnosis, 552 on other determinants, and 118 provided final comments (see S1 Text Survey Tool to review all sections of the survey). There were no major differences between respondents and non-respondents by country, occupation (rate of non-physicians 16% vs. 26%), and preferred language (English for 70% vs. 73%).

Representativeness

Despite drawing from a convenience sample, the survey obtained responses from 101 countries, including all continents and country-income groups (Fig 1; 36 HIC, 29 UMIC, 26 LMIC, and 10 LIC). The 101 countries included host 85.7% of the world population 0–14 years old[1], but Africa, Oceania, and LIC were somewhat under-represented. We believe this resulted from: 1) use of internet-based English-language platform, 2) relative scarcity of providers from these contexts eligible to participate (for example, only 14 LIC and 55 LIC providers were represented in the convenience sample) and 3) low proportion of LIC economies globally (only 34 countries were classified as LIC in 2010).

Respondents

Subjects were predominantly physicians (86%); pediatric hematologists-oncologists in particular (Fig 2A; also S1 Table for frequencies and p-values). Subjects from LMC were also mostly physicians (90%; only 8% were nurses, 2% psychologists, and no social worker responded), but less exclusively pediatric hematologists-oncologists compared to HIC (83% vs. 94%, respectively). Providers from LMC more frequently reported $\leq$10 years of experience (53% vs. 36%) as well as greater access to a local database documenting TxA (41% vs. 16%), compared to providers from HIC. As previously reported, provider experience was the only provider characteristic independently associated with magnitude of TxA in multivariable analyses; younger providers reported higher rates of TxA.[1]

The Centers

Most respondents (65%) worked in medium to large centers and only 3% of subjects reported working in private clinics (Fig 2B; see S1 Table for details on frequencies and p-values). Distribution by center volume was similar between LMC and HIC, but Children's Hospitals were less common in LMC than HIC (38% vs. 58%, respectively). While government funding was the main source of funding overall (72%), reliance on out-of-pocket expenses as the primary source of funding was higher in LMC than HIC (14% vs. 0.6%, respectively). The proportion of families experiencing economic hardship at the center (defined as living below the poverty line or having significant financial challenges) was high in LMC (75%), but also relatively high in HIC (28%). As previously reported, among center characteristics assessed, the country's income category, the center's reliance on out-of-pocket payments as primary source of funding for treatment and, to a lesser extent, higher prevalence of economic hardship, were identified as independent predictors of TxA $\geq$6% in multivariable analyses.[1]

Determinants of TxA

Diagnosis. We explored the role of diagnosis as a determinant of TxA. Subject were asked to report on the *likelihood* of TxA at their center for 10 individual diagnostic groups using an ascending scale: "never/almost never", "rarely", "sometimes", "often", and "always/almost

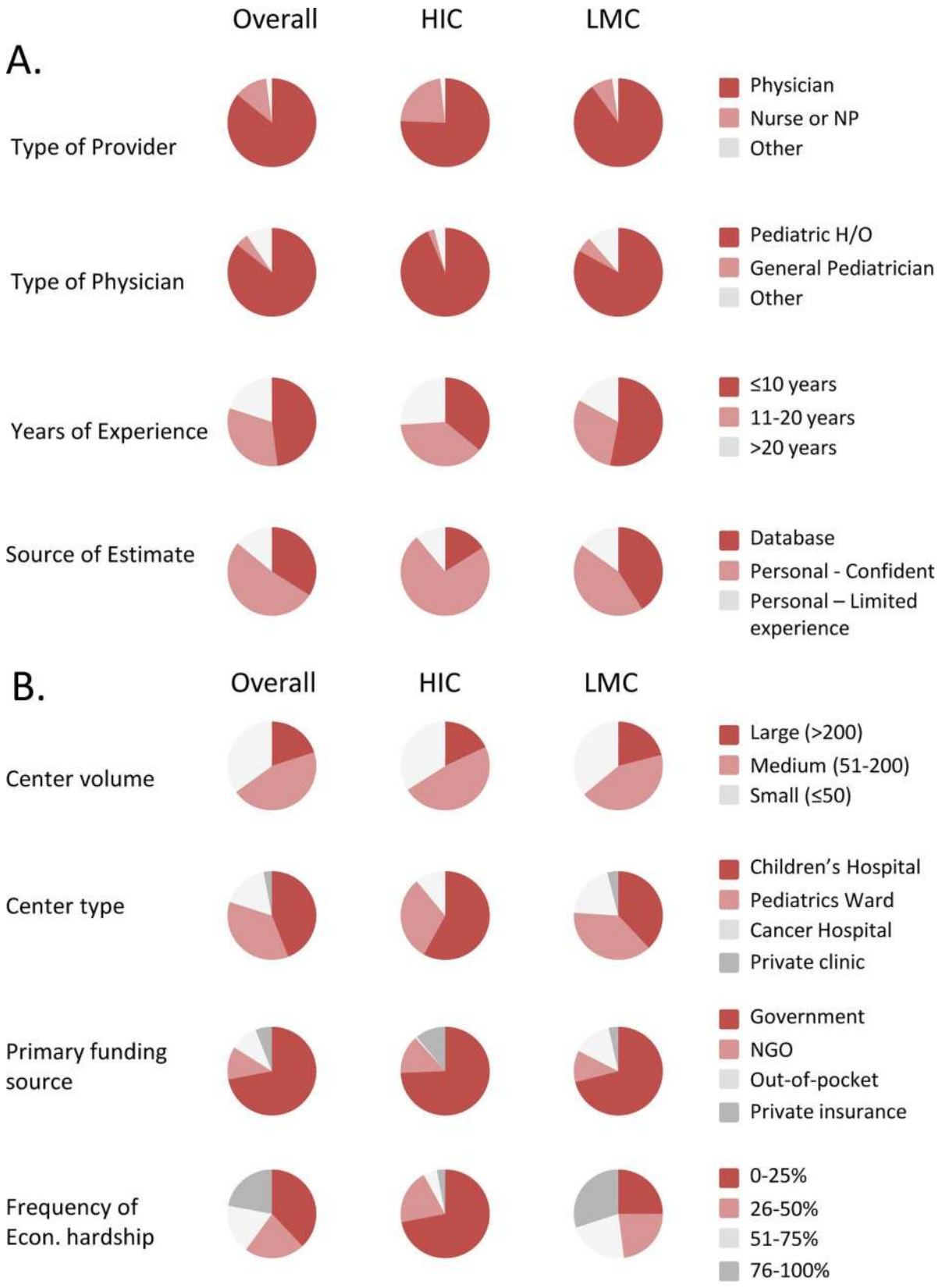
A.
Overall
HIC
LMC
Type of Provider
Physician
Nurse or NP
Other
Type of Physician
Pediatric H/O
General Pediatrician
Other
Years of Experience
≤10 years
11-20 years
>20 years
Source of Estimate
Database
Personal - Confident
Personal – Limited experience
B.
Overall
HIC
LMC
Center volume
Large (>200)
Medium (51-200)
Small (≤50)
Center type
Children's Hospital
Pediatrics Ward
Cancer Hospital
Private clinic
Primary funding source
Government
NGO
Out-of-pocket
Private insurance
Frequency of Econ. hardship
0-25%
26-50%
51-75%
76-100%

Fig 2. Provider (A) and center (B) demographics. Econ., economic; HIC, high-income countries; LMC, low-and-middle-income countries, NP, nurse practitioner; H/O, hematology/oncology; NGO, non-governmental organization. Percentages and further details of other provider and center characteristics are provided in S1 Table.

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always". For each of the 10 diagnoses analyzed, the overall *likelihood* of TxA increased as the country's World Bank income category decreased ($p<0.0001$ in each case). The categories "always/almost always" and "often" were aggregated to reflect *high-likelihood* of TxA. A "not applicable" option was available and it was removed from the denominator, resulting in a variable effective response rate by diagnosis; while retaining comparability across diagnoses. As seen in Fig 3, the likelihood of TxA varied by diagnosis. In LMC, *high-likelihood* was reported most frequently for bone sarcomas (20% of providers) and least frequently for Hodgkin disease and Wilms tumor (4%), although several diagnoses shared a similar range (10–13%); acute myeloid leukemia, retinoblastoma, acute lymphoblastic leukemia, brain tumors, and soft tissue

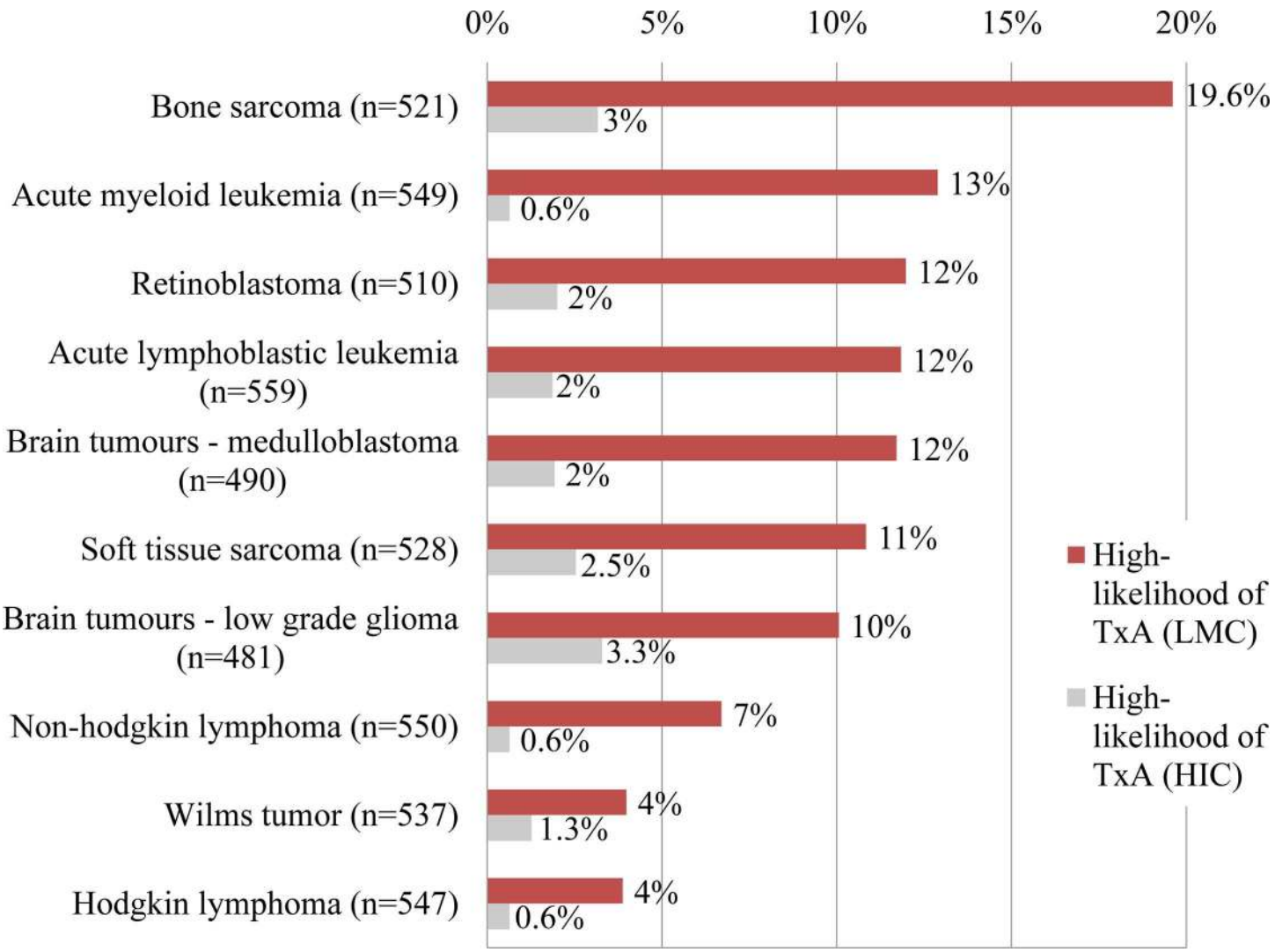

Fig 3. Likelihood of TxA by diagnosis. High-likelihood of TxA entailed report of TxA occurring "often" or "always/almost always". Variable sample size results from provision of a "Don't know" option in which case the subject was removed from the denominator. HIC, high-income countries; LMC, low- and middle-income countries; TxA, treatment abandonment; n, refers to the number of responses for each diagnosis.

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sarcomas. Each diagnosis frequency's ranking and range varied depending on the country's income category (S1 Fig). Differences in ranking by income category were most notable for retinoblastoma, medulloblastoma, and acute myeloid leukemias between the LMIC and UMIC subgroups; UMIC ranked retinoblastoma high for *high-likelihood* of TxA, while LMIC ranked it low. Interestingly, medulloblastoma and acute myeloid leukemias showed a reverse trend (S1 Fig). Finally, as expected, the range of reported *high-likelihood* of TxA by diagnosis increased as the country group income decreased; 1–3% in HIC and 1–10% UMIC to 7–31% in LMIC and 0–50% in LIC (S1 Fig). These findings suggest the role of diagnosis, as a determinant of TxA is sensitive to the overall socioeconomic context.

Treatment phase

In order to assess mechanisms of TxA, providers were presented with scenarios for acute lymphoblastic leukemia, Wilms tumor, and bone sarcoma and asked to select up to three stages in treatment during which risk of TxA was highest. Scenarios were selected based on a face validity exercise (see methods). Providers could respond "not applicable" and these responses were removed from the denominator. Across all three scenarios, high-risk of TxA was most frequently reported for children not responding to treatment or experiencing disease progression (27–31% of responses, Fig 4), particularly in HIC. In acute lymphoblastic leukemia, high-risk of TxA was otherwise similar between pre-treatment, induction, and maintenance therapy phases (20–24%; Fig 4A). However, by income group, TxA during acute lymphoblastic leukemia induction or intensification was reported with higher frequency by LMC providers (22%) than HIC providers (13%). In the case of Wilms tumor, the period after surgical removal of the tumor was also considered high-risk, particularly in LMC (19% of overall, 15% in HIC and 20% in LMC; Fig 4B). Very few providers from HIC reported TxA to occur in Wilms tumor before or after surgical resection (1.5% and 3%, respectively), compared to providers from LMC (6.5% and 15%, respectively). Finally, for bone sarcomas, the pre-amputation period was considered high-risk, particularly in LMC (28% overall, 11% in HIC and 31% in LMC; Fig 4C). Free-text responses manually reviewed supported the distributions described. Therefore, either the treatment phase itself or perceived prognosis appeared to influence the identified high-risk periods.

Socioeconomics, beliefs, preferences, comorbidities, and others

Subjects were asked how each of 15 factors would influence the *likelihood* of TxA in their setting. The S2 Fig shows the factors assessed and their distribution by income category. The categories "increases" and "strongly increases" were aggregated to describe factors perceived to increase the *likelihood* of TxA. All factors except older age and male gender were perceived as significantly more influential in LMC as in HIC (only older age and male gender had p-value >0.05, see S2 Fig). Based on the frequency and ranking of each factor, five patterns were identified.

1. Factors perceived to play a major role in LMC, but comparatively lower in HIC: low socioeconomic status, low parental education, and long travel time to center (these three are here on referred to as social/economic factors).
2. Factors perceived to play an important role in both LMC and HIC: preference for complementary and alternative medicine (CAM) and concern for adverse effects and toxicity.
3. Factors perceived to play a moderate role in HIC, but comparatively lower in LMC: strongly held faith or religious beliefs and older age/adolescent.

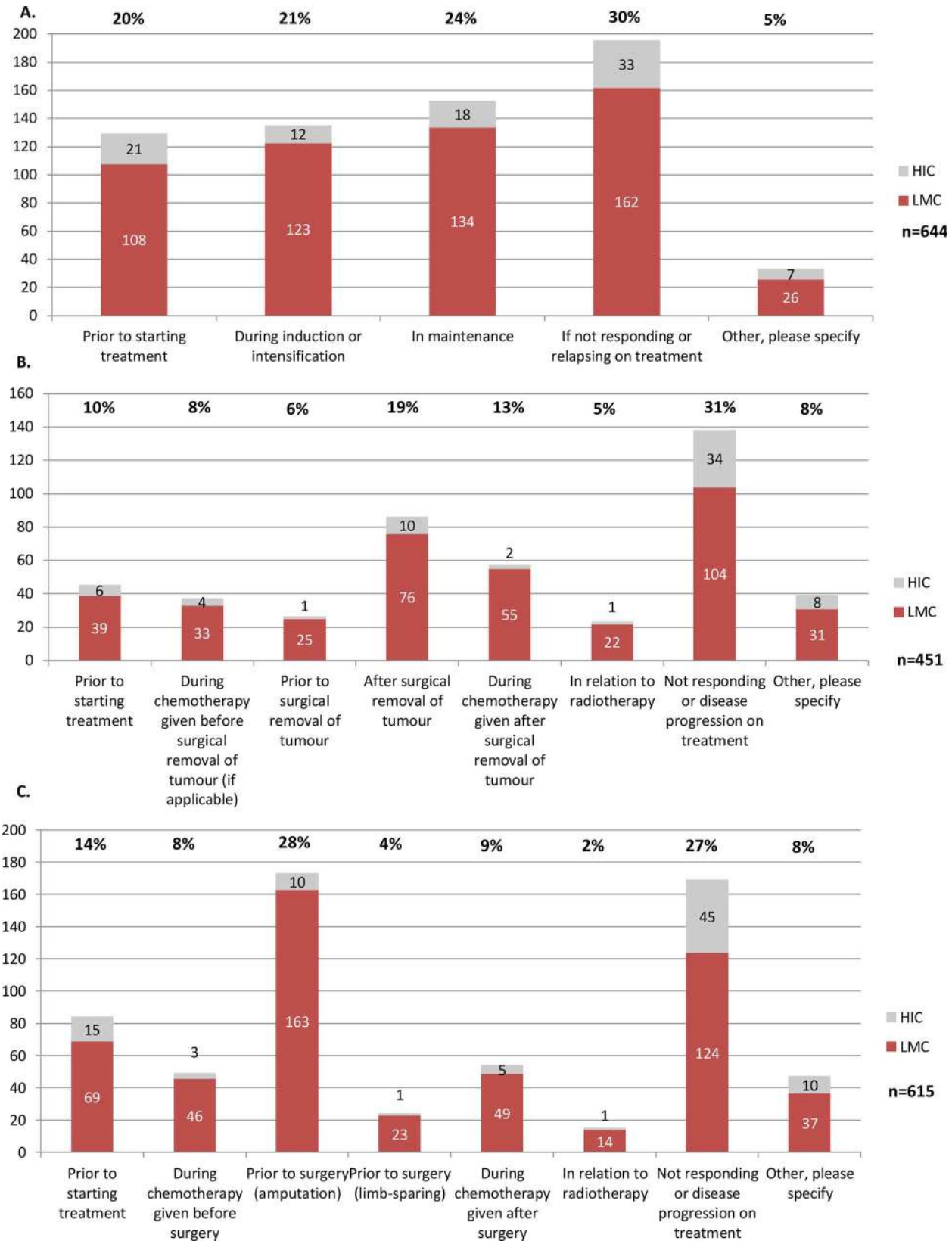
A.
20%
21%
24%
30%
5%
200
180
160
140
120
100
80
60
40
20
0
21
108
12
123
18
134
33
162
7
26
HIC
LMC
n=644
Prior to starting treatment
During induction or intensification
In maintenance
If not responding or relapsing on treatment
Other, please specify
B.
10%
8%
6%
19%
13%
5%
31%
8%
160
140
120
100
80
60
40
20
0
6
39
4
33
1
25
10
76
2
55
1
22
34
104
8
31
HIC
LMC
n=451
Prior to starting treatment
During chemotherapy given before surgical removal of tumour (if applicable)
Prior to surgical removal of tumour
After surgical removal of tumour
During chemotherapy given after surgical removal of tumour
In relation to radiotherapy
Not responding or disease progression on treatment
Other, please specify
C.
14%
8%
28%
4%
9%
2%
27%
8%
200
180
160
140
120
100
80
60
40
20
0
15
69
3
46
10
163
1
23
5
49
1
14
45
124
10
37
HIC
LMC
n=615
Prior to starting treatment
During chemotherapy given before surgery
Prior to surgery (amputation)
Prior to surgery (limb-sparing)
During chemotherapy given after surgery
In relation to radiotherapy
Not responding or disease progression on treatment
Other, please specify

Fig 4. Risk of TxA by treatment phase for three diagnostic scenarios. A: Acute lymphoblastic leukemia. B: Wilms tumor. C: Bone sarcoma. Each provider could mark up to 3 responses. Variable response rate results from provision of "not applicable" category, in which case response was removed from denominator. HIC, high-income countries; LMC, low- and middle-income countries; n, refers to the number of responses. Percentages at the top reflect distribution across columns. Values within the columns reflect count distribution by country-income group; HIC vs. LMC.

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4. Factors perceived to play a moderate role in both LMC and HIC: belief in incurability of cancer, insufficient communication, and painful diagnostic or therapeutic procedures.
5. Factors perceived to play minor role, but comparatively higher in LMC than HIC: malnourishment, HIV status, younger age, and female gender.

The same 15 factors were analyzed by geographical group (Fig 5) looking for regional differences in their appraisal. Responses from North America and Europe showed preference for CAM, concerns about toxicity, and older age as important factors in these regions. Parental education was perceived of higher influence in Eastern than Western Europe. Responses from Central and South America gave most importance to social/economic factors, followed by beliefs, toxicity, older age, and preference for CAM. Responses from North and Sub-Saharan Africa contrasted somewhat in their response patterns; while both groups weighted socioeconomic factors and toxicity highly, those from Sub-Saharan Africa gave added weight to

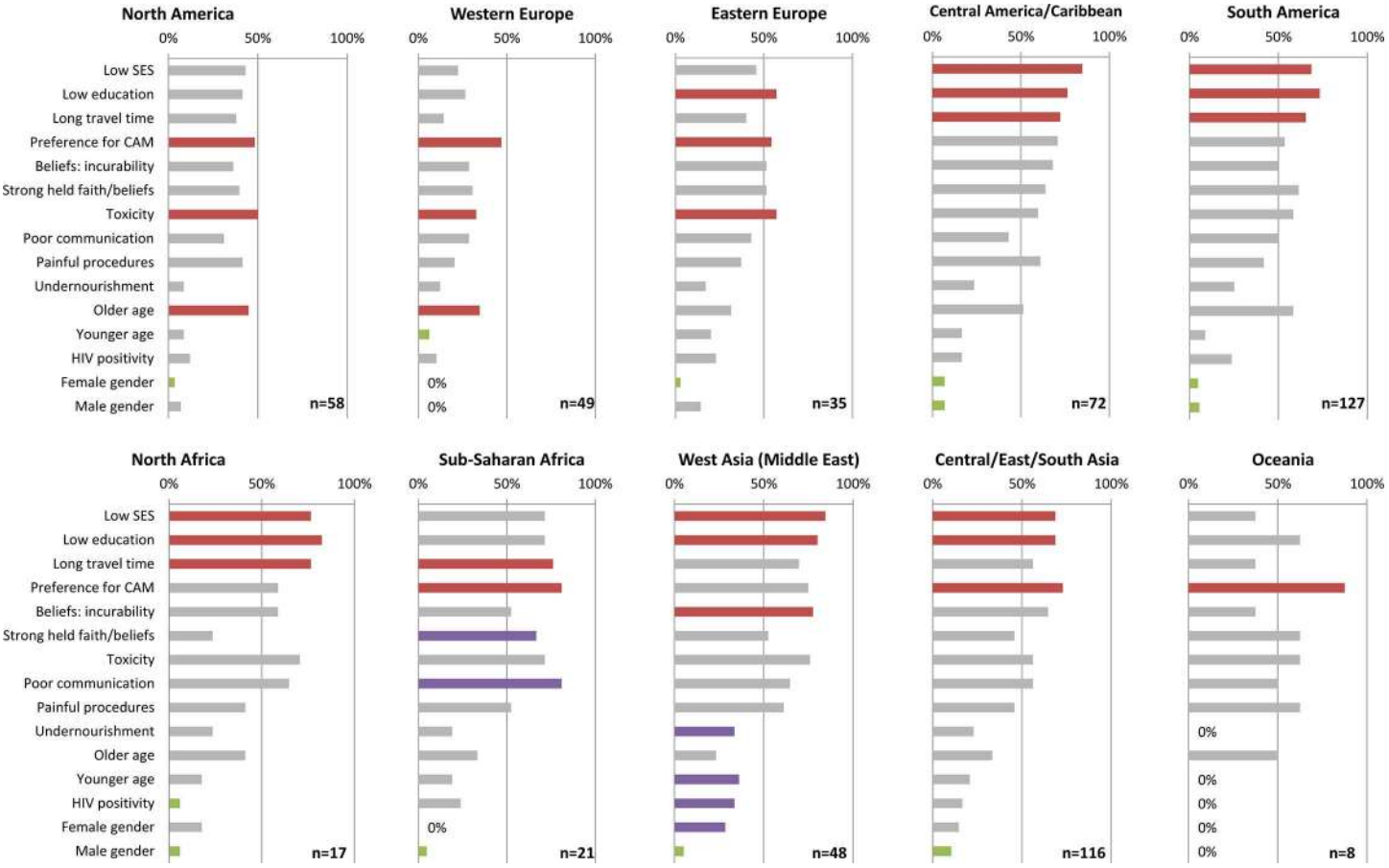

Fig 5. Report of high-likelihood of TxA by specific factors and geographic group. Positive responses arise from affirmative response to "increases" or "strongly increases" likelihood of TxA. The factors with the 3 highest frequencies for each region are reported in red. Factors with lowest frequency in green, except if response = 0%. Purple highlights interesting response pattern in the Middle East and Sub-Saharan Africa as discussed in the text. SES, socioeconomic status; CAM, complementary and alternative medicine.

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preferences, beliefs, and communication. Responses from West Asia (Middle East) rated most factors relatively high for their country income level. Of particular interest was the high rating of factors related to therapy (beliefs about incurability and concerns about toxicity) and factors related to vulnerable populations (younger age, HIV positivity, and female gender). Central-East-South Asia followed a similar pattern as Central-South America. Oceania (the smallest region analyzed) ranked preference for CAM as the dominant factor increasing TxA. Therefore, although social/economic factors achieved the highest ranking among LMC in the analysis by country income group, regional patterns were also readily identified and likely reflect cultural differences between providers and/or regions.

In an effort to identify additional and/or emerging factors, subjects were asked to provide comments and to suggest factors that influenced the *likelihood* of TxA in their setting. The summary from 194 interpretable responses provided by 104 subjects is presented in Fig 6 along with selected illustrative comments. All previously established or reported factors are listed at the top of the ecologic model and all newly identified or emerging factors below the ecologic model. A more detailed description of each construct and its frequency is also available (S2 Table). Most of the factors addressed in close-ended queries were supported by open-ended queries and free-text comments. Recurrent themes included: a) contextual factors such as the issue of healthcare financing, b) center and care delivery-related factors such as the negative impact of poor infrastructure and limited human resources at the center, c) family factors such as competing family crises and problematic family dynamics, and d) patient factors related to vulnerability or treatment, such as immigration status and need for/fear of aggressive surgery, respectively. Themes not previously reported included the protective impact of personal character and the negative impact of belonging to vulnerable populations, such as discriminated, native/indigenous, or immigrant populations. Immigration status was identified as a factor specifically important in UMIC and HIC, where other factors are presumably lessened.

Although comments from providers from HIC were less frequent, they expressed particular concerns regarding contextual factors such as lack of healthcare coverage for immigrant populations and the negative impact of mis-information in the media; care delivery factors such as informed consent for therapy when language barriers exist, and the issue of respecting adolescent autonomy in medical decision-making (particularly when there is refusal of certain aspects of treatment); and family and patient-related factors, such as parental worries regarding unexpected side effects, the impact of strong religious beliefs or preference for CAM, and the issue of non-adherence with oral medications.

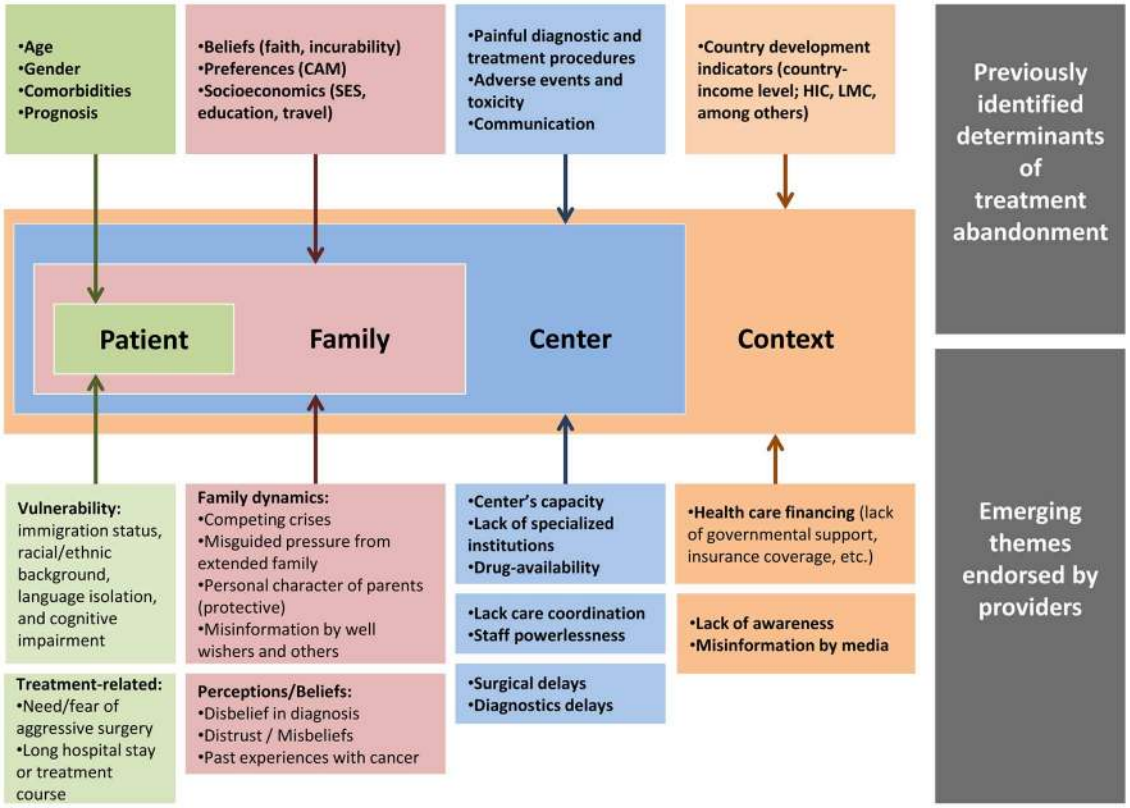
Discussion

Treatment abandonment (TxA) is complex and multifactorial, but understanding and addressing it is vital to bridge the survival gap between HIC and LMC. This is the first study to collect data directly from healthcare providers taking care of children with cancer in a wide variety of regional and economic settings globally. Our results provide valuable insights regarding the role of recognized determinants of TxA such as diagnosis, treatment phase, prognosis, social/economic factors, and beliefs in different geographical and economic contexts. Results also allow probing key established determinants by deliberating their mechanisms and building an expanded conceptual model that takes into account established and emerging patient, family, center, and context factors that influence the risk of TxA (Fig 6).

Diagnosis

Our results show variability in the likelihood of TxA by diagnosis (high for bone sarcomas and low for Hodgkin lymphoma and Wilms tumor), with the range of this TxA likelihood and the

A.



B.

Selected comments for illustration (country and income category in parenthesis)[3]:

Center's capacity to offer socioeconomic support:
"Families have financial difficulty when traveling repeatedly to the treatment facility for chemotherapy. Often parents ask if weekly visits can turn into bimonthly or monthly" (Brazil, UMIC)

Center's capacity -lack of human resources:
"The number of physicians and nurses is low, so the children are not always well nursed" (Romania, UMIC)

Center's capacity and powerlessness:
"Families understand our deadlocks so they abandon" therapy (Turkey, UMIC)

Center's capacity and distrust:
Lack of "confidence in the possibilities of treatment in the country and the belief that the possibility of treatment abroad [has] increased" (Bosnia and Herzegovina, UMIC)

Treatment-related (surgery):
"Although some patients abandon therapy completely, most 'abandonments' are for parts of the therapy, particularly surgery. This becomes critical where surgery is an essential component of curative intent therapy such as with osteosarcomas. They will often continue chemotherapy, but refuse ANY surgery." (Saudi Arabia, HIC)

Personal character, resilience:
"There are families or parents with low level of education and poor, but who have strength of character and are resourceful. This positively affects how the child is treated" (Philippines, LMIC)

Adolescent age group:
"The 'belief in invincibility' present in young adult patients [influenced TxA] in both of our cases within the past 2 years" (United States, HIC)

Misbeliefs:
"Wrongly thinking that the child is cured after resection or first clinical remission" (Egypt, LMIC)

Misguided pressure from extended family:
"Young parents [are] often willing for treatment, but grandparents control the family" (India, LMIC)

Negative influence of the media:
"In the US, a main contributor to abandonment--which is thankfully rare--is mis-information on the internet." (United States, HIC)

Strong religious beliefs:
"My centre sees mainly local children so abandonment rate is very low; but still there are isolated cases on/off, usually parents who are less educated and have poor understanding or hold strong religious beliefs." (Singapore, HIC)

Competing crises – financial:
-Some parents must be "ready to sacrifice the cancer affected child to adequately provide for the other many children in the family" (Nepal, LIC)

-TxA occurs from "lack of time to spend behind the child with cancer, [the parent] has to work to sustain family expenditure" (Bangladesh, LIC)

Health care financing:
-"As the government of Botswana provides the medications, pays all expenses, and provides free transportation to the hospital, abandonment is very low here" (Botswana, UMIC)

- TxA is very low. "I believe that the reason is that we have a good public health system and the general level of education is good. We have only seen sporadic cases due to religious beliefs...in which we have [had] to go to the judge." (Spain, HIC)

-"Administrative barriers imposed by insurance companies" influence TxA (translated from Spanish; Colombia, UMIC)

-"Patients in private clinics abandon treatment due to lack of money to pay for treatments" (translated from Spanish; Ecuador, LMIC)

Fig 6. New and previously identified factors of TxA (A) and supporting statements (B). CAM, complementary and alternative medicine. HIC, high-income countries; UMIC, upper-middle-income countries; LMC, low- and middle-income countries; LMIC, lower-middle-income countries; LIC, low-income countries. Details regarding frequency of each factor are available in S2 Table.

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ranking of specific diagnoses varying by socioeconomic context; a finding consistent with other studies documenting higher rate of TxA for specific diagnoses (sarcomas, retinoblastoma, etc.).[2, 14–16] However, experience demonstrates that when baseline income inequalities and frequency of TxA are high, a significant number of patients with lymphoma and Wilms tumor abandon therapy.[17–24] For these common and curable childhood cancers, even small percentages of TxA may be significant in crude numbers. Furthermore, there is no inherent mechanism by which having a specific diagnosis should cause TxA. The association is most likely mediated by determinants such as the social/economic context, beliefs, strategies needed or available for cure, and prognosis. Therefore, documentation of differences in risk or burden of TxA by diagnosis at centers should be interpreted taking into account the overall frequency of the disease as well as the overall frequency of TxA.

We believe documenting this differential in the likelihood of TxA by diagnosis offers two take-home messages. First, centers should track TxA by disease (and not assume that the frequency of TxA observed for one disease applies to other diseases) in order to identify patient populations at higher risk of TxA or for whom the current strategies to prevent TxA are not working. Second, as interventions and priorities are established, centers should keep in mind the potential untapped opportunities to increase survival outcomes through TxA prevention in children with curable cancer.

As previously mentioned, we hypothesized that social/economic context, aggressiveness of the treatment strategy, and prognosis could serve as mediators between diagnosis and TxA. Providers' comments supported our hypothesis. For example, the frequency rankings varied by country income group, the need for aggressive and/or mutilating surgery was repeatedly suggested to play a direct role, and the highlighting of specific diagnoses often reflected a comment on prognosis (for example "infant with CNS tumor" or "metastatic sarcoma"). The analysis also revealed the center's capacity (including human resources, supportive care, and drug-availability, among others) and perceived (rather than actual) prognosis as additional mediators. A recent assessment of pediatric oncology centers in Myanmar showed higher TxA for retinoblastoma compared to other oncologic diseases and supported the idea that lack of specialists, radiation services, and supportive care contribute to TxA for this diagnosis in their setting.[14] Perceived poor prognosis, by parents or providers, as a result of failed communication and education strategies are emerging determinants of TxA.[25, 26]

Treatment phase

The role of treatment phase as a determinant of TxA was considered of interest because most studies show TxA to occur early–in the first 3 months of therapy.[16, 27–31] TxA occurring predominantly at later stages of treatment has only been reported in the context of hospital detention policies that impede a patient from leaving the hospital until the bill has been paid.[32–34] However, higher risk of TxA at other phases of treatment (including maintenance therapy in leukemia, following removal of Wilms tumor, and prior to amputation in sarcomas) has also been reported.[16, 23, 31, 35] In our study, risk of TxA was reported as highest either when the prognosis clearly worsened (lack of response to therapy, relapse), when the general appearance of the child could allow parents to perceive the prognosis as favorable (induction completed, mass removed), or when aggressive/mutilating surgery was proposed. Therefore, as

seen for diagnosis, the mechanism for treatment phase as a determinant of TxA appeared more closely related to perceived prognosis than the treatment phase per se. Although challenging in busy, over-crowded clinics and wards, developing strategies for appropriate communication of treatment plans, expectations, and events may be a cornerstone for reducing TxA.

Established determinants

Based on published literature, several other determinants of TxA were assessed (toxicity, beliefs, pain, etc.). Providers from LMC placed social/economic factors at the top. This finding is consistent with single-institution retrospective studies showing economic constraints (low income or financial difficulties), low parental education (or literacy), and long travel time to be associated with increased risk of TxA[25, 27, 28, 30, 36–42] and treatment-related mortality.[43–45] Interestingly, by region, Sub-Saharan Africa, where 26 of the 34 poorest countries in the world are located, ranked poor communication and preference for CAM, rather than socio-economics, at the top. Studies from Kenya support these findings, prioritizing poor communication as a determinant of TxA.[25, 33]

Providers from HIC and LMC concurred on preference for CAM and concerns regarding treatment toxicity as important; in aggregate, these ranked highest in HIC and second highest in LMC. A possible increase in refusal arising from the appeal of CAM in HIC has been postulated,[46] supported by a survey of clinics in Germany documenting annual incidence of TxA at 0.5% and reporting parents' beliefs as the main reason for refusal or discontinuation of treatment.[47] Therefore, in HIC, TxA as a result of preference for CAM has often been related to families' efforts to reduce toxicity.[48] CAM is broadly used in LMC,[49] but provider appraisal of its role as a determinant of TxA in LMC had not been thoroughly evaluated. Interestingly, interviews with parents suggest preference for CAM in LMC may more closely relate to supporting community beliefs, managing symptoms, and searching for more affordable or accessible alternatives, and not necessarily to a focus on reducing toxicity.[50] In LMC, intensity of treatment appears to be a double-edged sword with side effects perceived by some parents as proof of efficacy,[50, 51] but a major source of concern for others.[51, 52]

Other factors ranked as contributing to TxA included belief in the incurability of cancer, insufficient communication, strongly held faith or religious beliefs, and painful procedures; determinants supported by several single institution studies.[27, 30, 38, 40, 42] The importance attributed to age, gender, nutrition, and HIV status was overall lower, but of greater importance in LMC than HIC. In this study, it was predominantly providers from West Asia (Middle East) who demonstrated a particular concern for vulnerable populations (based on nutritional status, age, gender, chronic illness, or immigration status) as a determinant of TxA. Of these, only malnutrition has been clearly reported to influence outcomes in LMC through correlation with prolonged neutropenia[53] and deaths due to TxA and treatment failure.[54] The impact of dose-modification, supervised nutritional supplementation, increased awareness and high vigilance for this patient population remains to be determined but is likely to be beneficial. The role of gender has been infrequently documented[30] and despite the historical stigma of HIV, particularly in Sub-Saharan Africa, higher TxA as a result of concurrent HIV infection has not been reported for children with cancer.

New themes and conceptual model

With increased recognition of the role of TxA on global pediatric cancer outcomes,[55] factors beyond social/economic factors and beliefs have emerged. Using free-text comments from providers, we were able to assess and expand our conceptual model of TxA to include a broader range of emerging individual, family, center, and contextual factors (Fig 6).

1. Vulnerability–Immigration status was brought up by providers from HIC, who described poor access to care when these children do not qualify for national health care coverage. Long-hospital stay and treatment course were also endorsed (presumably as a result of the additional time and financial burden they impose).

2. Family dynamics–The role of family dynamics and the connection between families and their communities were of particular interest. Studies show parents are motivated to cure their child with cancer, even in very low resource settings.[24, 50] However, in a recent study from Kenya, interviews with parents who abandoned treatment showed a large proportion of parents to be ill-advised by their community (74% of parents had been advised to seek alternative treatment and 54% to stop medical treatment).[32] Without the balancing act of good communication strategies by providers and social/economic supports to complete therapy (through governmental or non-governmental program assistance), it should be no surprise if families opt to follow the guidance provided by their established social networks.

3. Perceptions–Public perception of cancer is likely very different on HIC and LMC. In HIC, investment by private citizens in fundraising and awareness campaigns for cancer (and childhood cancer in particular) has been strong for decades, allowing cancer to inspire individual resilience and social thriving. In LMC, where the burden of cancer mortality is high and public awareness campaigns are relatively young, a diagnosis of childhood cancer may be poorly accepted or understood. The role of beliefs as a determinant of TxA presented by providers went beyond religiosity or disbelief in curability of cancer. Providers highlighted disbelief in the center's capacity and past family experiences with cancer as additional factors influencing the risk of TxA.

4. Center's capacity: This was highlighted as a determinant of TxA in terms of human resources, infrastructure, supportive care, and internal health delivery systems. Most studies looking at determinants of TxA focus on the family. However, the role providers and centers play in swaying this phenomenon are emerging[24, 26, 40, 52] and the benefits of an integral and multidisciplinary approach have been documented.[56–58] A shift in focus from static determinants of TxA (age, gender, diagnosis, prognosis, etc.) to more actionable factors such as perceived prognosis, communication, center's capacities, and public awareness, allows shifting from traits we can't necessarily control, to areas we can improve.

5. Context: The issue of healthcare financing for catastrophic illnesses and the need to protect families from financial suicide is one that burdens policy makers in HIC and LMC.[59] Regarding TxA, lack of governmental support has been associated with higher rate of TxA.[34, 60–62] Incomplete coverage by private insurers and administrative barriers imposed by insurance companies were additional factors raised by providers. Finally, as discussed in the context of preference for CAM and beliefs, lack of awareness and misinformation by the media were postulated by providers to play a role in LMC and HIC, respectively. Continuing to explore how the overall social context directly or indirectly influences TxA through policies, awareness, and perception remains of interest.

In conclusion, TxA is a complex and multifactorial phenomenon. Our results provide valuable insights regarding the role of recognized determinants of TxA in different geographical and economic contexts. Results also allow probing of key determinants by deliberating their mechanisms and building an expanded conceptual model that takes into account patient, family, center, and context factors that influence the risk of TxA.

Regarding the limitations of our study, by using an online English-language platform and drawing from a convenience sample, we likely lowered the chances of receiving information from LIC and possibly selected for more motivated individuals. However, when this study was conducted, the Cure4Kids online membership offered the largest and most diverse cohort of pediatric hematology and oncology providers available to conduct this study. Although not fully representative, the sample achieved was sufficient to meet the exploratory aims of the study. Furthermore, contact and cooperation rates achieved were comparable to other global surveys.[63–66] We also acknowledge the limitations inherent to the survey research methodology including the need to rely on standardization, possible recall bias, and the lack of a confirmatory source in particular. Mindful of these methodological limitations, doing this study has allowed us to explore in great detail, determinants of treatment abandonment which are currently relevant at a global level and explores regional variations in these determinants. We hope our results promote further comparative research on the subject of TxA and its determinants globally.

Supporting Information

S1 Table. Self-reported subject and center characteristics
(PDF)

S2 Table. Determinants of TxA as reported by providers on free-text comments
(PDF)

S1 Fig. Report of high-likelihood of TxA by diagnosis and country income group. Dark blue, HIC = high-income countries; light blue, UMIC = upper-middle-income countries; light green, LMIC = lower-middle-income countries; dark green, LIC = low-income countries; HL = Hodgkin Lymphoma, NHL = Non-Hodgkin Lymphoma; WT = Wilms tumor; RB = Retinoblastoma; STS = Soft tissue sarcoma; ALL = Acute lymphoblastic leukemia; GLIOMA = Brain glioma; AML = Acute myeloid leukemia; BS = Bone sarcoma; and MB = Medulloblastoma.
(PDF)

S2 Fig. Likelihood of TxA by specific factors and country income group. The category "increases likelihood of TxA" entailed report of "increases" or "strongly increases" likelihood of TxA. HIC, high-income countries; LMC, low- and middle-income countries; TxA, treatment abandonment; CAM, complementary and alternative medicine.
(PDF)

S1 Text. Survey Tool. The data presented in this manuscript pertains primarily to questions 1–12, 14–20, and 32 of the survey tool used for data collection. Results for other sections have already been (see text) or will be summarized in additional manuscripts.
(PDF)

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References

1. Friedrich P, Lam CG, Itriago E, Perez R, Ribeiro RC, Arora RS. Magnitude of Treatment Abandonment in Childhood Cancer. PloS one. 2015; 10(9):e0135230. doi: 10.1371/journal.pone.0135230 PMID: 26422208; PubMed Central PMCID: PMCPMC4589240.
2. Arora RS, Eden T, Pizer B. The problem of treatment abandonment in children from developing countries with cancer. Pediatr Blood Cancer. 2007; 49(7):941–6. Epub 2007/01/26. doi: 10.1002/pbc.21127 PMID: 17252565.
3. Arora RS, Pizer B, Eden T. Understanding refusal and abandonment in the treatment of childhood cancer. Indian pediatrics. 2010; 47(12):1005–10. Epub 2011/01/12. PMID: 21220796.
4. Mostert S, Arora RS, Arreola M, Bagai P, Friedrich P, Gupta S, et al. Abandonment of treatment for childhood cancer: position statement of a SIOP PODC Working Group. Lancet Oncol. 2011; 12 (8):719–20. Epub 2011/07/02. doi: S1470-2045(11)70128-0 [pii] doi: 10.1016/S1470-2045(11)70128-0 PMID: 21719348.
5. Gupta S, Yeh S, Martiniuk A, Lam CG, Chen HY, Liu YL, et al. The magnitude and predictors of abandonment of therapy in paediatric acute leukaemia in middle-income countries: A systematic review and meta-analysis. Eur J Cancer. 2013. Epub 2013/04/20. doi: 10.1016/j.ejca.2013.03.024 PMID: 23597721.
6. Sweet-Cordero A, Antillon F, Baez F, Valverde P, Weinberg V, Ruanu I, et al. Factors that influence abandonment of care among children with cancer in Guatemala [abstract] Pediatr Blood Cancer. 1999; 33(1):151.
7. Spinetta JJ, Masera G, Eden T, Oppenheim D, Martins AG, van Dongen-Melman J, et al. Refusal, non-compliance, and abandonment of treatment in children and adolescents with cancer: a report of the SIOP Working Committee on Phychosocial Issues in Pediatric Oncology. Medical and pediatric oncology. 2002; 38(2):114–7. Epub 2002/01/29. PMID: 11813177.
8. Ahuja S, Lederman S, Bagai P, Tsimicalis A, Martiniuk A, Arora RS. A pilot study to determine the out-of-pocket expenditures by families of children being treated for cancer at public hospitals in India [ABSTRACT]. 46th Congress of the International Society of Paediatric Oncology (SIOP) 2014: Toronto, Canada 22nd–25th October, 2014. Pediatr Blood Cancer. 2014; 61(S2):S159.
9. Salaverria C, Rossell N, Fuentes S, Vasquez F, Hernandez A, Lam CG, et al. Identifying causes of missing appointment and implementing inverventions in real time increases treatment compliance and reduces abandonment rates for childhood cancer in El Salvador [Abstract]. 46th Congress of the International Society of Paediatric Oncology (SIOP) 2014: Toronto, Canada 22nd–25th October, 2014. Pediatr Blood Cancer. 2014; 61(S2):S252.
10. Bustamante M, Rivas S, Caceres A, De Pernillo M, Luna-Fineman S, Martinuik A, et al. A prospective pilot study to describe the out-of-pocket expenses incurred by families of children newly diagnosed

with cancer in Guatemala [Abstract]. 46th Congress of the International Society of Paediatric Oncology (SIOP) 2014: Toronto, Canada 22nd–25th October, 2014. Pediatr Blood Cancer. 2014; 62(S2):S403.

11. Quintana Y, Nambayan A, Ribeiro R, Bowers L, Shuler A, O'Brien R. Cure4Kids—building online learning and collaboration networks. AMIA Annual Symposium proceedings / AMIA Symposium AMIA Symposium. 2003:978. Epub 2004/01/20. PubMed PMID: 14728482; PubMed Central PMCID: PMC1480170.
12. The World Bank: Country and Lending Groups. Available at: http://data.worldbank.org/about/country-classifications/country-and-lending-groups. Retrieved August 18, 2011.
13. American Association for Public Opinion Research "Response Rates—An Overview" and "AAPOR Response Rate Calculator". Available at: http://www.aapor.org/Education-Resources/For-Researchers/Poll-Survey-FAQ/Response-Rates-An-Overview.aspx. Retrieved August 20, 2016. Available from: http://www.aapor.org/Education-Resources/For-Researchers/Poll-Survey-FAQ/Response-Rates-An-Overview.aspx
14. Halbert J, Khaing AA. Overview of pediatric oncology and hematology in Myanmar. South Asian journal of cancer. 2014; 3(1):78–82. Epub 2014/03/26. doi: 10.4103/2278-330X.126548 PMID: 24665454; PubMed Central PMCID: PMC3961876.
15. Luna-Fineman S, Barnoya M, Bonilla M, Fu L, Baez F, Rodriguez-Galindo C. Retinoblastoma in Central America: report from the Central American Association of Pediatric Hematology Oncology (AHOPCA). Pediatr Blood Cancer. 2012; 58(4):545–50. Epub 2011/09/13. doi: 10.1002/pbc.23307 PMID: 21910211.
16. Friedrich P, Ortiz R, Strait K, Fuentes S, Gamboa Y, Arambu I, et al. Pediatric sarcoma in Central America: outcomes, challenges, and plans for improvement. Cancer. 2013; 119(4):871–9. Epub 2012/09/14. doi: 10.1002/cncr.27816 PMID: 22972687; PubMed Central PMCID: PMC3535564.
17. Castellanos EM, Barrantes JC, Baez LF, Gamboa Y, Pena A, Alabi S, et al. A chemotherapy only therapeutic approach to pediatric Hodgkin lymphoma: AHOPCA LH 1999. Pediatr Blood Cancer. 2014; 61(6):997–1002. Epub 2013/12/19. doi: 10.1002/pbc.24905 PMID: 24347509.
18. Sandlund JT, Fonseca T, Leimig T, Verissimo L, Ribeiro R, Lira V, et al. Predominance and characteristics of Burkitt lymphoma among children with non-Hodgkin lymphoma in northeastern Brazil. Leukemia: official journal of the Leukemia Society of America, Leukemia Research Fund, UK. 1997; 11(5):743–6. Epub 1997/05/01. PMID: 9180301.
19. Moleti ML, Al-Hadad SA, Al-Jadiry MF, Al-Darraji AF, Al-Saeed RM, De Vellis A, et al. Treatment of children with B-cell non-Hodgkin lymphoma in a low-income country. Pediatr Blood Cancer. 2011; 56(4):560–7. Epub 2011/02/08. doi: 10.1002/pbc.22905 PMID: 21298740.
20. Fadoo Z, Belgaumi A, Alam M, Azam I, Naqvi A. Pediatric lymphoma: a 10-year experience at a tertiary care hospital in Pakistan. Journal of pediatric hematology/oncology. 2010; 32(1):e14–8. Epub 2010/01/07. doi: 10.1097/MPH.0b013e3181bdf1f3 PMID: 20051771.
21. Madani A, Zafad S, Harif M, Yaakoubi M, Zamiati S, Sahraoui S, et al. Treatment of Wilms tumor according to SIOP 9 protocol in Casablanca, Morocco. Pediatr Blood Cancer. 2006; 46(4):472–5. Epub 2005/07/22. doi: 10.1002/pbc.20436 PMID: 16035094.
22. Israels T, Molyneux EM, Caron HN, Jamali M, Banda K, Bras H, et al. Preoperative chemotherapy for patients with Wilms tumor in Malawi is feasible and efficacious. Pediatr Blood Cancer. 2009; 53(4):584–9. Epub 2009/06/18. doi: 10.1002/pbc.22138 PMID: 19533658.
23. Abuidris DO, Elimam ME, Nugud FM, Elgaili EM, Ahmed ME, Arora RS. Wilms tumour in Sudan. Pediatr Blood Cancer. 2008; 50(6):1135–7. Epub 2008/04/04. doi: 10.1002/pbc.21547 PMID: 18384057.
24. Libes J, Oruko O, Abdallah F, Githanga J, Ndung'u J, Musimbi J, et al. Risk factors for abandonment of Wilms tumor therapy in Kenya. Pediatr Blood Cancer. 2014. Epub 2014/11/11. doi: 10.1002/pbc.25312 PMID: 25382257.
25. Njuguna F, Mostert S, Seijffert A, Musimbi J, Langat S, van der Burgt RH, et al. Parental experiences of childhood cancer treatment in Kenya. Supportive care in cancer: official journal of the Multinational Association of Supportive Care in Cancer. 2014. Epub 2014/10/17. doi: 10.1007/s00520-014-2475-x PMID: 25318695.
26. Mostert S, Gunawan S, van Dongen JA, van de Ven PM, Sitaresmi MN, Wolters EE, et al. Health-care providers' perspectives on childhood cancer treatment in Manado, Indonesia. Psychooncology. 2013; 22(11):2522–8. Epub 2013/05/25. doi: 10.1002/pon.3314 PMID: 23703746.
27. Sitaresmi MN, Mostert S, Schook RM, Veerman AJ. Treatment refusal and abandonment in childhood acute lymphoblastic leukemia in Indonesia: an analysis of causes and consequences. Psychooncology. 2010; 19(4):361–7. Epub 2009/05/13. doi: 10.1002/pon.1578 PMID: 19434599.

28. Bonilla M, Rossell N, Salaverria C, Gupta S, Barr R, Sala A, et al. Prevalence and predictors of abandonment of therapy among children with cancer in El Salvador. Int J Cancer. 2009; 125(9):2144–6. Epub 2009/07/09. doi: 10.1002/ijc.24534 PMID: 19585496.

29. Gao YJ, Pan C, Tang JY, Lu FJ, Chen J, Xue HL, et al. Clinical outcome of childhood lymphoblastic lymphoma in Shanghai China 2001–2010. Pediatr Blood Cancer. 2014; 61(4):659–63. Epub 2013/11/19. doi: 10.1002/pbc.24848 PMID: 24243691.

30. Ramzan M, Yadav SP, Sachdeva A. Treatment abandonment is a major hurdle to improving survival in childhood cancer in the developing world. Pediatr Blood Cancer. 2013; 60(1):159–60. Epub 2012/09/28. doi: 10.1002/pbc.24277 PMID: 23015274.

31. Kulkarni KP, Marwaha RK. Pattern and implications of therapy abandonment in childhood acute lymphoblastic leukemia. Asian Pacific journal of cancer prevention: APJCP. 2010; 11(5):1435–6. Epub 2011/01/05. PMID: 21198307.

32. Mostert S, Njuguna F, Langat SC, Slot AJ, Skiles J, Sitaresmi MN, et al. Two overlooked contributors to abandonment of childhood cancer treatment in Kenya: parents' social network and experiences with hospital retention policies. Psychooncology. 2014; 23(6):700–7. Epub 2014/05/03. doi: 10.1002/pon.3571 PMID: 24789661.

33. Njuguna F, Mostert S, Slot A, Langat S, Skiles J, Sitaresmi MN, et al. Abandonment of childhood cancer treatment in Western Kenya. Archives of disease in childhood. 2014; 99(7):609–14. Epub 2014/04/01. doi: 10.1136/archdischild-2013-305052 PMID: 24681695.

34. Mostert S, Njuguna F, van de Ven PM, Olbara G, Kemps LJ, Musimbi J, et al. Influence of health-insurance access and hospital retention policies on childhood cancer treatment in Kenya. Pediatr Blood Cancer. 2014; 61(5):913–8. Epub 2013/12/19. doi: 10.1002/pbc.24896 PMID: 24347434.

35. Kulkarni KP, Arora RS, Marwaha RK. Survival outcome of childhood acute lymphoblastic leukemia in India: a resource-limited perspective of more than 40 years. Journal of pediatric hematology/oncology. 2011; 33(6):475–9. Epub 2011/07/28. doi: 10.1097/MPH.0b013e31820e7361 PMID: 21792045.

36. Tang Y, Xu X, Song H, Yang S, Shi S, Wei J. Long-term outcome of childhood acute lymphoblastic leukemia treated in China. Pediatr Blood Cancer. 2008; 51(3):380–6. Epub 2008/05/29. doi: 10.1002/pbc.21629 PMID: 18506765.

37. Metzger ML, Howard SC, Fu LC, Pena A, Stefan R, Hancock ML, et al. Outcome of childhood acute lymphoblastic leukaemia in resource-poor countries. Lancet. 2003; 362(9385):706–8. Epub 2003/09/06. doi: S0140-6736(03)14228-6 [pii] doi: 10.1016/S0140-6736(03)14228-6 PMID: 12957095.

38. Malhotra P, Varma S, Varma N, Kumari S, Das R, Jain S, et al. Outcome of adult acute lymphoblastic leukemia with BFM protocol in a resource-constrained setting. Leukemia & lymphoma. 2007; 48(6):1173–8. Epub 2007/06/20. doi: 10.1080/10428190701343255 PMID: 17577781.

39. Slone JS, Chunda-Liyoka C, Perez M, Mutalima N, Newton R, Chintu C, et al. Pediatric malignancies, treatment outcomes and abandonment of pediatric cancer treatment in Zambia. PloS one. 2014; 9(2):e89102. Epub 2014/03/04. doi: 10.1371/journal.pone.0089102 PMID: 24586527; PubMed Central PMCID: PMC3931678.

40. Li EQ, Jin RM. Causes for refusal or abandonment during treatment of pediatric acute promyelocytic leukemia. Leuk Res. 2012; 36(9):e193–4. Epub 2012/06/26. doi: 10.1016/j.leukres.2012.05.017 PMID: 22727511.

41. Kumar A, Moulik NR, Mishra RK, Kumar D. Causes, outcome and prevention of abandonment in retinoblastoma in India. Pediatr Blood Cancer. 2013; 60(5):771–5. Epub 2013/01/11. doi: 10.1002/pbc.24454 PMID: 23303533.

42. Wang YR, Jin RM, Xu JW, Zhang ZQ. A report about treatment refusal and abandonment in children with acute lymphoblastic leukemia in China, 1997–2007. Leuk Res. 2011. Epub 2011/08/02. doi: S0145-2126(11)00333-X [pii] doi: 10.1016/j.leukres.2011.07.004 PMID: 21802727.

43. Gupta S, Bonilla M, Fuentes SL, Caniza M, Howard SC, Barr R, et al. Incidence and predictors of treatment-related mortality in paediatric acute leukaemia in El Salvador. Br J Cancer. 2009; 100(7):1026–31. Epub 2009/03/19. doi: 6604895 [pii] doi: 10.1038/sj.bjc.6604895 PMID: 19293804.

44. Gupta S, Bonilla M, Valverde P, Fu L, Howard SC, Ribeiro RC, et al. Treatment-related mortality in children with acute myeloid leukaemia in Central America: incidence, timing and predictors. Eur J Cancer. 2012; 48(9):1363–9. Epub 2011/11/16. doi: 10.1016/j.ejca.2011.10.009 PMID: 22082459.

45. Gupta S, Antillon FA, Bonilla M, Fu L, Howard SC, Ribeiro RC, et al. Treatment-related mortality in children with acute lymphoblastic leukemia in Central America. Cancer. 2011; 117(20):4788–95. Epub 2011/03/30. doi: 10.1002/cncr.26107 PMID: 21446043.

46. Alessandri AJ. Parents know best: or do they? Treatment refusals in paediatric oncology. Journal of paediatrics and child health. 2011; 47(9):628–31. Epub 2011/09/29. doi: 10.1111/j.1440-1754.2011.02170.x PMID: 21951447.

47. Laengler A, Martin D, Schuetze T, Tautz C, Kaatsch P, Seifert G, et al. Treatment refusal in paediatric oncology in Germany. Abstract. SIOP Meeting 2011. Pediatr Blood Cancer. 2011.

48. Lam CG, Rossell N, RC R. Global Snapshots of Treatment Abandonment in Children and Adolescents with Cancer: Social Factors, Implications, and Priorities. J Healthcare, Science and Humanities 2012; 2(1):81–110.

49. Ladas EJ, Rivas S, Ndao D, Damoulakis D, Bao YY, Cheng B, et al. Use of traditional and complementary/alternative medicine (TCAM) in children with cancer in Guatemala. Pediatr Blood Cancer. 2014; 61(4):687–92. Epub 2014/02/08. doi: 10.1002/pbc.24791 PMID: 24504792.

50. Israels T, Chirambo C, Caron H, de Kraker J, Molyneux E, Reis R. The guardians' perspective on paediatric cancer treatment in Malawi and factors affecting adherence. Pediatr Blood Cancer. 2008; 51 (5):639–42. Epub 2008/08/01. doi: 10.1002/pbc.21703 PMID: 18668516.

51. Gunawan S, Wolters E, van Dongen J, van de Ven P, Sitaresmi M, Veerman A, et al. Parents' and health-care providers' perspectives on side- effects of childhood cancer treatment in Indonesia. Asian Pacific journal of cancer prevention: APJCP. 2014; 15(8):3593–9. Epub 2014/05/30. PMID: 24870763.

52. Yeh CH, Lin CF, Tsai JL, Lai YM, Ku HC. Determinants of parental decisions on 'drop out' from cancer treatment for childhood cancer patients. Journal of advanced nursing. 1999; 30(1):193–9. Epub 1999/07/15. PMID: 10403996.

53. Israels T, van de Wetering MD, Hesseling P, van Geloven N, Caron HN, Molyneux EM. Malnutrition and neutropenia in children treated for Burkitt lymphoma in Malawi. Pediatr Blood Cancer. 2009; 53 (1):47–52. Epub 2009/04/02. doi: 10.1002/pbc.22032 PMID: 19338050.

54. Antillon F, de Maselli T, Garcia T, Rossi E, Sala A. Nutritional status of children during treatment for acute lymphoblastic leukemia in the Central American Pediatric Hematology Oncology Association (AHOPCA): preliminary data from Guatemala. Pediatr Blood Cancer. 2008; 50(2 Suppl):502–5; discussion 17. Epub 2007/12/08. doi: 10.1002/pbc.21398 PMID: 18064654.

55. Rodriguez-Galindo C, Friedrich P, Morrissey L, Frazier L. Global challenges in pediatric oncology. Curr Opin Pediatr. 2013; 25(1):3–15. Epub 2013/01/09. doi: 10.1097/MOP.0b013e32835c1cbe PMID: 23295716.

56. Ribeiro RC, Pui CH. Saving the children—improving childhood cancer treatment in developing countries. The New England journal of medicine. 2005; 352(21):2158–60. Epub 2005/05/27. doi: 10.1056/NEJMp048313 PMID: 15917380.

57. Samudio A, Figueredo D, Torres R, Mattio I, Jazmin S, Alcaraz E, et al. Estrategias para prevenir el abandono de tratamiento en niños con cáncer en un país en vías de desarrollo. Pediatría (Asunción). 2013; 40(2):119–23.

58. De Pernillo M, Rivas S, Fuentes L, Antillon F, Barr RD. Measurement of socio-economic status in families of children with cancer in Guatemala. Pediatr Blood Cancer. 2014; 61(11):2071–3. Epub 2014/04/23. doi: 10.1002/pbc.25060 PMID: 24753054.

59. Xu K, Evans DB, Carrin G, Aguilar-Rivera AM, Musgrove P, Evans T. Protecting households from catastrophic health spending. Health Aff (Millwood). 2007; 26(4):972–83. Epub 2007/07/17. doi: 10.1377/hlthaff.26.4.972 PMID: 17630440.

60. Rivera-Luna R, Correa-Gonzalez C, Altamirano-Alvarez E, Sanchez-Zubieta F, Cardenas-Cardos R, Escamilla-Asian G, et al. Incidence of childhood cancer among Mexican children registered under a public medical insurance program. Int J Cancer. 2013; 132(7):1646–50. Epub 2012/08/14. doi: 10.1002/ijc.27771 PMID: 22886984.

61. Gao YJ, Qian XW, Lu FJ, Zhai XW, Wang HS, Li J. Improved outcome for children with non-high risk acute lymphoblastic leukaemia after using an ALL IC-BFM 2002-based protocol in Shanghai, China. British journal of haematology. 2013; 160(3):363–7. Epub 2012/11/16. doi: 10.1111/bjh.12122 PMID: 23151178.

62. Klunder-Kluder M, Miranda-Lora AL, Dorantes-Acosta E, Zapata-Tarres M, Carranco-Hernandez T, Escamilla-Nunez A, et al. Frecuencia de abandono del tratamiento en pacientes pediatricos con leucemia linfoblastica aguda. Boletin Medico del Hospital Infantil de Mexico. 2012; 69(3):226–32.

63. Demoly P, Tanno LK, Akdis CA, Lau S, Calderon MA, Santos AF, et al. Global classification and coding of hypersensitivity diseases—An EAACI—WAO survey, strategic paper and review. Allergy. 2014; 69 (5):559–70. Epub 2014/03/22. doi: 10.1111/all.12386 PMID: 24650345.

64. Evans SC, Reed GM, Roberts MC, Esparza P, Watts AD, Correia JM, et al. Psychologists' perspectives on the diagnostic classification of mental disorders: results from the WHO-IUPsyS Global Survey. International journal of psychology: Journal international de psychologie. 2013; 48(3):177–93. Epub 2013/06/12. doi: 10.1080/00207594.2013.804189 PMID: 23750927; PubMed Central PMCID: PMC3725658.

65. Prescott SL, Pawankar R, Allen KJ, Campbell DE, Sinn J, Fiocchi A, et al. A global survey of changing patterns of food allergy burden in children. The World Allergy Organization journal. 2013; 6(1):21.

Epub 2013/12/07. doi: 10.1186/1939-4551-6-21 PMID: 24304599; PubMed Central PMCID: PMC3879010.

66. Delgado E, Barfield RC, Baker JN, Hinds PS, Yang J, Nambayan A, et al. Availability of palliative care services for children with cancer in economically diverse regions of the world. Eur J Cancer. 2010; 46 (12):2260–6. Epub 2010/06/15. doi: S0959-8049(10)00378-3 [pii] doi: 10.1016/j.ejca.2010.05.006 PMID: 20541395.