Childhood Cancer in Ethiopia: Treatment Abandonment Rate and the Cost and Cost-Effectiveness of Service Delivery

Mizan Kiros Mirutse

Thesis for the degree of Philosophiae Doctor (PhD)
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Dedication

I dedicate this academic work to all children suffering from childhood cancer in the hope that this little work may contribute to changing your sad fate.

I would also like to dedicate this work to individuals who have played an extraordinary role.

Bezayit Tesfaye (my love and brave soulmate), Yohanes Mizan, and Winta Mizan (my beloved children), you are my source of happiness, inspiration, and determination. Bezuye, I recognize and appreciate the sacrifice you made and the responsibilities you shouldered for this to happen. John and Wintu, I deeply feel your unspoken pain about our separation. I regret missing your early childhood years, and I hope we will do well in the future without much distance.

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Scientific Environment

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Abstract in English

Background: Unlike adult cancer, childhood cancer is highly curable, even in resource-constrained settings, if diagnosed early and treated effectively. However, a child's diagnosis with cancer can mean a good prognosis of cure or almost certain death depending on where in the world the child lives. On average, the overall survival of children with cancer is eight out of ten in high-income countries, while only two to three of ten survive in low- and middle-income countries (LMICs). This drastic difference in survival rates can be explained by the unavailability of pediatric oncology services, inadequately trained personnel, poor service quality, suboptimal availability of supportive care, late presentation, lack of social support, and high treatment abandonment rate in LMICs. To change this reality, a global call and solidarity movement has emerged to make childhood cancer control a major public health priority at the global and country levels. In the recently revised Ethiopian Essential Health Services Package (EHSP), however, childhood cancer control interventions (such as diagnosis and treatment) are given medium and low priority, a major setback to efforts to control childhood cancer in Ethiopia. Therefore, this thesis aims to inform the revision of the EHSP by providing evidence on the cost and cost-effectiveness of childhood cancer care (diagnosis and treatment) in Ethiopia and by assessing the magnitude and influencing risk factors of treatment abandonment, which is the major cause of treatment failure and poor survival in low-income countries.

Methods: We conducted three studies to pursue the aims of this thesis. The first study (Paper I) assessed the magnitude and influencing risk factors of childhood cancer treatment abandonment in Ethiopia from the health care provider perspective. This cross-sectional study was conducted from September 5–22, 2021 in three of the four pediatric oncology centers in Ethiopia at the time of the data collection. We used a validated, semi-structured questionnaire developed by the International Society of Pediatric Oncology Abandonment Technical Working Group and included all health care professionals (physicians, nurses, and social workers) (N = 38) at these centers who had more than one year of experience in childhood cancer service provision.

The second study (Paper II) estimated the cost of running a pediatric oncology unit from a provider perspective by examining the first and better-established pediatric oncology unit in Ethiopia at Tikur Anbessa Specialized Hospital (TASH) in Addis Ababa, the capital. We used TASH's historical annual cost data from 8 July 2018 through 7 July 2019 and estimated the cost of running the pediatric oncology unit using a mixed costing approach of macro-costing (top down) and micro-costing (bottom up). The direct costs of the pediatric oncology unit (HR, drugs, supplies, medical equipment), costs in

other relevant clinical departments, and the overhead cost share were aggregated to estimate the total annual cost of running the unit. Furthermore, we estimated unit costs for specific childhood cancers.

In the third study (Paper III), building on the costing study's findings (Paper II) as well as effectiveness estimates from similar settings, we estimated the overall cost-effectiveness of running a pediatric oncology unit at TASH. We built a decision-analytic model—a decision tree—to estimate the cost-effectiveness of running a pediatric oncology unit compared to a do-nothing scenario (no pediatric oncology care) from a health care provider perspective. We discounted both costs and effects to their present value at a 3% discount rate, taking a lifetime time horizon for effect and the treatment duration (two years) for costs. The primary outcome was incremental cost in US dollars (USD) per disability-adjusted life year (DALY) averted, and we used a willingness-to-pay (WTP) threshold of 50% of the Ethiopian GDP per capita (USD 477 in 2019). Uncertainty regarding the study's results was explored using one-way and probabilistic sensitivity analyses.

Results: The perceived mean abandonment rate in Ethiopia was 34% (standard error: 2.5%). The risk of treatment abandonment depended on the type of cancer (e.g., high for bone sarcoma and brain tumor), the treatment phase, and the treatment outcome. The highest risk was observed during maintenance, treatment failure, or relapse for acute lymphoblastic leukemia and during the pre- or post-surgical phase for Wilms tumor and bone sarcoma. The major influencing risk factors in Ethiopia included high cost of care, users' low economic status, long travel times to treatment centers, long waiting times, belief in the incurability of cancer, and poor public awareness of childhood cancer. The factors that were found to play an important role in influencing treatment abandonment include undernourishment, the adverse effects and toxicity of treatment, painful diagnostic and therapeutic procedures, insufficient communication by health care professionals, a preference for complementary and alternative medicine, and strongly held faith or religious beliefs.

The estimated annual total cost of running a pediatric oncology unit (8 July 2018–7 July 2019) was USD 776,060 (equivalent to USD 577 per treated child) and ranged from USD 469 to USD 1,085 per treated child in the scenario-based sensitivity analysis. Drugs and supplies and HR accounted for 33% and 27% of the total cost, respectively, while the outpatient and inpatient departments accounted for 37% and 63% of the cost, respectively. The annual cost per treated child ranged from USD 322 to USD 1,313 depending on the type of childhood cancer.

The incremental cost and DALYs averted per child treated in TASH's pediatric oncology unit were USD 876 and 2.4, respectively, compared to no pediatric oncology care. The incremental cost-

effectiveness ratio of running a pediatric oncology unit was USD 361 per DALY averted, and it was cost-effective in 90% of 100,000 Monte Carlo simulations at a USD 477 WTP threshold.

Conclusions: The perceived abandonment rate in Ethiopia was high, and the risk of abandonment varied according to type of cancer, phase of treatment, and treatment outcome. The major influencing risk factors for treatment abandonment in Ethiopia are the high cost of care, low economic status of households, long travel time to treatment centers, long waiting times, belief in the incurability of cancer, and poor public awareness of childhood cancer. Although other studies report a great similarity of influencing risk factors, the reported level of influence for some risk factor differs in Ethiopia from that in similar settings. Therefore, mitigation strategies to reduce the abandonment rate should identify specific risk factors and prioritize strategies based on their level of influence, effectiveness, feasibility, and affordability.

The provision of pediatric cancer services using a specialized oncology unit is most likely cost-effective and affordable in Ethiopia, at least for easily treatable cancer types in centers with minimal to moderate capability. We recommend reassessing the priority level of childhood cancer treatment in the current EHSP.

Keywords: childhood cancer, treatment abandonment, cost, cost-effectiveness, economic evaluation, low-income countries, Sub-Saharan Africa, Ethiopia

Abstract in Norwegian (Sammendrag)

Bakgrunn: I motsetning til mange typer kreft hos voksne og eldre, kan kreft hos barn ofte helbredes, selv i land med begrensede ressurser, hvis kreften diagnostiseres tidlig og behandles riktig. Et barns diagnose med kreft kan bety en god prognose for helbredelse eller nesten sikker død avhengig av hvor i verden barnet bor. I gjennomsnitt overlever åtte av ti barn med kreft i høyinntektsland, mens bare to til tre av ti overlever i lav- og mellominntektsland. Denne drastiske forskjellen i overlevelsesrater kan forklares med lav tilgjengelighet av pediatriske onkologiske tjenester, utilstrekkelig trent personell, dårlig kvalitet, suboptimal tilgjengelighet av støttebehandling, sen presentasjon, mangel på sosial støtte og høy andel behandlingsavbrudd. For å endre dette har mange store organisasjoner oppfordret til å gi kontroll av barnekreft høyere prioritet på globalt og landnivå. I den nylig reviderte etiopiske grunnleggende helsetjenestepakken er intervensjoner for kontroll av barnekreft (som diagnose og behandling) gitt middels og lav prioritet, et stort tilbakeslag for arbeidet med å kontrollere barnekreft i Etiopia. Denne avhandlingen har som mål å fremskaffe ny kunnskap om kostnadene og effekten av barnekreftomsorg i Etiopia, for å informere revisjonen av den grunnleggende helsetjenestepakken, og gi ny kunnskap om omfanget og risikofaktorene for behandlingsavbrudd. Avbrutt behandling er en av de viktigste årsakene til behandlingssvikt og dårlig overlevelse i lavinntektsland.

Metoder: Vi gjennomførte tre studier for å nå målene med denne avhandlingen. Den første studien (artikkel I) vurderte omfanget av og risikofaktorene for behandlingsavbrudd i Etiopia fra et helsepersonell perspektiv. Denne tverrsnitts studien ble utført fra i 2021 i tre av de fire pediatriske onkologisentrene i Etiopia på tidspunktet for datainnsamlingen. Vi brukte et validert, semi-strukturert spørreskjema utviklet av International Society of Pediatric Oncology Abandonment Technical Working Group og inkluderte alle helsepersonell (leger, sykepleiere og sosialarbeidere) (N = 38) ved disse sentrene som hadde mer enn ett år erfaring med tjenesteyting innen barnekreft.

Den andre studien (artikkel II) estimerte kostnadene ved å drive en pediatrisk onkologienhet fra et helsetjenesteperspektiv ved å undersøke den første og mest etablerte pediatriske onkologienheten i Etiopia: Tikur Anbessa Specialized Hospital (TASH) i Addis Abeba, hovedstaden. Vi brukte historiske årlige kostnadsdata fra TASH fra perioden 8. juli 2018 til 7. juli 2019 og estimerte kostnadene for hele den pediatriske onkologiske enheten ved å bruke en kombinert beregningsmetode

av som tar hensyn til makrokostnad (ovenfra og ned) og mikrokostnad (nedenfra og opp). De direkte kostnadene til den pediatriske onkologiske enheten (helsepersonell, legemidler, forsyninger, medisinsk utstyr), kostnader i andre relevante kliniske avdelinger og overheadkostnaden ble lagt sammen for å estimere de totale årlige kostnadene ved å drive enheten. Videre estimerte vi enhetskostnader for spesifikke barnekreftformer.

I den tredje studien (Artikkel III), basert på kostnadsstudiens funn samt effektestimater fra land som ligner, estimerte vi den totale kostnadseffektiviteten ved å drive en pediatrisk onkologisk enhet ved TASH. Vi bygde en beslutningsanalytisk modell – et beslutningstre – for å estimere kostnadseffektiviteten ved å drive en pediatrisk onkologisk enhet sammenlignet med et gjøre-ingenting-scenario (ingen pediatrisk onkologibehandling) fra et helsetjeneste perspektiv. Vi diskonterte både kostnader og effekter til nåverdi med en diskonteringsrente på 3 %, og valgte en livstidshorisont for effekt og behandlingsvarighet to år for kostnader. Det primære resultatet var inkrementelle kostnader i amerikanske dollar per avverget sykdomsjustert leveår (DALY), og vi brukte en betalingsvillighet (WTP)-terskel på 50 % av etiopisk BNP per innbygger (477 amerikanske dollar i 2019)). Usikkerhet angående studiens resultater ble utforsket ved hjelp av standard sensitivitetsanalyser.

Resultater: Den gjennomsnittlige behandingsavbruddsraten i Etiopia, vurdert av helsepersonell, var 34 % (standardfeil: 2,5 %). Risikoen for å avbryte behandlingen var avhengig av typen kreft (f.eks. høy for beinsarkom og hjernesvulst), behandlingsfasen og behandlingsresultatet. Den høyeste risikoen ble observert under perioder med vedlikeholdsbehandling, ved behandlingssvikt eller tilbakefall for akutt lymfatisk leukemi og under pre- eller postkirurgisk fase for Wilms tumor- og beinsarkom. De viktigste risikofaktorene i Etiopia inkluderte høye omsorgskostnader, brukernes lave økonomiske status, lange reisetider til behandlingssentre, lange ventetider, tro på at kreft er uhelbredelig og lav offentlig oppmerksomhet om barnekreft. Faktorene som ble funnet å spille en viktig rolle i å påvirke behandlingsavbrudd inkluderer underernæring, bivirkninger og toksisitet av behandlingen, smertefulle diagnostiske og terapeutiske prosedyrer, utilstrekkelig kommunikasjon fra helsepersonell, en preferanse for komplementær og alternativ medisin, og sterk religiøs tro.

Den estimerte årlige totale kostnaden for å drive en pediatrisk onkologisk enhet (2019-dollar) var 776 060 amerikanske dollar (tilsvarer 577 dollar per behandlet barn) og varierte fra 469 til 1085 dollar per behandlet barn i den scenariobaserte sensitivitetsanalysen. Legemidler og rekvisita og helsepersonell utgjorde henholdsvis 33 % og 27 % av totalkostnaden, mens poliklinikken og døgnavdelingen sto for henholdsvis 37 % og 63 % av kostnadene. Den årlige kostnaden per behandlet barn varierte fra 322 til 1313 dollar avhengig av type barnekreft.

Den inkrementelle kostnaden og DALYs avverget per barn behandlet i TASHs pediatriske onkologiske enhet var henholdsvis 876 dollar og 2,4 DALYs, sammenlignet med ingen pediatrisk onkologisk behandling. Det inkrementelle kostnadseffektivitetsforholdet ved å drive en pediatrisk onkologisk enhet var 361 dollar per DALY avverget, og det var kostnadseffektivt i 93 % av 100 000 Monte Carlo-simuleringer ved en WTP-terskel på 477 dollar.

Konklusjoner: Den opplevde behandingsavbruddsraten i Etiopia var høy, og risikoen for avbrudd varierte avhengig av krefttype, behandlingsfase og behandlingsresultat. De viktigste risikofaktorene for å avbryte behandling i Etiopia er høye omsorgskostnader, lav økonomisk status for husholdninger, lang reisetid til behandlingssentre, lange ventetider, tro på at kreft er uhelbredelig og lav offentlig bevissthet om barnekreft. Selv om andre studier rapporterer liknende funn, er det rapporterte nivået for flere av risikofaktorene forskjellige i Etiopia sammenliknet med andre liknende land. Tiltak for å redusere behandlingsavbrudd bør bygge på kunnskap om identifiserte risikofaktorer og tiltakenes effekt, gjennomførbarhet og realistiske kostnadsrammer. Tilbudet av krefttjenester for barn ved bruk av en spesialisert onkologisk enhet er sannsynligvis kostnadseffektive og innenfor realistiske kostnadsrammer i Etiopia, i det minste for krefttyper som er lett å behandle i sentre med minimal til moderat kapasitet. Vi anbefaler å revurdere prioriteringsnivået for behandling av barnekreft i gjeldende grunnleggende helsetjenestepakke.

Stikkord: barnekreft, avbrudd av behandling, kostnad, kostnadseffektivitet, økonomisk evaluering, lavinntektsland, Afrika sør for Sahara, Etiopia

List of Publications

Paper I

Mizan Kiros Mirutse, Mieraf Taddesse Tolla, Solomon Tessema Memirie, Michael Tekle Palm, Daniel Hailu, Kunuz Abdella Abdi, Ermias Dessie Buli, and Ole F. Norheim. The magnitude and perceived reasons for childhood cancer treatment abandonment in Ethiopia: From health care providers' perspective. *BMC Health Services Research* 22, 1014 (2022). https://doi.org/10.1186/s12913-022-08188-8

Paper II

Mirutse, M.K., Tolla, M.T., Memirie, S.T., Kefyalew,E.S., Hailu, Daniel., Norheim, O.F. The magnitude and perceived reasons for childhood cancer treatment abandonment in Ethiopia: from health care providers' perspective. BMC Health Serv Res 22, 1014 (2022). https://doi.org/10.1186/s12913-022-08188-8

Paper III

Mizan Kiros, Solomon Tessema Memirie, Mieraf Taddesse Tolla, Michael Tekle Palm, Daniel Hailu, and Ole F. Norheim. Cost-effectiveness of running a paediatric oncology unit in Ethiopia. BMJ Open 2023;13:e068210. doi: 10.1136/bmjopen-2022-068210

List of Abbreviations

AACCRU	Addis Ababa City Cancer Registry Unit
ALL	Acute lymphoblastic leukemia
CBHI	Community-based health insurance
CEA	Cost-effectiveness analysis
CVD	Cardiovascular disease
DALY	Disability-adjusted life year
DCP	Disease control priorities
EFS	Event-free survival
EHIA	Ethiopia Health Insurance Agency
EHSP	Essential health services package
EPSA	Ethiopia Pharmaceutical Supply Agency
ER	Emergency service
FRP	Financial risk protection
FTE	Full time equivalent
GDP	Gross domestic product
GUH	Gondar University Hospital
HCMIS	Health commodities management information system
HEP	Health extension program
HEW	Health extension worker
HIC	High-income country
HIV	Human immunodeficiency virus
HR	Human resources
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
IPD	Inpatient department
JLN	Joint Learning Network for Universal Health Coverage
JUH	Jimma University Hospital
LICs	Low-income countries
LMICs	Low- and middle-income countries
MoH	Ministry of Health–Ethiopia
MUH	Mekelle University Hospital
NCACCP	National Childhood and Adolescent Cancer Control Plan
NCDs	Noncommunicable diseases
NICE	National Institute for Health and Care Excellence
OOP	Out-of-pocket
OPD	Outpatient department
PHCU	Primary health care unit
SE	Standard error
SDG	Sustainable Development Goal
SHI	Social health insurance
SSA	Sub-Saharan Africa
TASH	Tikur Anbessa Specialized Hospital
TB	Tuberculosis
UHC	Universal health coverage
USD	United States dollar

WHO	World Health Organization
WHO-CHOICE	WHO CHOosing Interventions that are Cost-Effective
YLD	Years lived with disability
YLL	Years of life lost

Figures and Tables

Contents

1. Introduction

1.1. Thesis summary

The World Health Organization (WHO) Global Initiative for Childhood Cancer calls for low- and middle-income countries (LMICs) and development partners to invest in childhood cancer control in light of the higher burden and stark inequality in survival rates in LMICs compared to high-income countries (HICs). Nearly 90% of childhood cancer occurs in LMICs (1-3), yet only 20–30% survive (4), while the survival rate in HICs surpasses 80% (5, 6). However, childhood cancer is highly curable even in resource constrained settings. The effective strategy to improve survival rate is early diagnosis and provision of effective treatment. In addition, treatment abandonment must also be addressed, as it is the major cause of low survival in LMICs, and the burden is very high in such settings, reaching 50%–60% in some low-income countries (LICs) (7).

Despite the growing global attention to fighting this reality, childhood cancer control was given low and medium priority in Ethiopia's recently revised essential health services package (EHSP) (8), probably due to inadequate advocacy work (on the burden, the high chance of cure, and the potential cost-effectiveness) and the lack of national data on the cost and cost-effectiveness of childhood cancer care (diagnosis and treatment). This thesis aims to close the evidence gap and inform future revision of the EHSP by providing evidence on the magnitude of childhood cancer treatment abandonment and the influencing risk factors in Ethiopia in order to draw attention to the burden of treatment abandonment and to encourage the development of mitigation strategies tailored to contextual risk factors. This research estimates the cost and cost-effectiveness of childhood cancer treatment in Ethiopia to support evidence-informed advocacy and the revision of the current EHSP. We conducted three studies to pursue our aim. Paper I assesses the magnitude of treatment abandonment and the influencing risk factors, Paper II estimates the cost of running a pediatric oncology unit in Tikur Anbessa Specialized Hospital (TASH), and Paper III estimates the overall cost-effectiveness of running a pediatric oncology unit at TASH.

This thesis is structured in seven sections. The first provides an overview of childhood cancer's priority in the global public health agenda, the global inequality in the survival of children with cancer, the global fight against childhood cancer, and the challenges in that fight. Section two and three describe the aim of the thesis and the research methods employed in the three studies. Section four summarizes the studies' key results, while sections five to seven interpret and discuss the major findings and methodological limitations, present conclusions, offer recommendations, and describe future perspectives.

1.2. Background

1.2.1. Noncommunicable diseases

Noncommunicable diseases (NCDs) are the leading contributor the global burden of disease (9), causing 74% of all annual global deaths as of 2020. Close to 41 million people die every year due to NCDs, and around 17 million of those deaths (41%) occur before the age of 70 (commonly described as premature death) (10). Around 77% of those deaths and 86% of the premature deaths occur in LMICs, and the risk of premature death from NCDs is three to five times higher in such settings, notably in sub-Saharan Africa (SSA), as compared to HICs (10, 11). In most LMICs, the burden of disease is shifting from communicable diseases to NCDs, straining health systems with a double burden of communicable diseases and NCDs (11). The surge in NCDs is related mainly to population aging and increased exposure to modifiable behavioral risk factors, such as unhealthy diets (e.g., excessive salt intake), physical inactivity, tobacco use, and harmful consumption of alcohol. This is mainly driven by uncontrolled rapid urbanization, the lifestyle changes associated with globalization and economic development, and widening socioeconomic inequality (11). Nearly 86% of premature deaths from NCDs are caused by cardiovascular diseases (CVDs) (17.9 million), cancers (9.3 million), chronic respiratory diseases (4.1 million), and diabetes (2.0 million) (10).

As of 2020, CVDs (in 70 countries) and cancers (in 57 countries) were the leading causes of death in 127 countries (11, 12). In the remaining countries, CVDs and cancers were among the top three causes of death (13). Overall, cancers are the second-leading cause of death (next to CVDs) and account for 16% of the global death toll. In 2021, the estimated numbers of people diagnosed and dying of cancer were 20 million and 10 million, respectively (12, 14), and the incidence is expected to grow to 28.4 million by 2040 (a 47% increase from the 2021 baseline) (14). Close to one-third of cancer deaths are due to smoking, alcohol consumption, high body mass index, low vegetable and fruit intake, and lack of physical activity (15). Globally, the most common cancers (in descending order) are breast, lung, colorectal, prostate, and stomach cancer (15).

For many years, cancers were not given adequate global attention, despite the substantial disease burden. The World Health Assembly adopted the first cancer-control resolution in 2005 and reinforced it in 2017 (16). This was a major milestone in positioning cancer control as a major health priority at the global, regional, and national levels and in fostering global collaborative platforms to support LMICs, which bear the largest disease burden. Cancer control is included in the United Nations' sustainable development agenda as subgoals under Sustainable Development Goal (SDG) 3.4, reducing premature mortality from NCDs (including cancer) by one-third (from the 2015

baseline) and SDG 3.8, achieving universal health coverage (UHC) that includes financial risk protection (FRP) and access to safe, effective, quality health care services, medicines, and vaccines (17). Subsequently, cancer control has become more visible in the global health agenda. The survival rate of cancer patients is improving in countries, such as HICs, that are implementing a comprehensive NCD control program (including cancer), and 30–35 countries are expected to meet SDG 3.4 if their current declining trend continues (11). However, progress is very slow in most LMICs (11).

LMICs bear the largest burden of cancer, have the fastest incremental rate trend, and are expected to account for over 70% of the cancer death burden by 2040 (14), mainly due to population aging and increased exposure to behavioral and environmental risk factors (e.g., infectious diseases) (11). Nearly 30% of cancers in LMICs are related to infectious diseases, such as human papilloma virus, the hepatitis B and C viruses, human immunodeficiency virus (HIV), *helicobacter pylori*, and Epstein-Barr virus (15). Around 30–50% of cancers can be prevented by addressing modifiable behavioral and environment risk factors (15, 18). Of the remaining 50%, a significant share can be cured, if diagnosed early and treated effectively (15, 18).

However, LMICs are the least prepared to manage the burden of cancer, so millions of people have no access to timely diagnosis and quality care (19). For example, the reported availability of comprehensive cancer treatment in LICs is less than 15% (20), around 42% of patients in LMICs lack full access to chemotherapy packages (21), LMICs' share of global cancer financing is only around 5% (although they account for 70% of the global cancer burden), and close to 70% of African countries do not have radiotherapy services, an intervention needed in more than 50% of cancer patients (19, 22-25). Making cancer control a high-priority public health concern in LMICs could be challenging for various reasons, such as resource constraints, the growing cost of care, the fact that most cancers require disease-specific diagnosis and treatment (due to their heterogeneity), the need for advanced infrastructure, lack of qualified expertise (which takes time to build), cancer prevention's need of a multisectoral response, and conflicts of interest due to preventive measures' trade-offs with economic growth (26). Therefore, strategies should be closely tailored to local realities, such as local epidemiology, existing resource capacity (financial, human resources [HR], and diagnostic and treatment infrastructure), and evidence of value for money (26). Thus, countries should aim for progressive realization of universal coverage for cancer services (described in more detail in section 1.4). WHO identifies breast, cervical, and childhood cancer control as an immediate priority in LMICs (15) in light of the disease burden, the chance of prevention or cure, and the availability of cost-

effective, affordable, and feasible interventions in such settings. Accordingly, WHO calls for countries and the global community to make a high priority of combating these cancers.

1.2.2. Childhood cancer as a global public health challenge

Worldwide, close to 400,000 new cases of childhood cancer (age range: 0–19 years) are reported annually, and it accounts for 0.5–4.8% of countries' cancer incidence (27-29). Every year, nearly 328,000 children die of cancer, which is the leading cause of death from NCDs and the ninth-leading cause of disability-adjusted-life-year (DALY) loss in children (30, 31). The greatest share of this disease burden (90%) occurs in LMICs (3). Unlike adult cancers, most childhood cancers are highly curable if timely diagnosed and treated effectively (28). A child's diagnosis with cancer can mean a good prognosis of being cured or almost certain death depending on where in the world the child lives, which is the most important factor in predicting survival for a child diagnosed with cancer. The five-year survival rate in HICs is more than 80% (9-13), while it is 20%–30% in LMICs (4, 32).

This striking inequality in survival rates between HICs and LMICS can be explained by the unavailability of specialized pediatric oncology centers and supplies, inadequately trained personnel, suboptimal supportive care, late presentation, insufficient social support, and the high treatment abandonment rate in LMICs (21, 22, 32-36). For instance, the reported availability of comprehensive cancer care is greater than 90% in HICs but less than 15% in LICs (20), and the reported availability of chemotherapy and surgery in LICs is around 30% and 25%, respectively (28, 34). The major causes of inadequate childhood cancer service in LICs are resource constraints, the presence of competing high-burden public health problems, and insufficient attention and commitment due to prevailing assumptions, such as "cancer is not a problem of LICs," "it is not curable," and "it is costly, and not cost-effective" (2, 25, 30, 37). As a result, childhood cancer control programs in LICs faces many challenges as summarized below.

Failure to diagnose and late diagnosis

The most effective strategy in childhood cancer control is timely diagnosis and effective treatment, but close to 44% (55% in LICs) of children with cancer die before diagnosis (30). Of those diagnosed, more than two-thirds are diagnosed at an advanced disease stage (stage three or four) (30, 38-40). Patients with a late diagnosis present with a more advanced disease that is harder to cure (poor prognosis) and requires more intensive treatment, increasing the cost of treatment and the risk of treatment failure, treatment abandonment, and toxicity-related death (30, 40).

Treatment failure

The unacceptable level of treatment failure in children with cancer in LMICs results from shortcomings at every step of service delivery, including detection, diagnosis, referral, treatment, follow-up, and palliative care. The major causes of treatment failure are delayed diagnosis, missed diagnosis, inadequate health care infrastructure and service delivery networks, limited access and intermittent availability of quality medicines, an inadequate multidisciplinary health workforce, suboptimal availability of supportive care, a high prevalence of underlying malnutrition, adverse socioeconomic environments, cultural and educational barriers, and a low level of public awareness (21, 24, 30, 34).

Treatment abandonment

The International Society of Pediatric Oncology defines treatment abandonment as a failure to start (refusal) or continue treatment for four or more consecutive weeks (41). This does not include cases with a medical contraindication to starting treatment or those lost to follow-up after completing treatment. The four-week cutoff is based on empirical evidence that patients are unlikely to return after discontinuing for more than four weeks and that, even if they do return, they have less chance of survival (41). Abandonment is the leading cause of poor treatment outcomes and low survival rates in LMICs, and one-third of the survival gap between HICs and LMICs is explained by abandonment (7, 41). The magnitude of abandonment is high in LICs, reaching 50%–60% in some countries (7).

Lack of palliative care

Palliative care is critical to reducing suffering in children with cancer, and it is highly needed in LMICs, as most patients are diagnosed at an advanced stage, yet palliative care is limited in such settings. For instance, the availability of essential pain-relieving medication in LMICs is less than 15% (42).

Lack of good data

There is no good estimate of the incidence, prevalence, disease distribution, survival rate, recurrence, chronic complications, and trends of childhood cancers in LMICs (30), as there are few robust childhood cancer information systems, such as population-based registries. For example, only six of the 46 SSA countries have validated registries (43). As a result, the epidemiology, risk factors, and progress of childhood cancers are not well known in LMICs.

Despite all these challenges, hope exists for changing this reality in LMICs through other countries' commitment and global solidarity given that most childhood cancers are highly curable with effective treatment, even in centers with only modest capability (2, 4). A large portion of children with cancer can be cured with basic diagnosis, less intensive and low-cost treatment, and simple supportive measures (2, 30). There are documented success stories in some LMICs where countries made notable progress using a global partnership like twinning—pairing a pediatric oncology unit in a low-resource setting with a counterpart in a better setting). For example, the survival rate of Burkitt's lymphoma greatly improved (from 54 to 73% in three years) in eight African countries in the French African Pediatric Oncology Group initiative (44). In Recife, Brazil, a twinning program with St Jude Children's Research Hospital improved the five-year event-free survival (EFS) for acute lymphoblastic leukemia (ALL) patients from 32 to 63% (45). Some SSA countries (such as Kenya, Senegal, Ivory Coast, Cameron, Nigeria, Tanzania, and Mali) have achieved a 52% overall two-year EFS (46, 47). In addition, the remarkable success in HICs (where the five-year EFS rate has improved from less than 30% to over 80% in the past four decades) (48) indicates that we can change the stark inequality in a much shorter time through countries' strong commitment, global collaboration, and solidarity.

1.2.3. Global childhood cancer initiative

To narrow the global disparity in childhood cancer outcomes, WHO launched the Global Initiative for Childhood Cancer in September 2018 at the United Nations General Assembly High-Level Meeting on NCDs (16). The initiative aims to improve childhood cancer survival globally by at least 60% (doubling the 2015 baseline) and reduce suffering for all by 2030 (49). It is expected that an additional one million lives of children with cancer will be saved in the coming 10 years by building countries' capacities to provide quality childhood cancer care, by prioritizing childhood cancer control at the global, regional, and national levels, and by improving global collaborations. The initiative's identified key pillars are establishing centers of excellence equipped with well-trained multidisciplinary workforces, and medical infrastructures (for diagnosis and treatment); developing national standards of childhood cancer care; ensuring the stable availability of quality medicines and supplies; including childhood cancer control interventions in national health benefits packages; expanding high priority services for all children with cancer that well address the unique needs of children and adolescents; establishing cancer registries and investing in cancer research (50). Advocacy, leveraged financing, and governance are identified as crosscutting enablers of the initiative's success.

The initiative prioritizes six highly prevalent and highly curable childhood cancers (representing 50%–60% of all such cancers in LMICs), including ALL (a blood cancer), Hodgkin's lymphoma (a lymph gland cancer), Burkitt's lymphoma (a fast-growing lymph gland cancer), Wilms tumor (a kidney cancer), retinoblastoma (an eye cancer), and low-grade glioma (a brain cancer) (49). WHO and other global development partners have been conducting advocacy workshops and capacity-building trainings as well as disseminating guidelines, technical toolkits, and implementation frameworks (such as the CureAll framework) (50). The Disease Control Priorities (DCP3) project and the Lancet Oncology Commission recommend including childhood cancer control interventions in LMICs' essential UHC benefits packages (2, 30).

1.3. Childhood cancer in Ethiopia

1.3.1. Overview of Ethiopia

Located in the eastern part of the continent (commonly termed the Horn of Africa), Ethiopia is Africa's second-most populous country (after Nigeria), with an estimated population of 112 million in 2019 (51). Its population pyramid is dominated by the young (aged less than 15 years), who account for 39.5% of the population (52, 53), and the country's high fertility rate of 4.0 children per woman as of 2020 indicates rapid population growth that is expected to reach 214 million by 2050 (52). Nearly 80% of the population lives in rural areas, where 55% of women and 83% of men work in the agriculture sector (52, 53). Ethiopia has a federal political administrative system comprising 11 regional states and two city administrations. It is a country withs diverse culture embraces more than 80 ethnic groups and languages (54).

Over the past two decades, Ethiopia's economy has grown rapidly (averaging 9.5% per year), placing it among the world's fastest-growing economies, although the rate declined after 2019, mainly due to the COVID-19 pandemic, the civil war in Ethiopia, and the global impact of the war in Ukraine (55-57). Despite its rapid economic growth, Ethiopia remains one of the poorest countries, with a gross domestic product (GDP) of USD 944 per capita as of 2021 and a sizeable proportion of the population (23.5%) (58) living below the absolute poverty line. The country has a low human development index score of around 0.38 (lower than the SSA average), indicating a massive shortfall in human potential and development (55).

Ethiopia has made commendable progress in improving its population's health over the past three decades, with the life expectancy at birth increasing from 46.9 in 1990 to 68.8 in 2019 (59). This remarkable achievement resulted from great improvements in maternal and child health conditions

and the prevention and control of communicable diseases (such as tuberculosis [TB], HIV, malaria, pneumonia, and diarrheal disease), which enabled Ethiopia to meet or almost meet most of the health-related Millennium Development Goals (60). The vast improvement in health conditions is explained by great progress within and outside the health sector. Access to health care improved due to a pro-poor health policy that emphasizes rural communities and primary health care. The health sector also implemented various reforms to improve access, quality, equity, and financial risk protection (FRP) through a series of strategic plans, such as the Health Sector Development Plans (HSDP I–IV) and Health Sector Transformation Plans (HSTP I and II) (61). These reforms resulted in rapidly scaled up health facilities (particularly health posts and health centers), large number of trained HR (such as health extension workers, nurses, midwives, and medical doctors), improved access to essential medicine and supplies, and a large surge in the private health sector (61).

Ethiopia also implemented various macroeconomic development and poverty-reduction reforms that greatly improved the social determinants of health. For example, in 1990–2015, Ethiopia's key achievements included reducing poverty (from 48 to 23.5%) (58), increasing access to primary education (44 to 95%) (62), lowering the fertility rate (from 7.7 to 4.6 children per woman) (53, 63), raising the literacy rate (27 to 49%) (53, 63), and improving access to safe drinking water (18 to 88%) (53, 63).

Despite these astonishing achievements, Ethiopia's health system currently suffers from a double burden of diseases (communicable and non-communicable diseases or conditions) (61), and the progress toward UHC is slow (64). For instance, in 2019, the effective coverage index (which is further discussed in the priority setting for UHC section 1.4) score was only 38 (on 0–100 scale) which was among the lowest globally (64). This is due to low health service coverage and poor quality of care. Despite the massive scale-up of health facilities, a sizable portion of the population has limited physical access to health care, mainly characterized by poor access to primary hospitals in rural areas, and limited access to health centers and primary hospitals in pastoral areas. The situation is exacerbated by demand-side obstacles to access, such as poor public awareness and economic barriers. The quality of care is poor by many standards. For instance, nearly half of health facilities (health centers and health posts) lack basic utilities, such as water and electricity; essential drugs and supplies are not readily available; and the medical workforce, which is inadequate in both size and the mix of professions, is characterized by poor distribution, motivation, performance, and skills (61, 65). The medical workforce density (doctors, nurses, midwives) per 1,000 population in Ethiopia is 0.96 (61), far below WHO's recommended threshold of 4.3. Similarly, health spending in Ethiopia is low

(66), which may be a major explanatory factor for the poor access to quality care in Ethiopia (further discussed in section 1.3.7).

These challenges in the Ethiopian health system were further complicated by the Covid-19 pandemic and an ongoing conflict that greatly affected the economy and disrupted the health system, especially in the war zone (in the north of the country), where the system collapsed due to destruction, lack of supplies, and displacement of the workforce.

1.3.2. Health care delivery in Ethiopia

The Ethiopian health system has three tiers of health service delivery platforms that provide primary, secondary, and tertiary care (67) (Fig. 1). The primary tier (comprising primary health care units, or PHCUs) consists of five health posts (serving from 3,000 people in pastoral settings to 5,000 in agrarian settings), one health center (serving 25,000 people), and a primary hospital (providing services to 60,000 to 100,000 people) in rural area. In urban areas, a health center (serving 40,000 people) serves as a PHCU. Each tier provides a distinct package of health services and provides referrals to other tiers. The PHCU provides a package of health promotion, disease prevention, and basic curative services (67). Diseases and health conditions demanding greater specialization and better health care are referred to a higher tier.

The PHCU is linked to the community through a community-based primary health care services delivery platform, the health extension program (HEP), in which formally trained female health extension workers (HEWs) provide health promotion, disease prevention, and basic curative services at the community and health-post levels. In the rural areas, community structures such as one-to-five network, and health development team (figure 1) are used to implement the HEP packages described below. The HEP serves as a bridge between the community and the formal health care delivery platform. The Ethiopian government has done a tremendous job of training HEWs and constructing health posts, which serve as stations for HEWs and as the first contact point for formal health care. Two to three HEWs are deployed per health post. As of 2020, Ethiopia had 40,000 HEWs, 17,500 health posts, and 3,800 health centers (61). On average, there was one health post for every 4,500 people in rural areas, surpassing the national target of one health post per 5,000 people (67). The HEWs provide 18 package of health services that focus on five major program areas: family health; disease prevention and control; hygiene and environmental sanitation; NCDs and mental health; and health education and communication (67). NCD (including cancer control) was added to the HEP package in 2018 (67). Despite the impressive expansion of health posts, however, nearly half of health

facilities lack basic facilities (electricity, an improved water source, and sanitation facilities) (61), and only 29% are connected to the next health center by all-weather condition roads (67).

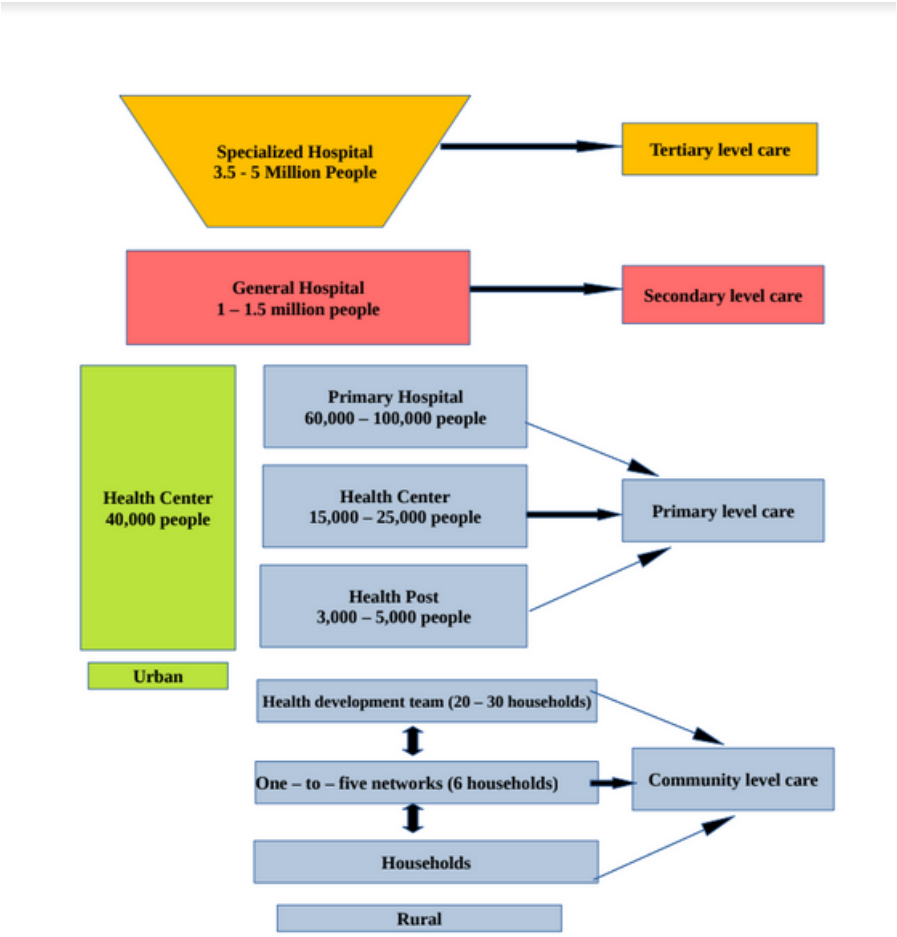

Figure 1. Ethiopia's health service delivery

The secondary tier comprises general hospitals, which provide service to 1 to 1.5 million people and receive referrals from PHCUs within their service domain. The tertiary tier is composed of specialized hospitals that provide service to 3.5 to 5 million people and accept referrals from the second tier (general hospitals) (67). As of 2020, there were 353 public hospitals in Ethiopia (61).

The private health sector, particularly private-for-profit health service delivery, has grown rapidly in Ethiopia and is greatly contributing to improvement in health and health coverage. In 2016, the private sector accounted for 20% of national service utilization and 50% of service utilization in urban areas (68).

1.3.3. Ethiopia's childhood cancer control plan

Cognizant of the global call for improved childhood cancer control and the country's current underinvestment in that area, Ethiopia's Ministry of Health (MoH) recently developed a National Childhood and Adolescent Cancer Control Plan (NCACCP) for the years 2019–2023, aiming to improve survival rates through early detection and the provision of quality treatment and supportive care. The overall goal is to achieve a cure rate of at least 40% for common and curable childhood and adolescent cancers. The priority interventions are improving early detection, diagnosis, treatment, and supportive care; strengthening psychosocial and family support; reducing the abandonment rate; enhancing cancer surveillance systems (especially cancer registries); and strengthening human resource capacity (66).

The key targets of the NCACCP include increasing the number of fully equipped, functional pediatric oncology units in Ethiopia from three to eight by the end of 2023, with 100% access to essential medicines, standard treatment protocols, functional pediatric intensive care units (ICUs), and psychosocial and family support at all pediatric oncology units; increasing the number of pediatric oncologists from six to 30 (along with similar gains in other relevant staff categories); disseminating basic childhood cancer information to 80% of the populace; training 50% of health workers in PHCUs; and decreasing abandonment by 60% (66). Obviously, the goals are highly ambitious and demand strong political commitment, large resource investments, and synergy.

1.3.4. Epidemiology of childhood cancer in Ethiopia

As in other LICs, the epidemiology of childhood cancer in Ethiopia is not well understood, as the country has no robust cancer information system (such as a population-level cancer registry). Only one of Ethiopia's 13 regions—the Addis Ababa city administration—has a cancer incidence registry for people in its jurisdiction (69).

Despite the paucity of data, the annual incidence has been estimated in the range of 3,800–6,000 (3, 70), accounting for 7% of the national cancer burden in 2019 (66, 71). The most common childhood cancers in Ethiopia are ALL (25.7%), non-Hodgkin's lymphoma (8.9%), rhabdomyosarcoma (8.9%), Wilms tumor (8%), and neuroblastoma (7.8%) (66).

1.3.5. Childhood cancer service delivery in Ethiopia

The recommended service delivery framework for childhood cancer comprises centers of excellence (for diagnosis and treatment) linked to clusters of other hospitals (satellite sites) and strong PHCUs with good early detection and referral capabilities (2, 30). In LMICs, a center of excellence, pediatric oncology unit, or treatment center (the terms are used interchangeably in this thesis) can be established as a dedicated unit within a specialized hospital or as a standalone treatment center, but the former approach is commonly practiced. Initially, the specialized oncology units in LMICs are required to meet only basic diagnostic and treatment needs to address the greater portion of their childhood cancer burden without a need for sophisticated technologies given that most childhood cancers are curable with less intensive treatment and that countries can progressively increase their capability over time (2, 30, 45).

Ethiopia is following such an approach, with childhood cancer treatment provided at selected specialized centers in tertiary hospitals, such as TASH, St. Paul's Hospital, and Gondar, Jimma, and Mekelle University Hospitals (GUH, JUH, and MUH, respectively) (66), which are linked to 25 general hospital–based satellite centers. The HEWs are expected to provide communities with health education on childhood cancer and to promote timely health-seeking behavior, while PHCUs and general hospitals are expected to timely detect and/or diagnose and refer children with suspected cancer cases to specialized centers (66). The best strategy for improving survival of childhood cancer is timely diagnosis and effective treatment; as prevention is not possible, because established behavioral or environmental risk factors are limited (2). This requires firmly integrating childhood cancer into PHCUs to timely detect and refer cases. The investment in specialized care and basic service delivery should occur simultaneously, as early detection is useless unless there is effective treatment and vice versa.

Integrating childhood cancer control into the broader health system is crucial to exploit existing capacity, maximize efficiency, and make visible progress in improving the survival of children with cancer. Countries must thoroughly assess their health service delivery (from community to tertiary levels) and identify areas for integration. For example, pediatric oncology centers require functional multidisciplinary teams to provide comprehensive care and establishing them requires integrating childhood cancer services within the various support departments, such as laboratory, pathology, surgery, radiology, blood products, and social support. Similarly, childhood cancer control should be integrated across the tiers of health service delivery, for example, by including basic childhood cancer training in PHCU training packages, in NCD and cancer training materials, in monitoring and

evaluation tools, in cancer registries, and in health education programs at the health facility and community levels.

The Ethiopia health delivery system is not well set up to timely detect, diagnose, and effectively treat childhood cancers. The public awareness of childhood cancer is low, most people do not know the potential symptoms or recognize the high probability of cure with timely treatment (66). A cancer module was recently introduced into the HEP package (in 2018), but it doesn't address childhood cancer (67). HEWs' knowledge of NCDs and cancer control is low, and so is the overall quality of the health education they provide during household visits (72, 73). Health-seeking behavior (for formal health care) in Ethiopia ranges from 53 to 75%, and a sizable portion of the populace seeks care from alternative traditional medicine, which delays first contact with formal health care (68). Health professionals' knowledge of childhood cancer and exposure to it at PHCUs and general hospitals is low, representing another missed opportunity and a further delay to the early diagnosis and treatment of children with cancer. The goal of the NCACCP providing basic childhood cancer training to 50% of the health workforce in PHCUs has not yet been reached. Furthermore, children's care givers may forgo or abandon treatment because of the long distance to specialized centers and the high cost of transport, food, lodging, diagnosis, and treatment, which puts families under great financial hardship (as explained in more detail in section 1.3.7). The centralized approach (treating childhood cancer in a dedicated center of excellence) may not bring the intended results unless such financial hardship is addressed and the childhood cancer control program (early detection or diagnosis and referral) is well integrated into the primary and secondary service delivery tiers, which is not the case in Ethiopia. Instead, the approach could exacerbate inequality in access to care, as it benefits those who are better-off (particularly the urban rich and literate).

Another challenge is the service quality gap in pediatric oncology centers, which are characterized by inadequate staffing, the absence of standard treatment protocols, and unavailable or intermittently available diagnostic procedures, medicines, supplies, and supportive care. Furthermore, inadequate cancer service delivery in various areas (including access, service quality, and financial hardship) can lead to treatment abandonment, a major problem in childhood cancer control.

1.3.6. Childhood cancer treatment abandonment in Ethiopia

Childhood cancer treatment abandonment (interchangeably described as *treatment abandonment* or *abandonment* in this thesis) is not well studied in Ethiopia, and the magnitude of the problem is not clearly known, but the findings of systematic literature reviews in LMIC settings show that it is a major problem affecting as much as 50–60% of patients in some LICs (7). Studies in Kenya found that

50%–54% of children diagnosed with cancers abandoned care (74, 75), and the corresponding rate was 45% in Zambia (76), 42% in Ghana (77), 35% in Sudan (78), 33% in Uganda (79), and 19% in Malawi (80). We hypothesized that the rate of abandonment would be high in Ethiopia given the limited access to care (including physical and financial obstacles), the poor quality of care, low public awareness, and the observed high abandonment pattern in countries with similar settings.

Likewise, studies on the reasons for treatment abandonment have not been conducted in Ethiopia. A 2014 study in Kenya found that families' most common reasons for abandonment were financial difficulties and lack of health insurance, followed by transportation difficulties (81). A retrospective study of children admitted with Burkitt's lymphoma in Nigeria found that cost of care (especially chemotherapy drugs) was the major driver of abandonment (82). A study in Indonesia found that financial and transportation difficulties were among the most common reasons as were excessive side effects from cancer treatment and the belief that cancer is incurable (83).

Abandonment is a major problem even in settings where treatment is free. Evidence from Zambia in 2008–2010 revealed a high abandonment rate of over 45% (76) despite free treatment due to the high cost of transport, food, and lodging. Another study in a free-of-charge setting was conducted in a Malawian hospital to explore common reasons for abandonment (excluding treatment fees). Despite not paying for treatment, these families were heavily affected by the other costs of accompanying their child to treatment. Some were direct costs, such as transport to and from the facility, but there were also indirect ones, such as the opportunity cost of lost labor income while away from home (80). A study in El Salvador of patients under 16 years old with malignancies in 2001–2003 estimated an abandonment rate of 13% and found that low income and large household size predicted abandonment (27), even though a foundation paid for treatment, transport, hostel space, and even nannies to care for children undergoing treatment (84). The risk factors for treatment abandonment identified in other studies include competing household priorities, poor service quality, and a preference of alternative traditional medicine (7, 85).

1.3.7. Childhood cancer financing in Ethiopia

Achieving UHC, requires doing things right in all the building blocks of the health system, but the financing function is the cornerstone; as UHC is unthinkable without adequate, efficient, and fair financing mechanisms (86). As of 2019, the annual spending of Ethiopia's health system was USD 3.63 billion (USD 36.4 per capita) (87). This represented good progress from a low starting point, but it was far below the estimated spending required to finance essential health services in LICs (USD 79-86 per capita) (88, 89). In addition to its low health spending, the system was highly donor dependent,

as 34% of the spending was from development assistance, which affects the sustainability and predictability of the financing and the flexibility of resource allocation to priority services (90, 91). The share of direct out-of-pocket (OOP) health payments in total health spending was also very high (30.5%) and even worse in the case of NCD financing, as OOP payment accounts for 46% of NCD and 49% of cancer spending (87). Heavy reliance on OOP health payment greatly impacts the economic welfare of the worst-off (such as the poor, illiterate, and those living in rural areas) and puts households under enormous pressure in choosing between health care and meeting other basic needs, such as food, housing, clothing, and education (92, 93). As a result, households may delay or even avoid seeking care, face catastrophic or impoverishing health expenditures that force them to shift resources from basic needs to health care, lose their assets, or end in financial bankruptcy when the expenditure is large enough (39). Annually, close to 1.8 million individuals face catastrophic health expenditure in Ethiopia (94), and the situation is higher for NCDs (95), especially cancer care. For example, a study conducted in TASH estimated the incidence of catastrophic health expenditure among cancer patients to be around 77%, which is a very alarming figure (96).

Therefore, Ethiopia should minimize OOP health payment as much as possible and finance the health system with either a general government budget (tax based) or a large, unified, and progressive prepayment-based financing mechanism to realize the aspiration for UHC (86, 92, 97). Efforts to scale up the health insurance system are in their infancy, and it covered only 2% of health spending in 2019 (87). The current functional health insurance system is a community-based health insurance (CBHI) program that covers people in the informal economy sector (mainly rural dwellers and farmers), and a plan exists to institute national social health insurance in 2023 for people in the formal economy sector (those in an organized system of employment and earning) (98). The CBHI is a district-level, government-led program. In 2021, around 8.9 million households (41.6 million individuals) were covered in 920 of the country's 1,116 districts (84%), with an average enrolment rate of 60% (99). Close to 20% of the enrolled households were poor people whose CBHI contributions were covered by the government. The program covers health services that are not included in the list of exempted health services (described below) (98). Even though childhood cancer diagnosis and treatment services are part of the CBHI benefits package, however, it does not provide a real benefit, as users are restricted to scheme contracted health facilities within their districts (most in rural areas), where childhood cancer services do not exist.

In Ethiopia, the cost of care for major communicable diseases (such as TB, HIV, malaria, and maternal and child health conditions) are fully exempted for the user in public health facilities, at least at a policy level, as the costs are covered by the government, a donor, or both (100). For other health services (including childhood cancers), the HR and administrative costs (including utilities) are covered by the government, and users are expected to cover the remaining expenses, such as diagnostics, drugs, supplies, and procedures (a cost-sharing approach) (100). In addition, efforts are underway to cover 50% of the cost of cancer drugs (chemotherapy), but it has not been successfully implemented, and most of the drugs are unavailable in public treatment centers, forcing patients to buy from the private market and even on a black market (96).

Although their efforts are very small compared to the need, a few civil society organizations support the pediatric oncology units and provide hospice services for people from distant areas who cannot afford lodging, food, and transport.

1.4. Priority setting for UHC

UHC—the delivery of quality and equitable health services (including promotive, preventive, curative, and palliative services) to all people as per their need while ensuring FRP (86, 97)—is the central theme of the sustainable development agenda, as health is a fundamental human right and a cornerstone of sustainable development (17). For multiple reasons, states have a moral, legal, economic, social, and political obligation as well as a responsibility and development interest in accelerating progress toward UHC. First, the right to health and wellbeing is an internationally recognized human right that is deeply rooted in international resolutions and countries' constitutions and policies (101, 102) due to the critical role of health in determining individuals and families' wellbeing and the possibility of reaching one's maximum potential in livelihood (102-104). The right to health demands that every person has equal access to quality health care, which implies a commitment to ensuring equity. Second, there is a well-documented economic argument for investing in UHC, as investing in health is investing in human potential, which drives growth and development. A dollar spent on health is expected to yield returns of 9–20 times higher (105). In 2000–2011, 24% of economic growth in LMICs could be attributed to improved health (105). Third, good health is also a foundation for inclusive and sustainable development (including social, economic, and political development) (17). Any development not built on good health can be lost quickly as it was well illustrated in the early phase of the Covid-19 pandemic, which showed that a crisis that starts in the health sector can paralyze all aspects of life (social, economic, and political) in an instant.

UHC has gained momentum as a global health agenda in almost all countries (106, 107), which are at different stages of adopting, attaining, and sustaining UHC (64, 107). The progress to UHC is currently measured by a UHC service coverage index – a geometric mean of 14 selected health service coverage indicators rated from 0 (worst) to 100 (best) coverage, and with the incidence of catastrophic health expenditure (as a measure of financial hardship) (64). Efforts to embrace the equity dimension of UHC are not yet well established due to limited data availability in many countries. As of 2019, the global median UHC service coverage index was 67, ranged from 27 to 89, and was highly correlated with other measures of health and development, such as the human development index (ρ=0.91), life expectancy (ρ=0.9), under-five mortality rates (ρ=-0.86), and gross national income per capita (ρ=0.8) (64). Although countries' economies and their UHC performance are correlated—the stronger the economy, the greater the likelihood of achieving UHC—differences exist within and across countries' economic strata. For instance, most HICs have achieved UHC, but some still struggle. Some middle-income countries have performed impressively, even better than some HICs, while others fare worse than LICs. For instance, Nigeria's health coverage is far below that of many LICs, with a high incidence of financial hardship (64).

According to a 2019 WHO and World Bank report, countries can be categorized in seven broad groups (stages) according to their progress toward UHC (figure 2). Countries in group one, mostly HICs (such as the Scandinavian countries, the United Kingdom, Germany, Australia, Canada, Luxembourg, Thailand, and Slovenia) (64), have achieved both the coverage and FRP elements of UHC but are now struggling to sustain it due to an increasing cost of care related to demographic change, evolving epidemiology, expensive new technologies, and growing expectations. Group two countries such as China, Chile, Belgium, and Portugal, have long met the coverage requirement of UHC (like group one) but face great financial hardship (64, 106). Group three countries are on track to achieve UHC (in both the coverage and FRP dimensions, heading toward group one), and some are on the verge of attaining UHC. Turkey, Mexico, Slovakia, and Panama are good examples of group three (64, 106). Group four countries, such as Egypt, Tunisia, Morocco, Georgia, and Lebanon, are taking promising steps on the coverage aspect of UHC but lag in reducing financial hardship (having a high rate of catastrophic health expenditure) (64, 106). Group five countries such as Rwanda, Kenya, and Zambia, have made modest progress in improving health coverage and have low financial hardship (64, 107). Group six countries are those with low service coverage and low financial hardship. Most LICs and some lower-middle-income countries, such as Ethiopia, Benin, and Burundi, fall under this category (64). The low financial hardship in groups five and six may be partly explained by the low service coverage rather than by true FRP as in groups one and three. Group

seven includes countries (such as Nigeria, Sierra Leone, Sudan, and South Sudan) with low service coverage and high financial hardship (64).

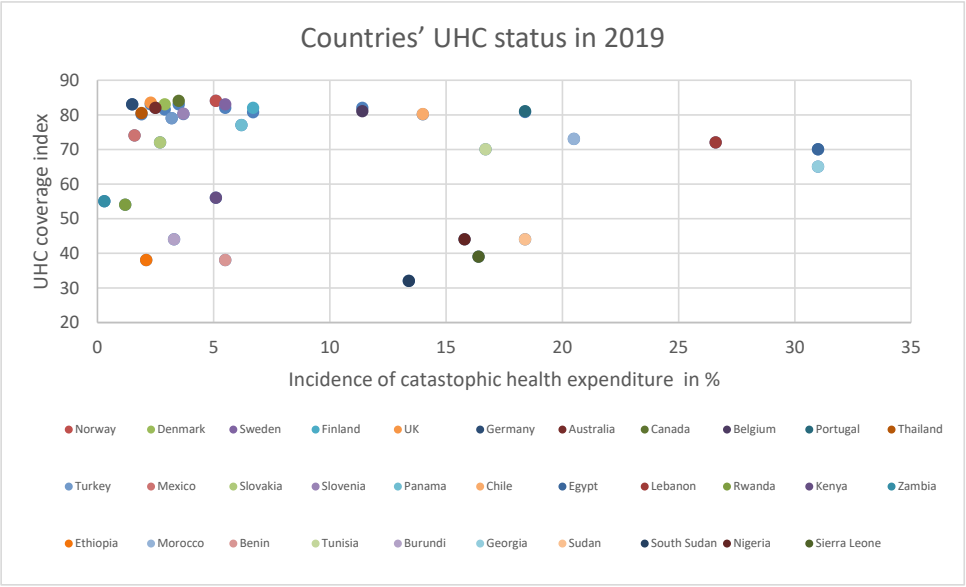

Figure 2. Countries' UHC status in 2019

Countries follow different paths on the long journey to UHC due to their diverse capabilities, health needs, political and socioeconomic situations, and health-system and institutional arrangements, but it is critical that they learn from the successful and failed policies of countries at various stages of UHC realization. Whichever path countries choose, they face the key and crosscutting challenge of securing adequate resources to meet an ever-increasing cost of care (108, 109). It is not realistic to provide all needed services immediately given the macroeconomic constraints and the time needed to build the technical capabilities to deliver UHC, such as skilled workforces, expanded infrastructure, strong supply chain management systems, and mechanisms to handle demand-side barriers (106-108). Hence, countries should aim for a progressive realization of UHC (an incremental approach) rather than making unrealistic efforts to meet all health needs at once (97, 105, 108). Progressive realization of UHC should not be confused with providing a minimum package of services, rather it represents a commitment to offer a comprehensive range of key services that can be provided with the maximum resources that a country can afford, moving incrementally toward full realization of UHC (97).

While there is no single, magic pathway to progressive realization of UHC (97, 107), global experience suggests that countries should progress in three dimensions (commonly described as the

"UHC cube") (97): expanding priority services, covering more people, and reducing OOP health payments. However, myriads of ethical dilemmas and questions of fairness arise on the path to progress in the three dimensions of UHC, as there are trade-offs within and across these dimensions, and the scarcity of resources pushes decision-makers to exclude some interventions or give less priority to some groups (97, 110). The major dilemmas are: Which services should be included and expanded first? Who should be covered first for priority services? Which services and what subpopulations should be lifted first from high OOP health payment and how? Basically, the quest is to establish a fair priority-setting mechanism and a just order of addressing unmet health needs in which interventions and their recipients are ranked by priority level (high, medium, low) on the basis of agreed-upon principles and criteria; the priority ranking determines which services will be financed first and which later (97, 109).

To address these trade-offs systematically and fairly, countries must establish a strong priority-setting mechanism based on an explicit, agreed-upon set of criteria that are well informed by societal values, evidence, and local context (97, 109). Although not discussed in this thesis, the process to be followed in the priority-setting mechanism is as important as the agreement on a set of ethical principles and criteria. Applying the principles of Daniels and Sabin's widely accepted "accountability for reasonableness" ethical framework could facilitate agreement on priority-setting decisions and improve acceptance and the ownership of implementation (111). The accountability for reasonableness framework sets the conditions for a fair, legitimate priority-setting process through the meaningful engagement of all relevant stakeholders, openness to diverse values and points of view (democratic), transparent discussion, active public involvement, and opportunities for appeal and revision. Baltussen et al. have also proposed a framework for stakeholder deliberation (112).

Textbooks and the literature propose various definitions of *priority setting*. This thesis defines it as the rank ordering of health interventions and of the recipients of those services on the basis of agreed-upon ethical principles and criteria to guide a systematic resource allocation beginning with high priorities and proceeding to medium and low priorities until the budget ceiling is reached (109). It also implies ongoing efforts to progressively include the remaining medium or low priority services by mobilizing new resources or eliminating inefficient services (de-prioritization of services through periodic revision) (109, 110).

Priority setting is practiced in almost all health systems, albeit to a greatly varying extent, as resource scarcity is a universal phenomenon. Decision-makers in LMICs may face priority-setting decisions more frequently due to scarce resources and multiple competing health needs. Priority setting in

LMICs is commonly implicit, as the values or criteria guiding the decision are not clearly documented and communicated (113). Priority setting is practiced at every tier of health service delivery, including the global, national (macro), subnational (meso), and point-of-provision (micro) levels (109, 114). At the macro and meso levels, decision-makers try to prioritize specific health interventions, population groups, and geographical areas over others, while, at the micro level, health professionals deal with bed-side prioritization, such as determining which treatment to give and which patient groups to prioritize. For example, who should be admitted first to the ICU? Who should have priority for scarce, lifesaving equipment? This thesis focuses on macro-level prioritization, evaluating the provision of a specialized pediatric oncology unit in the context of health maximization at the national level, although some of its recommendations may inform facility-level prioritization. Despite encouraging progress toward applying systematic priority setting, priority setting in many LMICs is based on implicit criteria and reflects political decisions guided by a small, ad hoc team with limited stakeholder participation, little transparency, and not based on robust evidence (110, 115, 116). Furthermore, despite an increasing NCD burden, it is mostly skewed to communicable diseases and maternal and child health conditions(117).

Countries that are institutionalizing systematic prioritization adopt various criteria, but the most widely used and recommended criteria are cost-effectiveness, FRP, and priority to the worst-off, with a strong inclination toward cost-effectiveness (109, 115, 118-121). WHO's consultative group on equity and UHC (comprising leading global economists and ethicists) recommends using these criteria for priority setting (97). These criteria are well aligned with health system goals, such as maximizing health (total population health), equity (fair distribution), and FRP and with the fundamental ethical theories of justice and fair distribution, including utilitarianism (the "maximization of health benefits for a given budget") (122) and prioritarianism (prioritizing the worst-off) (123).

Priority to cost-effective interventions

A major goal of any health system is improving the population's health (124), but, because the cost of health needs surpasses the available resources, attaining this goal is always made difficult by resource scarcity. As a result, decision-makers struggle to efficiently allocate and use scarce resources to maximize population health within a given budget (ensuring the best value for money) (108, 109). The global recommendations (lead economists, ethicist, global institutions specialized on priority setting) and lessons from countries' practice is to use cost-effectiveness of health interventions (based on a utilitarian theory of justice) as a guiding ethical principle (or core criteria) (125, 126) to prioritize services in rank order of their value-for-money and allocate resource starting from first top priorities

and then to the medium and low priorities (97, 109). It would be inefficient and unfair not to cover a cost-effective (cheap and effective) service that avert a big population health burden while simultaneously covering not cost-effective services— for which the opportunity cost is high, due to the many lost health benefits that could have been obtained by investing the same resource in the next best alternative cost-effective health intervention (109, 115, 122, 127, 128). As the health system aims to achieve more than one goal, e.g., the distribution of health in addition to the maximization of health, it is imperative to combine the ethical principle of priority to cost-effective interventions with other societal values, such as prioritizing interventions that benefit the worst-off and promote better FRP.

The prioritization of cost-effective interventions is informed by evidence from cost-effectiveness analysis (CEA), which estimates the incremental resource requirements of implementing a given intervention to avert a unit of a health burden (commonly measured in disability-adjusted life years [DALYs] averted or quality-adjusted life years [QALY] gained) compared to the alternative comparators (the current best practice). The result of CEA is commonly presented as an incremental cost-effectiveness ratio (ICER) (129), and a lower ICER indicates the need for a relatively small additional investment per unit of health gain compared to the alternative intervention; thus, investing in the intervention improves health better than the alternative within a given budget, while the opposite is true for a higher ICER. However, the ICER-based approach assumes that the current practice (intervention or mix of interventions) that serves as a comparator is efficient, and it does not account for existing inefficiencies (129). An alternative approach is to use the average cost-effectiveness ratio (ACER), in which both the intervention under consideration and the current practice (the comparator) are compared to a do-nothing scenario (130, 131), which helps to account for existing inefficiencies. This approach is preferred for comparing broad ranges of health interventions, for example, when designing benefits packages (131).

The key challenges to using CEA evidence, especially in LMIC settings, are (1) a lack of robust data, (2) the need for advanced technical expertise (which is often lacking), (3) inconsistent evidence, and (4) the limited transferability of evidence from one setting to another due to great variations in analytical approach (such as scope, perspective, choice of model and comparator, and the comprehensiveness of cost inputs) as well as context-specific factors, such as disease burdens and patterns, the effectiveness of interventions, the cost-of-care profile, and differences in service quality and treatment protocols. These factors have limited the use of CEA in LMIC settings (115, 130, 132-135). To address these challenges, global partners, such as DCP3 (136, 137), WHO's CHOosing Interventions that are Cost-Effective (WHO-CHOICE) (138), the National Institute for Health and

Care Excellence (NICE) (139), and the Tufts University CEA registry (140), offer cost-effectiveness estimates and advise countries on "high priority" (137) and "best buy" packages (141) in various settings. Other diverse guidelines and tools have been developed, but more investment is needed to build countries' local capacity to generate and use CEA data and to generate multinational CEA estimates (of countries with similar settings).

Priority to services benefiting the worse-off

A priority-setting decision based on CEA may not always lead to UHC (109), as standard CEA by its nature does not capture the distributional effect of the total health benefit (115, 120, 142). It measures only the aggregate health benefit of an intervention without identifying who benefits. Some interventions could be more cost-effective than the alternative but mainly benefit the better-off, further (and unfairly) aggravating inequality. The global commitment to UHC requires tackling inequality even at an extra cost (97); thus, states, leaders, and societies agree to forgo some benefits for the sake of equalizing health, and empirical evidence supports this approach (143, 144). In other words, interventions that benefit the worst-off are more highly valued (are given greater weight) than the same unit of benefit in the better-off. How much extra weight they are given depends on the value and level of commitment that countries give to prioritizing the worst-off; obviously, countries that strongly emphasize reducing inequality place a higher value on it.

Although the term *worst-off* lacks a single, standard definition (97, 115, 142), in a health context it generally describes (1) those with the worst health (currently or over their lifetime), such as those with the largest individual burden of disease; and (2) people who experience unequal access to health care because of diverse settings and social characteristics, such as income/wealth (the poor), geography (those living in rural areas, hard-to-reach-areas, or areas with regional disparities), gender, sexual orientation, education, ethnicity, and race (97, 115, 142). States should first tackle the barriers to groups that are disproportionately affected by poor health and poor health service coverage; in other words, they should first expand high priority services to the worst-off individuals or groups. Similarly, it is appropriate to close the coverage gap in high priority services before addressing the coverage gap in medium or low priority services for the worst-off groups (97). Most of the time, health maximization goes hand in hand with prioritizing the worst-off and ensuring FRP, especially for prevalent health conditions, so the intervention under consideration could score high in all parameters (97, 105, 109, 137). In such a situation, the priority-setting decision is easier, as investing in such an intervention brings progress in all three dimensions of UHC without a need for trade-offs.

Priority to services that improve FRP

As noted in the section on financing childhood cancer treatment (1.3.7), direct OOP health payment at the point of care is regressive and prevents a sizable portion of society from accessing health care, contrary to the main goal of UHC and the right of all to health and wellbeing (92, 97). This potentially affects everyone in the society but disproportionately and unfairly hits the worst-off groups (64, 97), who have the greatest health needs (86). It affects the health of individuals and families (due to avoiding or delaying health care) as well as their social and economic welfare, as the financial hardship of paying for care (or the loss of productivity) may push people into poverty or worsen the status of the already poor (86, 97, 145). This commonly occurs in diseases or conditions that incur high cost of care or prolonged treatment, but it is important to note that health conditions that seem to impose a small financial burden at the individual level may cause a great aggregated financial hardship, especially among the poor and near poor (97). Other things being equal, giving extra weight to interventions that offer the highest FRP could reduce the financial barrier to utilization of care, mitigate the economic consequences of poor health, and reduce unfair inequality. OOP health payments should be reduced for high priority health services before medium and low priority services, and they should be lowered first for the worst-off individuals or groups (97).

At the macro level, ensuring FRP requires a wider economic reform aimed at poverty reduction and equitable development. In the narrow scope of health financing, ensuring FRP requires a shift from direct OOP health payment to progressive compulsory prepayment (in the form of tax or health insurance) with a unified pooling arrangement (92). The prepayment should be designed as mandatory, because voluntary schemes are prone to adverse selection (92), in which mainly people with high health risks (such as the elderly or sick) join the pool; the resulting small pool is not adequate to sustainably finance their health needs. As discussed in section 1.3.7, states must ensure that the wealthy and healthy members of society (e.g., the young) cross-subsidize the poor, the unhealthy, and those with greater health risks to make possible a fair, equitable distribution of health and income. Contributions to the pool should be based on users' ability to pay, and the use of service should be based on health needs (92). The financial pool should be unified to enhance cross-subsidization and minimize fragmentation and inefficiencies.

Priority setting is only the starting point on the UHC journey, and many key steps must be taken to ensure that the promised packages are delivered per the values entertained adopted during the prioritization process (106, 107, 124). Although not addressed in this thesis, the following key

questions must be asked before implementing the prioritized health interventions: How can stakeholders (state and non-state actors) be engaged in implementing the priority services? What capabilities (infrastructure, HR, medicine and supplies, equipment, infrastructure, information systems, regulations, institutions) should be established to deliver the priority services? What institutions and capabilities are needed? How can we reform the revenue generation, pooling, and purchasing function of health financing? How will we reach the prioritized population groups, e.g., (a) from the supply side, should we prioritize investing in hard-to-reach areas? rural areas? primary health care? (b) from the demand side, how do we target the worst-off groups, for example, to raise awareness and reduce their economic burden through social protection measures and covering their cost of care? How do we know whether the implementation is moving in the right direction? What is working, and what is not?

1.5. Rationale of the study

In 2019, the MoH revised EHSP (8), prioritizing health services by the criterion of cost-effectiveness in combination with other criteria, such as FRP, disease burden, budget impact, priority to the worst off, and public and political acceptability. A total of 1,018 health interventions were mapped for prioritization, and 594 (58%) services were classified as high priority, 213 (21%) as medium, and 211 (21%) as low priority services (145).

All childhood cancers were classified as low or medium priority services (most as low), contrary to the NCACCP (66) and the global call to prioritize childhood cancer in national health benefits packages. A year before revising the EHSP, the MoH, answering WHO's call, launched a NCACCP that aimed to scale up childhood cancer services with public health spending. However, this ambition was not reflected in the EHSP, and such contradicting priority may have profound consequences to the fight against childhood cancers. For example, the EHSP planned to deliver all childhood cancer interventions through a cost-sharing approach, which is unaffordable to many households.

The EHSP's failure to reflect the values of the NCACCP regarding the priority to be given to childhood cancer interventions may be due to the source and quality of the evidence used as well as to the inadequate participation of the childhood cancer community in the priority setting process. Another possible explanation is the lack of robust evidence on cost-effectiveness for many of the health interventions, which may have caused inconsistency in the technique of prioritization. For example, only 552 interventions (54%) had cost-effectiveness data (145), and it is unclear how, beyond expert judgment, the rest of the health interventions were managed in the priority ranking. This also applies to childhood cancers, as evidence is limited in LMICs and generally comes from

HICs and some middle-income countries. Such inconsistency may lead to biased conclusions. Lacking adequate evidence of cost-effectiveness, the prevailing assumption that cancer care is generally costly, unaffordable, and not cost-effective in LICs may have further influenced the MoH's decision in the EHSP.

However, to challenge the EHSP decision and argue for the inclusion of selected childhood cancer control interventions as a high priority, one must present convincing evidence on childhood cancer interventions that aligns with the EHSP's prioritization criteria (such as cost-effectiveness, equality, FRP, and budget impact). The limited evidence from other LMICs offers some indications, but local evidence remains necessary given countries' differing disease burdens and cost-of-care profiles as well as the fact that Ethiopia's WTP threshold is lower than that of other LMICs. There is also a global need for more evidence on the cost and cost-effectiveness of childhood cancer interventions in LMIC settings (e.g., as recommended by DCP3) (2). Therefore, this research aimed to fill the local evidence gap regarding the cost and cost-effectiveness of childhood cancer treatment (specialized pediatric oncology care delivery) to inform the revision of the EHSP and augment global efforts to generate evidence on childhood cancer control interventions. The NCACCP aims to reduce Ethiopia's treatment abandonment rate by 60% by 2023 (66), but little is known about the starting baseline and the influencing risk factors for treatment abandonment. Filling this evidence gap was a second motivation of this research.

2. Objectives

This research aimed to generate policy-relevant evidence on the risk factors and magnitude of treatment abandonment in Ethiopia as well as on the cost and cost-effectiveness of childhood cancer care delivery.

Specifically, the research pursued the following aims:

1. To assess the magnitude of and reasons for childhood cancer treatment abandonment in Ethiopia
2. To estimate the cost of running a pediatric oncology unit in Ethiopia
3. To estimate the cost of care for specific childhood cancers
4. To compare the cost-effectiveness of running a pediatric oncology center in Ethiopia compared to a do-nothing scenario (no pediatric oncology care)

3. Methods

This thesis comprises three studies (Papers I–III) that answer the four specific objectives presented in section two. The first study (Paper I), using primary data collected from three treatment centers at TASH, GUH, and JUH, assesses the magnitude of treatment abandonment and the perceived risk factors from the health care provider perspective. Paper II, drawing upon primary data collected from TASH, estimates the overall cost of running a pediatric oncology unit (overall cost of delivering childhood cancer care) and the cost of treating specific childhood cancers. Paper III builds on the costing study findings of Paper II (primary data) and estimates the overall cost-effectiveness of running a pediatric oncology unit (overall cost-effectiveness of a childhood cancer delivery platform) by using effectiveness estimates from similar settings (secondary data). This section of the thesis summarizes the methods (which are detailed in each paper) by first providing an overview of the setting of all the studies and then briefly describing the specific methods (study design, sampling, data collection, and analysis) paper-by-paper.

3.1. Study setting

The treatment abandonment study (Paper I) was conducted in three of the four pediatric oncology units in Ethiopia: TASH (in the Addis Ababa city administration), JUH (in the Oromia region), and GUH (in the Amhara region). The original plan to include MUH (in Tigray) was abandoned because war had erupted in Tigray at the time of the study. Because of various shortcomings (e.g., in skilled human resources, infrastructure, service standards, and the availability of medicine and supplies), these pediatric oncology units were generally far from meeting the standards of an ideal center of excellence (66).

The costing and cost-effectiveness studies (Papers II and III) were conducted at the specialized pediatric oncology unit at TASH, which is the largest specialized hospital in Ethiopia, with 81 clinical departments, 735 beds, and close to 500,000 outpatient department (OPD) visits yearly (20). TASH's pediatric oncology unit, the nation's first, was established in 2013 as a twinning program of TASH and Georgetown University Hospital in Washington, DC (the Aslan Project) (146). It is well set up in comparison to the other pediatric oncology centers and is staffed by pediatric oncologists, trained oncology nurses, oncology pharmacists, social workers, and pediatric residents who work on a rotation basis. It shares numerous services with other departments at TASH, such as pharmacy,

laboratory, pathology, radiology, emergency, intensive care, and surgery. At the time of the study, TASH was the only hospital providing radiotherapy treatment in Ethiopia.

3.2. Childhood cancer treatment abandonment (Paper I)

3.2.1. Study design and sampling

We employed a cross-sectional study design and sampled three of the four pediatric oncology centers in Ethiopia (TASH, JUH, and GUH). We interviewed all the health care professionals (physicians, nurses, and social workers) who had worked in childhood cancer service provision at these centers for over a year. We excluded those with less than a year of experience and those who did not meet the professional criteria (physician, nurse, social worker).

We originally planned to examine both the health care providers' and the caretakers' (patients' guardians') perspectives, but we faced challenges in contacting the guardians due to a poor registry, nonworking phone lines, wrong numbers, and changed phone numbers (as described in detail in Paper I). The number of inaccessible guardians (70 of 186) was too high to obtain representative data, so we conducted the study from the providers' perspective only.

3.2.2. Data collection and analysis

We used a validated, semi-structured questionnaire developed by the International Society of Pediatric Oncology Abandonment Technical Working Group, which had been previously used in a global childhood cancer treatment abandonment estimate survey (7). The questionnaire mainly covered the incidence of treatment abandonment, the influencing risk factors, the availability of essential interventions, and strategies to reduce childhood cancer abandonment (Table S1 in Paper I). We administered the questionnaire in English using tablets and a central server. The field supervisors and principal investigator had real-time access to de-identified data and provided feedback to data collectors whenever they identified gaps. Trained data collectors conducted face-to-face interviews on September 5–22, 2021. We conducted descriptive analysis using Stata/SE version 17.0.

3.3. Cost of running a pediatric oncology unit (Paper II)

We selected the pediatric oncology unit at TASH as the study site of the costing study, as it was relatively better staffed and equipped than the other, recently opened treatment centers (GUH, JUH, MUH) and was the major referral center for children with cancer across the country during the study period (2018–2019), when the other centers were newly established (66). In addition, most of the cost drivers were relatively similar among the centers—e.g., staff salaries/benefits and the prices of drugs,

supplies, and medical equipment—as the latter items were procured and distributed to the treatment centers by the same public organization, the Ethiopia Pharmaceutical Supply Agency (EPSA). Therefore, a costing estimate at TASH could provide a representative estimate of the annual cost of treating a child with cancer in Ethiopia.

3.3.1. Identification, measurement, and valuation of cost inputs

The costing study for the pediatric oncology unit was part of a broader costing exercise for all TASH departments conducted by the Ethiopia Health Insurance Agency (EHIA) from 8 July 2018 through 7 July 2019. This enabled better mapping of the relationships of various departments (from a childhood cancer service delivery and cost perspective) and capturing their cost share in the final cost estimation, unlike the commonly conducted (due to budget constraints) department-specific costing, which is prone to large over- or underestimations. We simultaneously collected additional data elements to establish a disease-level unit costs beyond the scope of the overall TASH costing, which aimed to determine department-level unit costs.

The costing study was facility based, took a provider perspective, and considered all costs related to delivering services regardless of the payer. It followed a retrospective approach and collected historical data for 8 July 2018–7 July 2019 on the assumption that full-year data would account for seasonality and avoid cost distortions resulting from seasonal utilization. The study employed a mixed costing approach with a predominantly top-down estimation in which aggregate costs at the hospital level (such as indirect costs) were allocated to departments. This was supplemented by a bottom-up approach, particularly for allocating department-level direct costs to the disease level (childhood cancers). Direct costs—those directly attributable to a specific department or service output, that is, costs of HR, medical equipment depreciation, and drugs and other supplies—were computed by estimating the amounts consumed by the unit in a year (consumed quantity) and multiplying by their unit costs. Indirect costs—those that cannot be tied directly to a specific department and are shared across departments—were allocated to specific departments on the basis of various allocation criteria. Indirect costs include utilities, administration, and other overhead costs. The identification, measurement, and valuation of major cost inputs are described below.

Human resources

We collected from each department a list of all staff who were active during the study period. The staff mix was categorized by cadre and qualification (e.g., nurse, BSc). The time allocated to each department by each cadre of staff, including patient-facing and non–patient-facing time, was collected from interviews with heads of departments. Next, the total number of full-time equivalents (FTE) was calculated for each cadre and qualification category (see Paper II's methods section for details). The average personnel cost per cadre (including salaries, benefits, and allowances) was calculated for clinical and administrative staff employed from 8 July 2018–7 July 2019 based on data from the HR and/or finance department. Staff costs were assigned on the basis of a department's staff mix as defined during key informant interviews with department heads. The average annual salary plus allowances for each cadre, as defined by HR data, was used to determine the cost of staff in each department.

Drugs, lab reagents, and supplies

Purchase costs and the volume of internally distributed drugs, laboratory reagents, and supplies among departments were collected from the central pharmacy unit using the facility's Health Commodities Management Information System (HCMIS). When an item's unit cost was not found in the HCMIS, the unit cost was obtained from EPSA. For donated items with no unit cost at EPSA, we used international unit prices, such as those of Management Sciences for Health (147) and NICE's drugs and pharmaceutical electronic market information tool (eMIT) (148).

Medical equipment

An inventory of all functional medical equipment available at the time of the visit was collected for all departments. This study included only costs related to functional clinical equipment (excluding administrative equipment, such as desks, chairs, and communication equipment). The value of equipment was estimated using three-year average procurement data from EPSA for the study period and reflected the equipment replacement cost. A straight-line depreciation rate of 10%, which is in line with government capital-item accounting standards (149), was used to amortize the equipment over 10 years and to estimate the yearly equipment cost.

Intermediate departments and overhead services

Shared services or departmental costs, such as radiation, imaging, pathology, surgical operating room, ICU, pediatric emergency services (ER), inpatient food services, laundry, utilities (rent, electricity, telecommunication, water, and other charges), along with other overhead costs (such as office supplies, printing, educational supplies, fuel, per diems, and training costs), were costed by allocating the share of each of the services used by the pediatric oncology unit through the use of various allocation bases as appropriate in each case (for further details, see Supplementary Table S1in Paper II).

Service statistics

Utilization data were collected from department-specific registries and service statistic reports. For cases in which this information was unavailable, we used hospital-level HCMIS reports. This included total patient visits, bed days, visits by service/procedure (laboratory, pathology, imaging tests, surgeries), and length of stay information.

Allocation technique

Service statistics collected across departments were used to allocate shared costs to various departments and to compute departmental unit costs. For example, laundry and food were allocated to inpatient departments based on the share of total bed days; utilities, such as rent, electricity, and water, were allocated based on the square meter size of the department; other overhead costs were allocated based on the department's share of total hospital staff. The costs for administration (e.g., HR and finance) were allocated based on the department's share of personnel. The costs of intermediate (clinical support) departments, such as the operating room, laboratory, and radiology, were allocated to other OPDs and IPDs in the final step of cost allocation (Figure 3).

We computed the total cost of the unit by adding (1) the direct costs (personnel, drugs, supplies, medical equipment), (2) the share of indirect costs (food services, laundry, utilities, other overhead cost), (3) the cost share from crosscutting departments (such as administrative offices and the liaison office), and (4) the cost share from intermediate clinical support departments (such as laboratory, pathology, radiology, triage, operating room, pediatric ER, pediatric ICU, and radiotherapy) (Figure 3). We converted the final cost estimate in Ethiopia birr to USD using the 2019 exchange rate (24).

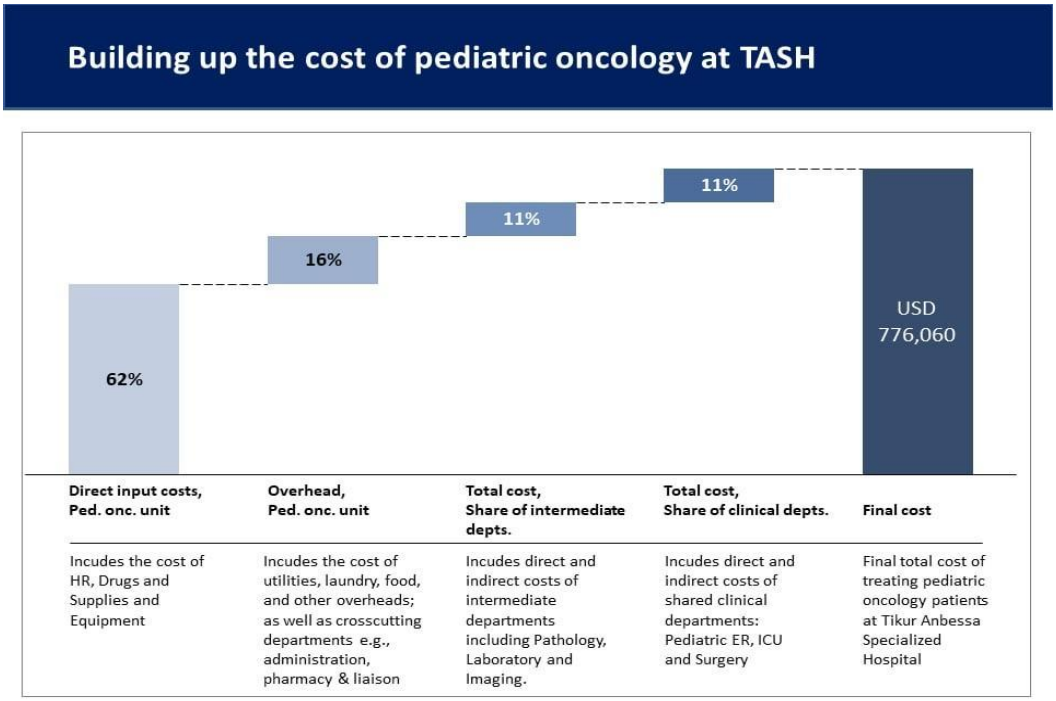

Figure 3. Department/unit level cost aggregation approaches. The figure illustrates how the department's direct input costs (such as those for personnel, drugs, supplies, and equipment), which are dedicated only to pediatric oncology services, are combined with the department's overhead cost share in the total hospital overhead cost and the costs from intermediate and clinical departments that also serve pediatric cancer patients (in addition to provision of other services).

We took diverse approaches to disaggregate the costs for specific childhood cancers. To allocate the estimated fixed costs at the pediatric oncology unit level (such as HR, medical equipment, and overhead costs) to specific cancers, we used each childhood cancer's disease-level service utilization share in each department. For intermediate clinical support departments, such as laboratory, pathology, radiology, triage, ER, ICU, and surgery, we used childhood cancer–specific utilization rates for each department. When available and reliable, each department's registry book was transcribed to identify the relative patient load for various cancer types, and we found childhood-cancer disease-specific utilization data for surgery, ER, ICU, pathology, and X-ray services. The costs for these departments were then allocated to each cancer type according to its relative share of total utilization (assuming one visit or bed day required equal resource use for all cancer types). For cases in which registry data were not available (in the case of the lab and the radiology department except for X-ray), the relative consumption share among the childhood cancer types on the chart review (described below) was used to determine cost distribution.

To distribute the cost of drugs and supplies from the pediatric oncology unit to specific childhood cancers, we applied the following techniques. First, with the help of a senior pediatric oncologist, we matched the drugs and supplies consumed in the pediatric oncology unit (collected from the hospital's HCMIS database) to specific disease types. This helped to determine which items matched specific cancer types. We did one-to-one matching for medicine that was used for only a single cancer type, meaning 100% of the cost transferred to that specific type. For items that were matched with two or more cancer types, we used the relative prescription rate share for that item (among the childhood cancer types) in the chart review to allocate the total cost of a specific drug or supply to childhood cancer types. For example, if the relative prescription rate of item X on the chart review was 60% ALL, 30% acute myeloid leukemia, and 10% Hodgkin's lymphoma, then the total cost allocated for X at the pediatric oncology unit level was distributed according to those percentages.

3.3.2. Patient chart review

Because historical costing captures only actual expenditures in a given period (without considering the quality of care), it may not measure the full cost of treating patients with sufficient quality of care, leading to an underestimation of cost. For instance, the national average essential drug availability estimates in 2018 was 28% (25), which may have been even lower for pediatric oncology drugs given their high cost and neglected status. The same shortcoming in service readiness existed in laboratory, radiology, imaging, and pathology services. To account for such gaps, we embedded a patient chart review in the study in parallel with the top-down costing during the same study period (8 July 2018–7 July 2019). We reviewed 345 randomly sampled charts to estimate the total annual clinicians' orders (quantity of consumption) for drugs, supplies, laboratory, pathology, and imaging (the sampling technique is described in Paper II). The consumption of inputs was annualized at the patient and pediatric oncology unit levels. Next, we computed the cost of each cost input by multiplying the quantity consumed in a year by the unit cost. Subsequently, the costs of HR, radiotherapy, surgery, and overhead from the top-down costing approach were added to the cost findings for drugs, supplies, laboratory, radiology, imaging, and pathology from the chart review to compute total cost, representing the upper-bound cost estimate in the scenario-based cost sensitivity analysis for the pediatric oncology unit cost sensitivity analysis (further details described in section 4.2).

As indicated above, while detailed service statistics at the diagnosis level were collected for pediatric oncology and associated departments, the data availability and quality varied, and data were not available at the diagnosis level in some instances. The chart review therefore offered the secondary benefit of enabling more precise cost estimates at the disease level by providing indicative data on the

distribution of services among cancer types for those departments with service-statistic data gaps (more details are given in Paper II's methods section).

3.3.3. Data collection process and data quality control

The data collection was undertaken by experienced costing-data collectors who had previously participated in similar costing studies by EHIA. The team attended a one-day training session that covered the study objective, data collection tools, and guidelines and routines for data collection. The data collection tools were paper based and derived from the Simple Cost Analysis Tool for Hospitals previously used by EHIA (150). The team was closely supervised on-site (by three author of Paper II), with check-ins at the beginning and end of each day.

Once the data collection was finalized and the data entered into the Excel-based tool (from the paper-based data collection templates), an iterative process of data validation was conducted. First, the collected data were compiled and a preliminary analysis was performed. Gaps and suspicious values in the data were identified, and follow-up was undertaken in person with hospital staff. Follow-up was done very frequently in the weeks immediately after the data collection but continued ad hoc over several months as the data were compiled and analyzed. The cost analysis was conducted using an Excel-based model adopted from the Joint Learning Network for Universal Health Coverage (JLN) (151), which was previously used by EHIA for a similar exercise.

3.4. Cost-effectiveness of running a pediatric oncology unit (Paper III)

3.4.1. Decision-analytic model

We built a decision-analytic model—a decision tree—to estimate the cost-effectiveness of running a pediatric oncology unit compared to a do-nothing scenario from a provider perspective (Fig. 4). We chose a pediatric oncology unit–level CEA rather than a disease-level one (for specific childhood cancers), as it was not possible to further disaggregate the disease-level unit costs to various health states due to the retrospective nature of the costing study and the difficulty of obtaining cancer-specific transition probabilities for the health states. Further details on the choice of analytic model are presented in Paper III's methodological discussion section.

We simulated a child with cancer (without specifying the diagnosis) receiving services from the pediatric oncology unit compared to a do-nothing scenario. The model depicts a two-year treatment duration (considering an average cancer treatment duration) divided into three eight-months treatment

intervals: months 1–8, months 9–16, and months 17–24. We considered the average treatment duration to be around two years, as acute lymphoblastic leukemia (which can take more than three years of treatment) was the dominant type of cancer at TASH, and we took estimates from other centers with comparable cancer patterns (further included in table 1 of paper III). We used EFS and death as outcome measures, and events were defined as abandonment and recurrence, or death. The eight-month treatment intervals accounted for the time-dependent nature of the health outcomes (survival or death) and minimized the overestimation of cost and health gains (DALYs averted); for example, most childhood cancer treatment abandonment and deaths occur within the first eight months after diagnosis. Abandonment is captured as an event equivalent to death in our model (for reasons explained in the methods section of Paper III). For the do-nothing scenario (no pediatric oncology care), we assumed that all patients would die at the end of six months. We assumed that some patients would seek and use non-oncology health care at various tiers of the health system during the six-month period.

Some children who survived at the end of the two-year treatment (cured children) were assumed to develop late treatment complications. The probabilities for EFS and death for a child receiving pediatric oncology care at TASH were taken from a literature review of similar settings (Table 1).

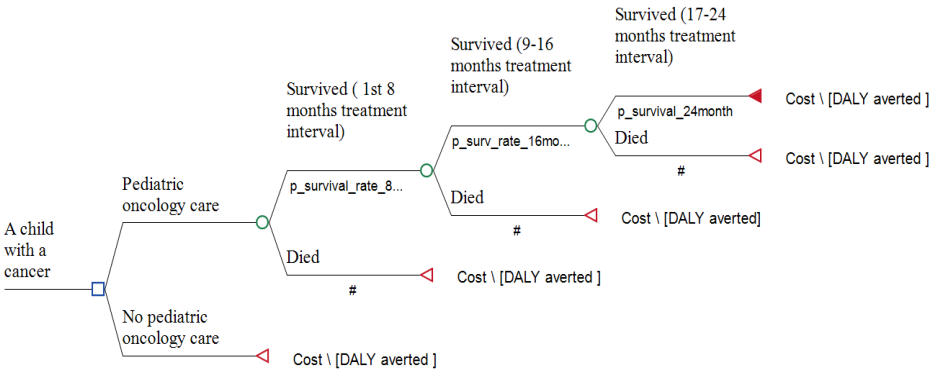

Figure 4. A decision-analytic model structure (decision tree) with an average two-year childhood cancer treatment duration divided into eight-month treatment intervals. The model compares a simulated child with cancer (without a specific diagnosis) who receives services from the pediatric oncology unit to a do-nothing scenario (defined as no pediatric oncology care). The p_survival_rate_8 represent the probability of survival in 1st 8 months of treatment. Similarly, p_survival_rate_16., is the probability of survival in 9-16 months of treatment, and p_survival_rate_8 is the probability of survival 17-24 months of treatment.

During the eight-month treatment intervals, we assumed that the health condition of a surviving child would be improved compared to his/her previous treatment interval due to response to treatment and reduced treatment toxicity, although this will not always hold true. Similarly, for each eight-month treatment interval, a child in the survival arm was assumed to have an overall better health condition (utility) during that treatment period compared to a non-surviving child (in the death arm).

3.4.2. Estimation of cost

The cost estimate of the CEA was taken from Paper II. For each arm of an eight-month treatment interval, we calculated the total OPD cost (by factoring OPD visits per patient and cost per OPD visit) and total IPD cost (by factoring the bed days per patient and cost per bed-day). Next, the OPD and IPD costs were aggregated to compute the total cost for each arm. We assumed the OPD and IPD costs of non-survivors to be 1.5 and 2 times the OPD and IPD costs of surviving patients, respectively, as the child was likely to use more and/or costlier services before the event occurrence (death). These estimates were derived from the overall costing study for pediatric departments in TASH, which considered the cost distribution between regular OPDs and departments related to critical patients and which anticipated differing service utilization patterns between surviving and non-surviving patients. We discounted cost using a discounting rate of 3% (152) for one year, as cost was captured only over a two-year treatment period.

3.4.3. Estimation of health benefits

We used DALYs averted as the effectiveness metric (129) as computed by the following formula:

DALYs = years of life lost (YLL) + years lived with disability (YLD)

For the no pediatric oncology scenario, we estimated the YLD by assuming that patients would survive only six months without treatment (multiplying the disability weight without treatment by the average survival duration) (Table 1), and we computed YLL by taking the difference between the age at death and life expectancy at that specific age. For easier computation of the DALYs averted, we compared both scenarios to a theoretical worst-case situation in which a child dies immediately after cancer diagnosis.

To estimate the DALYs averted, we used combinations of the model variables shown in Table 1of paper III, which were taken from a literature review of comparable settings, as no local data were

available (Table 1 and supplementary material [supplementary text S1, Table S2, and Table S3] in paper III). We conducted a scoping literature review to identify studies documenting the effectiveness of childhood cancer treatment in African LICs. The literature search was done in six electronic databases, including PubMed, Embase, ScienceDirect, Scopus, Web of Science, and African Journals OnLine by combining terminologies covering the spectrum of childhood cancer types, country names (LICs in Africa), and treatment outcomes (survival or mortality). We identified 14 studies fulfilling our criteria and prioritized the evidence based on systematic review or meta-analysis, followed by prospective studies based on cancer registries, multicountry/multicenter studies, and those with large sample sizes, broad cancers coverage, long survival periods, and recently conducted studies. We substantiated the survival-rate findings from the scoping review using experts' judgments and local evidence on treatment abandonment and survival rates drawn from expert opinion (supplementary text S1 in paper III). We set cautious survival rates in our model to avoid biased cost-effectiveness conclusions. The aim was to avoid the bias of overestimating the effectiveness and cost-effectiveness of an intervention to an extent that did not match the level of investment and quality of care in TASH. We assumed the two-year childhood cancer survival rate at TASH to be 25%, with a 95% confidence interval (CI) of 15%–35%, despite commonly reported overall survival rates ranging from 35% to 45% in pediatric oncology centers in LICs in Africa. Further details on the scoping review process, key findings, and transferring approach are provided in the supplementary material of paper III (supplementary text S1, Table S2 and Table S3).

We discounted DALYs averted by 3% as recommended by WHO (152), using a lifetime horizon to bring future benefits to their present value.

3.4.4. Cost-effectiveness analysis

Cost-effectiveness in this generic model was expressed as an ICER and was computed by dividing the incremental costs (ICs) of establishing a specialized oncology unit to the incremental DALYs averted (IE) due to interventions.

$$ICER = IC/IE$$

In our study, an intervention was considered cost-effective if the ICER was less than 50% of the Ethiopian GDP per capita and not cost-effective otherwise (153). We used TreeAge software to build the decision model and run the CEA.

3.4.5. Uncertainty

We did one-way sensitivity analysis and probabilistic sensitivity analysis (Monte Carlo simulations) to assess the impact of uncertainty surrounding the model parameters. We varied cost, EFS, life expectancy gap after treatment, and disability weights and used the 95% confidence interval (CI) reported in the literature review to estimate the effect of the model variables' uncertainty on the estimated result (see Table 1 in Paper III).

3.5. Ethical approval

Childhood cancer treatment abandonment (Paper I)

We obtained ethical approval for the treatment abandonment study (Paper I) from the Regional Committee for Medical and Health Research Ethics (REC Western Norway approval no. 64245), the Ethiopian Public Health Institute Scientific and Ethical Review Office (approval no. EPHI–IRB-268-2020), and the Pediatric and Child Health Department of the Research and Publication Committee of Addis Ababa University Medical Faculty (approval no. DRPC/011/13). Participation in the study was voluntary, and written consent to participate in the study was obtained from all the participants prior to the data collection. The participants were informed that they could withdraw consent at any point without negative consequences. The consent and the data were documented confidentially in a de-identified file. The institutional review boards approval letter and consent form are annexed (annex 2).

Cost and cost-effectiveness of running a pediatric oncology unit (Papers II and III)

We obtained ethical approval for the costing study from the Regional Committee for Medical and Health Research Ethics (REC Western Norway approval no. 64245) together with the approval for Paper I, and we received data use approval from EHIA (አጤመኴ/ሰጉ./999/014) (see annex 2).

4. Results

This section presents the main results of the three studies. Paper I assesses the perceived risk factors and the magnitude of the childhood cancer treatment abandonment rate from the health care providers' perspective. Paper II estimates the aggregated cost of running a pediatric oncology unit as well as the cost per specific childhood cancer at TASH, while Paper III uses the cost findings from Paper II to estimate the cost-effectiveness of operating a pediatric oncology unit at TASH.

4.1. Childhood cancer treatment abandonment (Paper I)

The mean perceived childhood cancer treatment abandonment rate in Ethiopia was 34% (standard error [SE]: 2.5) (Table1). The estimate was the lowest at TASH at 28.3% (SE 3.5%), while at JUH it was 40.7% (SE: 4.4%) and at GUH 40.6% (SE: 3.7%).

Table 1. Perceived estimate of childhood cancer treatment abandonment rate

Pediatric oncology center	Mean	SE	95% CI
Tikur Anbessa Specialized Hospital	28.3%	3.5%	21.2–35.5%
Gondar University Hospital	40.6%	3.7%	33–48%
Jimma University Hospital	40.7%	4.4%	31.4–49.8%
Overall	34.7%	2.5%	29.7–39.7%

Physicians who were asked whether differences existed in the likelihood of treatment abandonment among the various childhood cancers reported that the risk of treatment abandonment was relatively higher for brain tumor and bone sarcoma and lower for Hodgkin's lymphoma and non-Hodgkin's lymphoma (see Fig. 1 in Paper I). In addition to cancer type, the risk of treatment abandonment varied by the phase of cancer treatment. For example, patients with ALL were highly likely to abandon care

in the maintenance phase of the treatment cycle (46%), while children with Wilms tumor (38%) or bone sarcoma (58%) were highly likely to abandon treatment while waiting for surgery or in the postsurgical period (Figure 5).

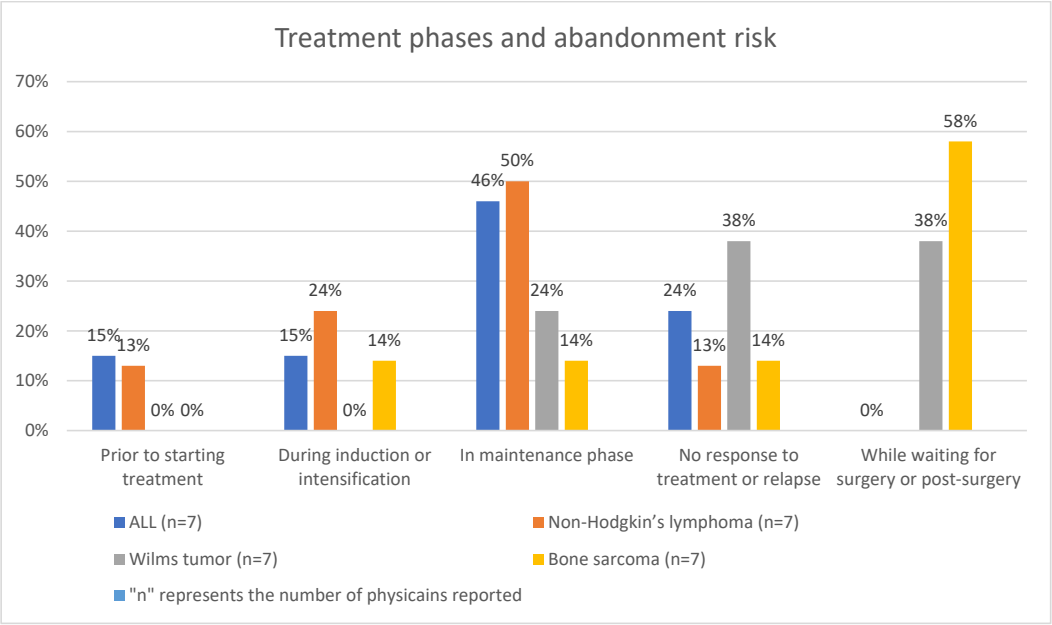

Figure 5. Abandonment risk associated with childhood cancer treatment phases and outcomes

The participants were asked to indicate the level of influence (i.e., the likelihood of leading to abandonment) of certain globally pre-identified risk factors of treatment abandonment at their center (see Table S4 and Supplementary Text S1 in Paper I). The health care providers reported that low economic status, high cost of care (related to diagnostics, chemotherapy, radiotherapy, surgery, supportive care, food, and lodging), a long travel time to the treatment center, belief in the incurability of cancer, and a low level of parental education play major roles in treatment abandonment (Fig. 6). Also found to play an important role in influencing treatment abandonment were undernourishment, the adverse effects and toxicity of treatment, painful diagnostic and therapeutic procedures, insufficient communication by health care professionals, a preference for complementary and alternative medicine, and strongly held faith or religious beliefs.

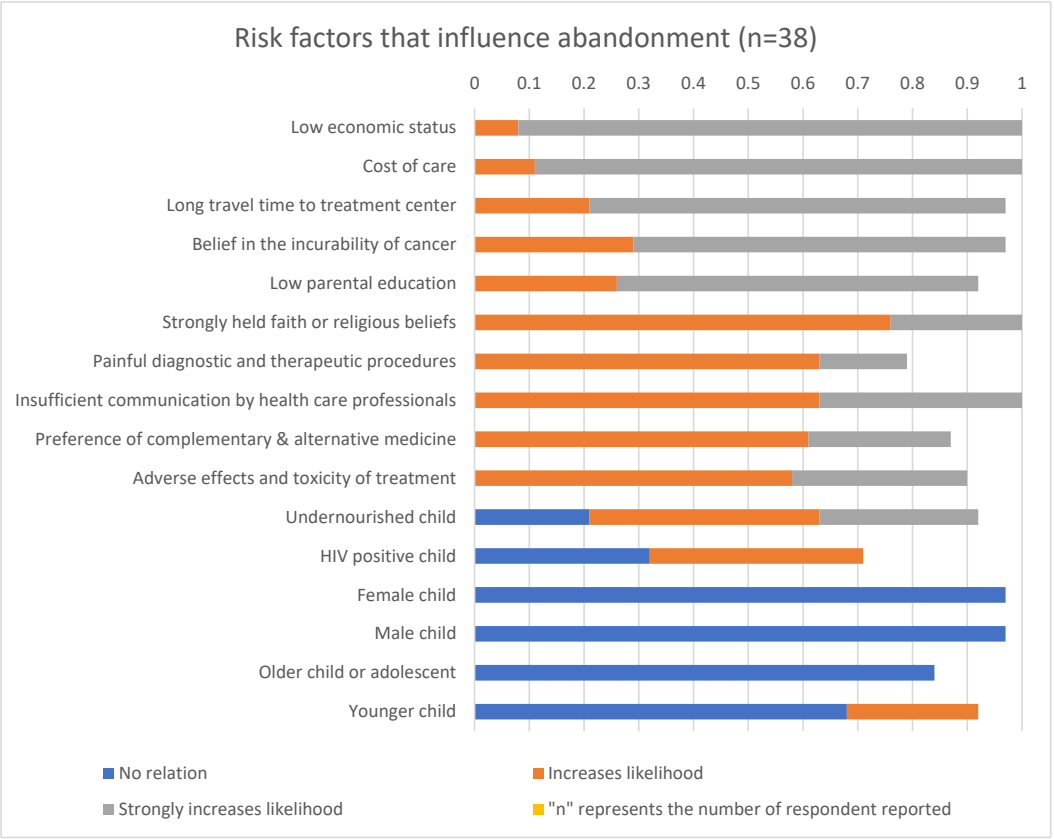

Figure 6. Risk factors associated with treatment abandonment

The efforts of health care providers to counsel guardians who considered discontinuing care were affected by the clinical prognosis of patients. Nearly 86% of the physicians reported that they would accept the decision of guardians to abandon care without making many efforts to convince them to change their mind or connect them to social support if the child had a poor prognosis. By contrast, 100% of the physicians reported they did everything in their power (such as counseling and connecting guardians to social workers and social support) to change the guardians' decision if the child had a good prognosis (see Table S3 in Paper I).

4.2. Cost of running a pediatric oncology unit (Paper II)

The pediatric oncology unit at TASH was staffed by 42 health professionals (corresponding to 32 FTE): three FTE oncologists, 11 FTE postgraduate residents, and 18 FTE nurses. The unit provided service to 1,345 patients and recorded 7,842 OPD visits, 1,302 IPD admissions, and 12,180 bed days in 2019. The annual OPD visits per patient and bed days per patient were 5.8 and 9.1, respectively.

The top seven pediatric cancer types at TASH during the study period were ALL, Wilms' tumor, Hodgkin's lymphoma, rhabdomyosarcoma, retinoblastoma, neuroblastoma, and non-Hodgkin's lymphoma. Further details on the cancers' specific service utilization are presented in Table 1 in Paper II.

The total annual cost of running a pediatric oncology unit at TASH was around USD 776,000 (equivalent to USD 577 per treated child). Thirty-seven percent (USD 289,953) of the total cost was attributable to OPD services and the remaining 63% (USD 486,108) to IPD services. Drugs and supplies (33%) and HR (27%) were the top two drivers of direct cost. In the pediatric oncology unit, the cost per OPD visit, cost per bed day, and cost per episode of hospital admission were USD 37, 40, and 373, respectively (Table 2).

The overall cost of running a pediatric oncology unit per treated child ranged from USD 469 to USD 1,085 in the scenario-based sensitivity analysis (Supplementary Table S2 in Paper II). The upper bound of the cost estimate (USD 1,085) was computed by taking the cost findings from the chart review to account for potential cost underestimation in the top-down costing approach using historical cost data. As a result, the baseline annual total cost estimate for running a pediatric oncology unit increased by 45% (from USD 766,060 to 1,459,325).

At the level of specific childhood cancers (a disease-level cost estimate), the annual cost per patient ranged from USD 322 to USD 1,313, but the estimates for the top six cancer types were in the range of USD 433 to USD 676. Further details on the unit costs for specific cancers are presented in Table 3 in Paper II.

Table 2. Annual cost of treating childhood cancers at TASH, July 2018–July 2019

Pediatric oncology OPD (including radiotherapy) and IPD	Annual total cost, USD (%)	Annual cost/patient (USD)
Personnel	212,367 (27)	157.9
Drugs and supplies	258,391 (33)	192.1
Equipment depreciation	11,649 (2)	8.7
Overhead	121,642 (16)	90.4
Intermediate departments		

Lab	21,112 (3)	15.7
Pathology	14,231 (2)	10.6
Radiology	43,885 (5)	32.6
Triage	5,733 (1)	4.3
Other clinical departments		
Pediatric ER	65,875 (8)	49.0
Pediatric ICU	15,509 (2)	11.5
Pediatric surgery	5,667 (1)	4.2
Total	766,060 (100)	577.0
Distribution by departments		
Department	Cost (%)	Cost per service utilization
Outpatient department (OPD)	289,953 (37)	USD 36.9 per OPD visit
Inpatient department (IPD)	486,108 (63)	USD 39.9 per bed day USD 373.3 per episode of admission

4.3. Cost-effectiveness of running a pediatric oncology unit (Paper III)

The incremental cost and incremental DALY averted per full course of treatment for a child with cancer were USD 875.9 and 2.49 DALY averted, respectively. The ICER of running a pediatric oncology unit at TASH compared to a do-nothing scenario was USD 361 per DALY averted (Table 3), which is below the WTP threshold in Ethiopia (USD 477) in 2019 (defined a 50% of GDP per capita).

Although the uncertainty regarding the individual parameters did not impact the main cost-effectiveness result, uncertainty surrounding the EFS rate, cost per OPD visit, and life expectancy gap had the largest impact on the estimated ICER in the one-way sensitivity analysis (Fig.2 in Paper III). At a WTP threshold of USD 477, running a pediatric oncology unit was cost-effective compared to a no pediatric oncology care scenario in 90% of the Monte Carlo simulations (100,000 simulations)

(Fig. 3 in paper III), which tested the combined impact of the model parameters' uncertainty in changing the cost-effectiveness conclusion.

Table 3. ICER of running a pediatric oncology unit compared to no pediatric oncology care at TASH in 2019

Strategy	Cost (USD)	Incremental cost	Effectiveness (DALYs averted)*	Incremental effectiveness	ICER (USD/DALY averted)	WTP for Ethiopia (2019), USD/DALY averted
No pediatric oncology care	19.07		0.06			477
Pediatric oncology care (unit)	894.95	875.89	2.49	2.43	360.76	
* The DALY averted was computed in comparison to a theoretical worst-case situation in which a child dies immediately after cancer diagnosis.						

5. Discussion

5.1. Discussion of main findings

5.1.1. Childhood cancer treatment abandonment (Paper I)

As expected, the perceived magnitude of childhood cancer treatment abandonment was high in Ethiopia at 34% (SE: 2.5%), and the finding was consistent with reports from similar settings, such as Uganda, Sudan, and Zambia, which range from 32 to 46% (76, 78, 79). The risk of treatment abandonment was perceived to be higher in some cancer types (bone sarcoma and brain tumor) and varied with the phase of treatment. For example, the highest risk for ALL patients was during the "maintenance phase," and in that case the misunderstanding that early-stage improvement indicates a cured child (false sense of security) (154) is probably compounded with the other major influencing risk factors described below. On the other hand, most patients with Wilms tumor and bone sarcoma abandoned treatment while waiting for surgery or after surgery due to the long waiting time for surgery (or radiotherapy), poor coordination and communication between departments (such as the pediatric oncology unit, radiotherapy, and surgical departments), fear of surgical outcomes (e.g., fear of post-surgery functional impairment, such as loss of vision or amputation), and the lack of a defaulter tracing mechanism (78, 155). These variations indicate the need to understanding and address cancer-specific abandonment risk factors in addition to the crosscutting system-level risk factors described below.

Our findings show that the major drivers of treatment abandonment are similar to those found in comparable settings and to the globally recognized risk factors (7, 81, 156-158). The major perceived influencing risk factors in Ethiopia were high cost of care, low economic status, long travel time to treatment centers, long waiting time for diagnosis and treatment, belief in the incurability of cancer, and poor public awareness of childhood cancer. However, the reported level of influence of some risk factors were higher in Ethiopia than is reported in other settings in studies using the same methods (Kenya, Tanzania, Rwanda, Mozambique, Mali, Malawi, South Africa, and Nigeria) (7); specifically, strong religious beliefs and the preference for complementary traditional medicine in Ethiopia were found to play important roles in influencing treatment abandonment. As indicated in the results section, the perceived risk factors of treatment abandonment were many, interrelated, and complex (sometimes even beyond the scope of the health sector) and to some extent context and disease specific. Thus, addressing treatment abandonment obviously demands prioritizing and mitigating the

influencing risk factors that play a major role and developing and implementing short-, medium-, and long-term multipronged mitigation strategies that are highly impactful, affordable, and feasible to implement in the local context. Paper I highlights the key mitigation strategies that could facilitate progress toward the ambitious target set in the NCACCP: reducing treatment abandonment by 60% by 2023 (66). Below, I briefly describe and discuss the three major contributors to treatment abandonment in Ethiopia that Paper I does not cover in detail: delayed diagnosis, poor quality of care, and financial hardship.

Abandonment can generally be understood as a mirror that reflects how a childhood cancer control plan is performing in a given country. A high abandonment rate correlates to multiple malfunctions in the tiers of service delivery, both on the supply side (service provision) and the demand side (community) (30, 41, 156) as elaborated below under three themes: (1) gaps in the lower health system delivery platforms (PHCUs and general hospitals), (2) poor quality of service in specialized oncology units, and (3) low public financing and high financial hardship, which is a crosscutting issue to the entire childhood cancer control program.

Gaps in the lower health system delivery platforms

Previous research reports and the findings of our study clearly show the relationship between delayed diagnosis (hence poor prognosis) and a high risk of treatment abandonment (156). The perception of poor prognosis by both guardians and health workers as well as the high chance of treatment toxicity and adverse events increase the risk of treatment abandonment. Delayed diagnosis could relate to low public awareness, limited access (physical and financial) to health care, poor capacity in the lower health delivery platforms to timely recognize and refer cases to specialty centers, and poor service quality in the pediatric oncology centers (expert capacity and diagnostic facilities). This is a critical problem in Ethiopia given that two-third of patients are diagnosed at the advanced stages (stage three and fours) (38, 39). Therefore, reducing abandonment requires mitigation strategies that go beyond addressing the barriers in the pediatric oncology centers, such as improving early detection and diagnosis by strengthening the lower-level health service delivery platforms. It is important to note that close to 55% of children with cancer in LICs die before diagnosis (30), so improving early detection and diagnosis will bring great benefits beyond reducing abandonment. A sustained, tailored program to promote awareness as well as engagement with the community (such as traditional healers and religious and village leaders) are vital to address poor public awareness and the negative influence of religion and cultural norms, such as a preference for alternative traditional medicine. Introducing of childhood cancer in NCD HEP packages could partly address the poor public awareness in the rural

areas. Integrating childhood cancer into key service contact points and building the capacity of health professionals in PHCUs and general hospitals (through short-term training and the provision of job aids) could improve timely detection. Establishing a referral network between PHCUs and selected satellite sites (general hospitals with relatively well-trained experts) could accelerate referral and hasten diagnosis. In this regard, the recent expansion of satellite sites in 25 hospitals is commendable (159), while the integration of childhood cancer control into PHCUs, including the community interface, needs serious attention (159).

Poor service quality

Poor service quality is among the critical challenges that fuel abandonment in Ethiopia and was reflected in our findings as the unavailability or intermittent availability of diagnostics and treatment (mainly chemotherapy), long waiting times for surgery and radiotherapy, suboptimal human resource capacity, poor pain and toxicity management, poor rapport between the patient/guardian and clinician, environments that were not friendly to kids and guardians, the lack of a defaulter tracing mechanism, and poor coordination and integration among critical departments. Improving the quality of childhood cancer care in Ethiopia demands implementing multiple interventions, such as enhancing investment in the diagnostic and treatment infrastructure, standardizing treatment protocols, providing ongoing training for staff, strengthening multidisciplinary care, ensuring the stable availability of drugs and supplies through a dedicated fund, and incorporating cancer medicines into the national essential medicine list and long-term procurement framework.

Low public financing and high financial hardship

For several reasons, the shortfall in childhood cancer control financing seems to be the most important rate-limiting factor that influences treatment abandonment. First, financing gaps (reported as high cost of care, low economic status, and lack of health insurance) are the most consistently reported major influencing risk factors for treatment abandonment in many countries, including Ethiopia. This becomes even more important when we consider the high absolute poverty burden in Ethiopia (the proportion of households below the national poverty line was 23.5% in 2016) (58). Second, in addition to its direct effect on abandonment, the financing gap is a crosscutting factor that influences early access and quality of care. Utilizing and adhering to care is not sufficient to change the fate of a child with cancer unless that care is of adequate quality. Third, financial hardship disproportionately

affects the worst-off members of society, particularly the poor and people in rural areas (86, 145), which further increases health inequality. This is compounded by limited physical access to specialized childhood cancer treatment centers, as there were only four pediatric oncology centers in Ethiopia, all in big cities (30). From a health perspective, this leads people to avoid, delay (by spending a long time securing money), or abandon care, which contributes to poor prognosis and a low chance of survival (2). From a socioeconomic perspective, it pushes many households into financial and social catastrophe (93), with long-term implications for future wellbeing and economic welfare.

The direct medical cost of care, which is the OOP health payment for diagnosis and treatment (e.g., drugs, supplies, surgery, and radiotherapy), accounts for the largest share of financial hardship. The situation is alarming in Ethiopia, as the share of OOP health payment in cancer financing is around 49% (87); research reports (both published and unpublished) describe a high incidence of catastrophic health expenditure in cancer care ranging from 70–80% (96, 160). In low-income settings, such as Ethiopia, the financial hardship of cancer care is almost universal; even better-off households could be challenged by a self-financed mechanism (OOP health payment), as the treatment is expensive and prolonged (161). Therefore, alleviating financial hardship will benefit all, but especially the worst-off.

In addition to the direct medical cost, direct nonmedical costs (such as food, lodging, and transport) and the loss of earning due to childcare (parental absence from work) contribute significantly to influencing abandonment (7, 156). The impact may be higher in Ethiopia given that childhood cancer services are delivered at few treatment centers, and many patients are forced to travel far from their home to big cities, where the cost of living is high (e.g., food and housing). This creates both financial and social distress due to competing family and social responsibilities. Therefore, tackling the financial hardship of paying for transport, food, and lodging could be as important as eliminating the medical OOP health payment (for diagnosis and treatment) in improving health and economic welfare (83, 84, 162). In our study, more than 97% of health professionals in childhood cancer centers believed that covering the cost of transport, food, and lodging would have a high impact on reducing abandonment (Table 3 in Paper I). Hence, the provision of targeted financial support for the poor, near poor, and people traveling from distant areas should be considered.

The other key element in reducing abandonment and the burden of childhood cancer is improving access to quality treatment centers, which requires additional investment in the quality of existing centers and the addition of new centers aligned to the need. The survival of children with cancer is higher when treatment is delivered in a specialized center—a dedicated unit with a multidisciplinary

team that is equipped with optimal infrastructure and support services that meet the unique needs of children with cancer—rather than through a widely decentralized service delivery approach (2, 30). In addition, the centralized approach is cost-effective compared to a decentralized approach given that specialized pediatric oncology centers are more effective, the incidence of childhood cancer is small, and the cases are widely scattered (2, 30). However, it should be noted that a centralized approach does not necessarily mean a small number of centers; rather, countries should conduct a situation analysis of their existing capacity (HR, infrastructure, finance) and their need for specialized treatment centers and develop a clear road map to progressively scaling up to the needed level (30). In this regard, Ethiopia plans to increase its number of pediatric oncology units from three to eight by 2023 (66). Given the resource constraints, such a plan must be supported by evidence on the cost, cost-effectiveness, and budget impact of running and scaling up pediatric oncology units to encourage the leadership's confidence, trust, and commitment.

5.1.2. Cost and cost-effectiveness of running a pediatric oncology unit (Papers II and III)

Taking USD 477 as a WTP threshold (50% of Ethiopia's 2019 GDP per capita), our CEA indicates that running a pediatric oncology unit (pediatric oncology service delivery platform) could be cost-effective compared to a do-nothing scenario. The ICER of USD 361 per DALY averted was cost-effective in 90% of the Monte Carlo simulations in the probabilistic sensitivity analysis, which accounted for the impact of multiple uncertainties on the estimated ICER value. Furthermore, the ICER was cost-effective in 100% of the simulations at a WTP of USD 600 (the highest estimated ICER in the probabilistic sensitivity analysis), indicating a higher degree of cost-effectiveness certainty if the decision were based on a higher WTP threshold, such as the widely used WTP of 1 × GDP per capita (in the Ethiopia case, USD 954 in 2019).

Childhood cancer treatment was also found to be cost-effective in studies in Tanzania, Uganda, Zimbabwe, Ghana, and Nigeria, although the ICER estimate varied widely, from USD 97 to USD 2,940 per DALY averted. Similarly, the WHO Global Childhood Cancer Initiative and DCP3 indicate that investing in childhood cancer control programs is highly cost-effective, affordable, and feasible in LMIC settings, particularly the treatment of ALL, Hodgkin's lymphoma, Burkitt's lymphoma, retinoblastoma, Wilms tumor, and low-grade glioma (brain tumor) (2, 49). Although our estimate lacked childhood cancer–specific cost-effectiveness estimates, it provides insight on the overall cost-effectiveness of a specialized oncology center, which substantiates the global recommendations in the local context and could enhance confidence and trust in further investment to improve the quality of

existing centers and scaling up of new centers in Ethiopia. In addition, there is a high chance that our overall cost-effectiveness findings at the pediatric oncology unit level are driven by the treatment of ALL, Wilms tumor, Hodgkin's lymphoma, and retinoblastoma given their relatively high prevalence at TASH, their greater chance of survival (compared to other cancers) with modest treatment-center capability (2, 30), and their low cost per treated patient at TASH (USD 433–587 per patient). However, future cancer-specific cost-effectiveness estimates are important to confirm our assumptions and to support the efficient utilization of resources in pediatric oncology units.

In addition to improving value for money, investment in childhood cancer treatment could reduce inequity, as children with cancer face a large lifetime health burden due to the high rate of premature death, which qualifies them for inclusion in the worst-off category. In Ethiopia, addressing equity is one of the major objectives of Health Sector Transformation Plan II (2021–2025), and children are among the priority groups (61). Therefore, prioritizing childhood cancer treatment as a high priority health intervention could be fair, as it is likely highly cost-effective, benefits the worst-off, and provides high FRP, thus accelerating progress toward UHC.

Beyond being cost-effective, running a pediatric oncology unit could also be affordable and feasible. With an annual cost per treated child of USD 577 (which could be as high as USD 1,085 when adjusted for suboptimal care), the budget impact of investing in childhood treatment is likely affordable, as the population in need of care is small (the annual incidence of childhood cancer is around 3,800–6,000) (3, 70) and treatment is provided in selected centers. Of course, the cost of running a pediatric oncology unit and the cost per treated child could increase as more centers, beds, trained staff, advanced diagnostics, and safer treatment become available, but such an investment will provide a higher return on investment, as it will dramatically improve access, quality of services, and the survival rate (163).

Differing contexts and issues related to methodology make it difficult to do a one-to-one unit cost comparison, but the annual cost of treating a child with cancer was lower in our study than the estimates employing relatively comparable costing techniques in similar settings. In 2019, for example, the annual cost of treating a child with Burkitt's lymphoma in Uganda was USD 1,479 (compared to USD 468 in Ethiopia) (164). Similarly, in Rwanda, the annual cost of treating a child with Hodgkin's lymphoma was USD 1,757 (USD 433 in Ethiopia) and that of Wilms tumor was USD 1,345 (USD 459 in Ethiopia) (165). These variations may be explained by differences in quality of care, treatment protocols, service utilization, analytical approaches, and the countries' overall cost-of-care profiles. Generally, the cost of providing health services in Ethiopia is lower than in Rwanda and

Uganda, as the HR salary wage is low and most utilities (such as water and electricity) are subsidized in Ethiopia (166-168) (more details are provided in Paper II). The low unit-cost estimate at TASH may also be explained by economies of scale, as the service utilization statistics (annual OPD visits and bed-days) for the pediatric oncology unit were much higher than in the other pediatric departments at TASH (150).

5.1.3. The findings in a nutshell

Having a national childhood and adolescent cancer control plan is not enough to address the health burden of children with cancer unless it is tied to the national health priority agenda and a real financial commitment. To attain the goals established in Ethiopia's NCACCP (e.g., improving the survival rate of children with cancer to > 40% and reducing abandonment by 60%) (66), childhood cancer control interventions should be prioritized and adequately financed (particularly early detection, effective treatment, and reduced abandonment). The findings of the treatment abandonment study show that there was a policy-level interest in offering pediatric cancer services at an affordable price (as most interventions are planned to be delivered at no cost or at a subsidized cost) (Fig. 4 and Table 3 in Paper I), but most services were not adequately available, because the policy-level interest was not linked to a real financing commitment. This gap was well recognized by health professionals in the treatment centers and increasing government commitment was the most frequent recommendation of the study participants to improve childhood cancer control (see Table 4 in Paper I). The slow progress toward achieving the targets in the NCACCP can be taken as another example of inadequate ownership and commitment. To date, there are five pediatric oncology centers (the plan was to increase the number from three to eight), 10 hemato-oncologists (the plan was to improve from 6 to 30), and no major progress in increasing access to essential medicines (the plan proposed 100% access), in improving public awareness (the plan was to reach 80% of the population), or in building the capacity of the medical workforce in the lower tiers of service delivery (the plan aimed to train 50% of the workforce in PHCUs) (159).

Childhood cancers are not highly prioritized in the recently revised EHSP (8). For example, three of the six high-priority childhood cancers identified in the WHO Global Initiative for Childhood Cancers (Burkitt's lymphoma, retinoblastoma, and Wilms tumor) are classified as low priority, and two (ALL and Hodgkin's lymphoma) are classified as medium priority (8, 49). This discrepancy in priority between the NCACCP and the EHSP could be a major setback in the effort to control childhood cancer, as it will continue to be under the leadership's radar and underfinanced. It could also partly

explain the slow progress in achieving the planned targets of the NCACCP, described above. The findings of this thesis may suggest that childhood cancer care should be given a higher priority.

Beyond including childhood cancer treatment as a high priority intervention in the EHSP and allocating more resources, Ethiopia urgently needs to reform its childhood cancer financing mechanism, shifting from OOP health payments to pooled financing through either general tax revenue, donor funding, or health insurance. Such measures have yielded significant impacts in many countries (30). Studies in Kenya, Rwanda, Nigeria, and China show that households with health insurance have a significantly lower risk of abandonment and higher chance of survival (75, 169-171). In Mexico, the inclusion of childhood cancer in the health insurance package reduced treatment abandonment from 35% to 1% (162). Ethiopia has long experience of exempting payment for high-priority health services, such as TB, HIV, and maternal and child health conditions (100), so including childhood cancer control interventions in the exemption list and allocating additional funds for it could be considered an immediate, realistic solution, which is a shift from the current EHSP decision that aims to finance childhood cancer control through a cost-sharing approach (8).

As described above, targeted financial support for transport, food, and lodging is fundamental to reducing abandonment, improving the overall survival rate, and fairly distributing health gains. Civil society organizations and development assistance could play immediate, important roles in filling this gap, but doing so requires strong government ownership and extensive mobilization efforts. Likewise, making maximum use of the opportunities afforded by the global childhood cancer control solidarity movement could partly close the immediate financial resource gap and, more importantly, build the technical capacity of the health system, which cannot be fully addressed by merely increasing the financing. This requires training the pediatric oncology medical workforce, standardizing treatment protocols, and equipping treatment centers (with drugs, supplies, and medical equipment, including diagnostics). To achieve this, priory should be given to twinning the existing treatment centers with better centers in HICs, and the government should take the lead in mapping and fostering such collaboration. It is also vital to be a pioneer in the global multinational support initiatives to mobilize additional resources. Unfortunately, Ethiopia is not part of the recently launched initiative of WHO and St. Jude Children's Research Hospital that aims to give free childhood cancer medicine (in 2022–2027) to countries participating in the pilot phases (172).

The other untapped potential is improving the efficiency of health spending, which can increase fiscal space to finance health interventions including childhood cancer control. Close to 33% of the health spending in Africa is wasted (86, 173), which can be minimized through better regulation, tackling

operational inefficiencies, and establishing fair, systematic, evidence-informed priority-setting mechanisms (86). Financing childhood cancer control through general tax revenue or donor funding threatens long-term sustainability because of the greatly increasing cost of health care, decreasing donor assistance, and slow economic growth. For several reasons, it is not realistic to base cancer financing solely on general tax revenue in Ethiopia. First, it is hard to generate adequate tax revenue due to the slow formalization of the economy (e.g., close to 33.5% of the GDP is in the informal sector and cannot be taxed) (174), the slow economic growth of individuals and businesses, and poor tax administration and management capacity (e.g., the tax revenue to GDP ratio was around 6% in Ethiopia in 2020) (175). Second, competing high-burden diseases and health conditions could challenge the allocation of adequate resource to childhood cancer control (61). A third, the low government willingness to spend on health. In 2019, for example, health spending's share of total government spending was 8.5% (87), which is below the Abuja Declaration's target of 15% (176), and it has been stagnant for many years. Although the fiscal constraints are undeniable, there is a need to improve the political willingness and commitment to greater health investment to pursue UHC. The health sector must devise an innovative strategy and intensively advocate with political leaders to increase their appetite for investing in health and allocating more resources to health as a share of the annual government budget. It is important to learn from the practical experiences of African countries that have met the Abuja target (such as Rwanda, Tanzania, and South Africa) (176).

While making every effort to increase government health spending, there is a need to establish and strengthen sustainable complementary revenue-generation mechanisms, such as national health insurance. For citizens to have access to quality health service without excessive financial risk, states have the responsibility to establish systems in which the healthy and wealthy members of society subsidize the unhealthy, poor, and those with high health risks (86, 92). Of course, this financing reform is not unique to childhood cancer control but rather an overarching strategy for sustainable health system financing in Ethiopia, as there are similar concerns about sustainably financing other high priority health programs (100). Strengthening the existing CBHI (to have a broader population coverage, a unified pooling arrangement, and strong strategic purchasing mechanisms) and establishing a national social health program could complement efforts to ensure sustainable financing by increasing general tax-based financing and improving efficiency gains.

5.2. Methodological discussion

The methodological strengths and limitations of the research are discussed in detail in each paper. This section briefly describes the overall strengths and limitations of the thesis.

The major strength of this thesis is its use of primary data sources to examine the policy-relevant but under-studied topic of childhood cancer control in Ethiopia. Two of the studies (treatment abandonment and costing) were based on primary data collection, and the third (cost-effectiveness of running a pediatric oncology unit) drew from hybrid data sources (primary costing data combined with secondary effectiveness data). All three papers are the first to address their specific topics in Ethiopia and are well linked to Ethiopia's present five-year NCACCP and to the MOH's need for nationally contextualized evidence.

5.2.1. Treatment abandonment (Paper I)

The abandonment study (Paper I) has additional strengths that increase its internal validity (measuring what it intended to measure and reaching a sensible conclusion about the study population). First, it was based on a validated tool that was previously used in a global abandonment estimation survey. Second, it was a multi-center study in three of Ethiopia's four pediatric oncology centers at the time of the study (currently, there are five centers). Third, all health professionals who had direct experience of children's cancer care for more than one year were included in the study, and the response rate was 100%.

Ideally, the incidence of abandonment and the influencing risk factors should be estimated from a well-established, population-based cancer registry and should adopt a prospective approach. However, Ethiopia has only one cancer registry, located in the Addis Ababa city administration (for city residents only), and it was not well established due to limited staff numbers and a poor IT infrastructure. The registry captures only incidence and does not follow patients to monitor their health outcomes (e.g., overall survival, EFS, death, abandonment, and recurrence). In addition, it does not provide a nationally representative picture, as it embraces only city residents, whose context is quite different from the national characteristic of a predominantly rural population. Similarly, the influencing risk factors would have been better assessed had they been considered from both from the guardians' and the health providers' perspectives, but our study captured only the latter side of the story. We tried to incorporate the guardians' perspective of Addis Ababa city residents using the registry unit as an entry point, but the attempt failed due to the difficulty of contacting guardians as described in detail in Paper I. Thus, the only feasible option was to use the health professional perspective as a proxy measure to estimate the treatment abandonment rate and influencing risk factors.

Because almost all centers and health professionals who directly encountered the guardians of children with cancer were included and because we used a globally validated data collection tool and a

rigorous data control procedure, the internal validity of our findings is probably high, although it lacks comprehensiveness in identifying context-specific (sociocultural) risk factors, as the guardians' perspective was not included. Similarly, there is a strong likelihood of external validity, that is, the generalizability of our finding beyond the population study (in this case, to other LICs), given that we used a standard data collection tool, applied a commonly used perspective (the health care provider perspective), and observed a similar pattern of findings with those in other, relatively similar settings. Therefore, our findings are relevant for informing national childhood cancer control programs and augmenting global knowledge of the incidence and risk factors of childhood cancer treatment abandonment.

5.2.2. Cost and cost-effectiveness of running a pediatric oncology unit (Papers II and III)

Various factors may affect the internal and external validity of costing and CEA, such as the objective of the costing; the perspective adopted; the selected study site and sample size; how resource inputs are identified, measured, and valued; the choice of analytic model and model parameters; the availability of reliable data; and the data quality control procedure. This section describes the methodological concerns of the cost and cost-effectiveness studies and the measures taken to improve their internal validity.

The costing study followed a rigorous process from planning to execution and covered all the hospital departments at TASH (86 departments). The data collection tool was adopted from the JLN (151), which has been used in various countries and had previously been used to cost PHCUs and general and tertiary hospitals in Ethiopia. Senior costing data collectors were recruited who had direct experience of health facility–based costing data collection and who had a good track record of participation in similar costing exercises. We performed thorough quality assurance at every stage of the data collection and analysis. Data clearance and validation took around six months and involved much back-and-forth communication and correcting of errors.

Details on the limitations of the costing and cost-effectiveness studies are included in each paper. This section describes crosscutting methodological limitations that are not well covered in those papers.

5.2.2.1. Choice of perspective

Economic evaluations are based on welfare economics theory, which is concerned with the impact on total societal welfare of any change or decision (177). The cost and cost-effectiveness of health interventions can be narrowly examined, for example, from a health care provider (or health care

payer/purchaser) perspective or can adopt a broader perspective (described as societal) (178). The provider or payer perspective captures costs that fall on the provider or purchaser, such as direct medical costs (diagnosis and treatment). The societal perspective accounts for all relevant costs regardless of who pays them, and this includes additional cost inputs, such as direct nonmedical costs (e.g., transport, food, and lodging) and nonmedical costs related to loss of productivity (178). The decision on which costs and effects to include is mainly determined by the choice of perspective, which consequently affects the estimation of cost and cost-effectiveness, resource-allocation decisions, and societal welfare. Welfare economists argue that determinations of cost and cost-effectiveness should adopt the societal perspective, as cost-effectiveness decisions based on the narrow perspective (provider) may maximize health but not necessarily maximize social welfare (177, 178). Similarly, the goal of the health system is to improve societal health and welfare, so examining the cost and cost-effectiveness of health interventions from a societal perspective contributes to establishing mechanisms of priority-setting and resource allocation that align with the broader goals of the health system. However, the use of the societal perspective is constrained by the high cost of obtaining data, by methodological complexity (especially in identifying, measuring, and valuing nonmedical costs), and by limited data availability. Kimet al. conducted an extensive review of the literature and of national guidelines (for 1974–2018) and found that about 74% of costing and CEA adopted the provider perspective and that the trend of taking a provider perspective was increasing (178). Around 67% of national guidelines (e.g., those of England and Scotland) recommend adopting the provider perspective, 27% take a societal perspective (e.g., Germany, Finland, Sweden, and the Netherlands), and the remainder take a combined approach (e.g., Norway, Ireland, and Italy) (178). The choice of perspective is also determined by the research question, the objective of the costing and cost-effectiveness, and countries' or organizations' specific guidelines. Ethiopia has no specific guideline or recommendation on costing and cost-effectiveness studies, but almost all the cost-effectiveness evidence in the recently revised Ethiopia EHSP was from the provider perspective. Therefore, we adopted the provider perspective to align with the EHSP, as our aim was to estimate the cost and cost-effectiveness of running a pediatric oncology unit to close the evidence gap related to childhood cancer treatment in the EHSP prioritization process.

5.2.2.2. Costing approach

Measuring the use of relevant cost inputs can be done with (1) a macro-costing approach (*top-down costing* or *average costing*), (2) a micro-costing approach (also described as *activity-based costing* or

the *bottom-up* approach), or (3) a mixed-methods approach (151, 177). The top-down costing approach disaggregates the total cost of services at the organizational or department level to each service and/or patient on the basis of their service utilization or patient load as an allocation base. That is, this approach assumes that each service (such as an OPD visit or bed-day) or patient consumes an equal amount of resources; it assumes that a single OPD visit of a child with Wilms tumor will consume an equal amount of resources as an OPD visit of a child with ALL. In other words, it treats children with cancer as homogenous cases. Micro-costing takes a representative sample of services and/or patients and measures the use of inputs at the service and/or patient level; this is a preferred approach for nonhomogeneous services or patients, such as childhood cancer patients. In general, most childhood cancers are heterogenous and differ in their disease nature, cost inputs, use of services (e.g., some use bone marrow aspiration, while others use biopsy, imaging, or clinical diagnosis), and treatment (e.g., some use chemotherapy and others a combination of chemotherapy with surgery and/or radiotherapy). Furthermore, the choice of chemotherapy differs among the cancers. From a technical point of view, micro-costing is obviously the better approach for childhood cancer services, but it is costly, involves a long time for data collection, and requires a great amount of data and robust health information systems.

The need for detailed cost information must be balanced against the cost of data collection and analysis, the feasibility and time required of getting the data, and the expected impact of the additional detailed data on the conclusion. Our study used a mixed costing approach in which the pediatric oncology unit–level cost estimate was dominantly informed by the top-down costing approach and the cancer-specific cost estimates were strongly complemented by a patient chart review (micro-costing) to map the heterogenous consumption pattern among childhood cancers and account for the under-provision of services. We chose the mixed approach (rather than full-blown micro-costing) due to resource constraints, the poor health information system at TASH, and challenges related to time and feasibility (as the costing was done for the entire hospital); the heterogeneity concerns were partly addressed by the chart review, and the mixed approach can provide an estimate fairly close to that of the micro-costing approach at less cost, much more quickly, and with less complexity.

Our study was based on the documented historical spending of TASH but did not account for the quality of service provided. We know how much TASH spent during the study period, but we do not know the service quality resulting from that spending. We tried to account for this through the chart review and by estimating the cost of care on the basis of clinicians' prescription frequency as a proxy measure for estimating the consumption of services (including medicine, supplies, laboratory, pathology, imaging, and blood), but these steps may not have completely mitigated the risk of

underestimating the cost of care, as clinicians' prescriptions could also be affected by the unavailability of care. For example, they might not order an important intervention for a patient if they knew that it was not available in the hospital or believed that the patient could not afford to buy it in the private market. It is important to note, however, that, even if the historically based costing affected our cost estimate, it is unlikely to change the cost-effectiveness conclusion, as the costing approach is augmented by patients' chart review (clinician prescription) that accounted for under provision of services and as the uncertainty was already factored into the probabilistic sensitivity analysis, in which running a pediatric oncology unit was cost-effective in 90% of the Monte Carlo simulations. Furthermore, the increment in cost of care using a normative costing approach could lead to marked improvement in the survival rate and high value for money. However, normative costing, which assumes an ideal service as per national standards and guidelines, can give better cost estimates to address additional policy questions (not addressed in this thesis): What will be the cost of delivering quality pediatric oncology services (as defined by the national standard)? What will be the budget impact of improving the quality of the existing pediatric oncology centers and establishing new centers?

5.2.2.3. Choice of analytical model (Paper III)

Our model is generic and offers only a broad insight on the cost-effectiveness of running a pediatric oncology service without showing which cancers contribute to the aggregated result. It also does not account for the heterogeneity among patients with respect to prognosis or the various clinical scenarios among childhood cancers.

Due to large gaps in the availability of input data, we failed in our efforts to build a Markov-based or individual-level micro-simulation analytic model that accounted for the various clinical scenarios of childhood cancers (such as remission, disease progression, recurrence, and death), the transitions between health states, and the heterogeneity of childhood cancers. It was difficult to obtain cancer-specific evidence on treatment effectiveness, health status–specific utility data, and data on the probability of transitions between health states. It was also not possible to further disaggregate the disease-level unit costs to various health states due to the retrospective nature of the costing study. Due to these limitations and to facilitate a national-level policy dialogue, we decided to limit the scope of the study, using a decision-analytic tree to provide only a broad overview of the cost-effectiveness of running a pediatric oncology unit (at a service-delivery platform level) compared to a no-pediatric oncology care scenario. Therefore, to ensure precise estimation and prioritization among childhood cancers, it is crucial in the future to conduct further cancer-specific CEAs (at least for the common

types) with state-transition models (cohort- or individual-level microsimulations) but this require establishing a robust survival registry.

5.2.2.4. Data quality

Health facility costing exercises strongly rely on quality data, which presented a significant obstacle in the resource-poor setting of TASH due to its poor IT infrastructure (most department-level recording and reporting were paper based), poor culture of data utilization and evidence-informed decision-making, suboptimal data quality improvement and assurance, inadequate staff numbers, and lack of accountability. The challenges included the incomplete recording of provided services in the departmental registry (such as OPD visit, date of admission, date of discharge, and number of procedures and lab services provided), inconsistency between the hospital-level report and the department-specific registries, lack of disaggregation by cancer types, data errors on the prices of drugs and medical equipment, lack of price sources for some donated medical items, and mismatches between department-level direct HR inventories and the hospital-level aggregated data from the finance, payroll, and HR departments. Despite multiple rounds of rigorous data validation and the resulting corrections, there are undeniable data-quality issues in the hospital records generally, and it is nearly certain that we did not correct all these data errors; this may have introduced bias in the form of both overestimation and underestimation of costs, but underestimation is much more likely. The other limitation was obtaining local survival-rate data for childhood cancers for the cost-effectiveness study (Paper III). We used survival estimates from similar settings using a scoping review, but there may still be bias, as the quality of service could be different. We sought to minimize the bias on the effect estimate by taking cautious values that aligned with the low service quality in Ethiopia and by taking a range of values in the uncertainty analysis. Papers II and III further discuss the limitations of the costing and cost-effectiveness studies.

5.2.2.5 Internal and external validity of the costing and cost-effectiveness studies

We believe that the internal validity of the costing study is probably high due to the comprehensiveness of our study, which covered the entire hospital and all cost inputs; the use of a mixed costing approach (micro- and macro-costing approach) to account for heterogeneity and for underestimation of costing due to under provision of services; the rigorous data collection and data quality assurance process; and the similarity in the major cost drivers among the various public pediatric oncology units (such as salary, benefits for staff, and prices for medicines, supplies, medical equipment, and utilities). However, the external validity (generalizability to other LICs) is limited due

to differences among countries in disease patterns, service quality, treatment protocols, general cost profiles (such as drug and supply prices, staff salaries and benefits, and utility costs).

For Paper III, which draws on the costing data from Paper II, we obtained effectiveness estimates (mainly survival data) from relatively similar settings with accredited cancer registries (such as Rwanda) and took modest values that can match with the poor quality of service in TASH. We also conducted one-way and probabilistic sensitivity analysis to check the robustness of our model by testing the impact of uncertainty in the model parameter values on the cost-effectiveness conclusion. Our cost-effectiveness finding was cost-effective in 90% of the Monte Carlo simulations (100,000 simulations), suggesting a high probability of internal validity. However, the external validity of Paper III is limited for the reasons mentioned above.

6. Conclusions

The perceived treatment abandonment rate of childhood cancer in Ethiopia is high, and the risk of treatment abandonment varies by type of cancer and phase of cancer treatment. The major influencing risk factors for treatment abandonment in Ethiopia are the high cost of care, low economic status of households, long travel times to treatment centers, long waiting times, belief in the incurability of cancer, and poor public awareness of childhood cancer. Although our findings on influencing risk factors greatly resemble those of other study reports in similar settings, the reported levels of influence for some risk factors in Ethiopia differ from those in other studies. We find the provision of pediatric cancer services using a specialized oncology unit is most likely cost-effective and affordable in Ethiopia.

7. Recommendations and future perspectives

7.1. Recommendations

Reducing childhood cancer treatment abandonment requires developing and implementing multipronged short-, medium-, and long-term mitigation strategies that address supply and demand side barriers. The influencing risk factors for childhood cancers are many and reflect shortcomings in various aspects of the childhood cancer control program that will require time, resource investments, close coordination and alignment to fix. Thus, it is necessary to promote the alignment and commitment of various stakeholders within and outside the health sector and to prioritize the major influencing risk factors as well as high-impact, cost-effective, affordable, and feasible mitigation strategies, with special emphasis on early detection and diagnosis, quality improvement in the pediatric oncology units, and the alleviation of economic barriers. Paper I provides further details on the specific measures that should be taken in Ethiopia to address the major supply- and demand-side barriers to reducing treatment abandonment.

The findings of the childhood cancer abandonment study indicate the need for serious action on the financing mechanism of childhood cancer and the urgency of switching from OOP health payments to progressive prepayment-based pooled financing. However, this will take time in Ethiopia, and bold decisions must be made to finance the program from existing public financing (government) and/or pooled donor health funding (such as the SDGs pool fund). Therefore, we recommend revising the cost-sharing financing mechanism for childhood cancer in the EHSP. The financing should go beyond covering the cost of direct medical management (such as diagnosis and treatment) to consider covering the cost of transport, food, and lodging—at least for those in great need—to ensure the fair utilization of health care and the fair distribution of health gains in childhood cancer control. The financing mechanism should aim to improve access to and the quality of childhood cancer centers in addition to reducing financial hardship.

The findings of the studies on the cost and cost-effectiveness of running a pediatric oncology unit support Ethiopia's NCACCP strategy of expanding childhood oncology units in the country, as running a pediatric oncology unit is high likely cost-effective and affordable. Therefore, we recommend reassessing the priority level of childhood cancer treatment in the current EHSP. Strong leadership, ownership, and resource commitment (at both the national and subnational levels) are paramount to overcoming the obstacles to childhood cancer control. The local and international

childhood cancer community should engage in advocacy that explicitly demonstrates the burden and the great future potential to onboard political leaders and make childhood cancer one of their priority agenda. Ethiopia should make maximum use of a currently growing global opportunity—the solidarity movement to support LMICs in controlling childhood cancer and NCDs—to strengthen its health system.

7.2. Future perspectives

The epidemiology of childhood cancer in Ethiopia is not well known due to the limited availability of data. A strong childhood cancer control program requires robust, quality data on incidence, prevalence, distribution (age, sex, cancer types, geography), and survival outcomes (EFS, mortality, abandonment, recurrence), but such data does not exist in Ethiopia. Presently, Ethiopia has only one cancer incidence registry (for Addis Ababa residents), which is far short of the actual need, so establishing a national cancer registry will be critical. Similarly, economic evaluations are an integral part of a systematic priority-setting mechanism, which strongly relies on quality data from the routine health information system and cancer registry. Digitizing and improving the quality of routine health information is also crucial to obtaining quality evidence.

In the future, similar work on treatment abandonment using a robust registry and taking the guardians' perspective could provide a better understanding of the magnitude of the problem and the influencing risk factors, especially in terms of identifying context-specific, demand-side risk factors. Additional studies that provide childhood cancer–specific cost-effectiveness estimates (including comparing treatment protocols) and that offer equity impact analysis, budget impact analysis, and estimations of financial hardship could further substantiate the argument for giving higher priority to childhood cancer control and would enable comprehensive comparisons across the childhood cancers and the package of interventions.

8. References

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9. Appendix

Appendix 1. Papers I-III

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BMC Health Services Research

RESEARCH Open Access

The magnitude and perceived reasons for childhood cancer treatment abandonment in Ethiopia: from health care providers' perspective

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Abstract

Background: Treatment abandonment is one of major reasons for childhood cancer treatment failure and low survival rate in low- and middle-income countries. Ethiopia plans to reduce abandonment rate by 60% (2019–2023), but baseline data and information about the contextual risk factors that influence treatment abandonment are scarce.

Methods: This cross-sectional study was conducted from September 5 to 22, 2021, on the three major pediatric oncology centers in Ethiopia. Data on the incidence and reasons for treatment abandonment were obtained from healthcare professionals. We were unable to obtain data about the patients' or guardians' perspective because the information available in the cancer registry was incomplete to contact adequate number of respondents. We used a validated, semi-structured questionnaire developed by the International Society of Pediatric Oncology Abandonment Technical Working Group. We included all ($N = 38$) health care professionals (physicians, nurses, and social workers) working at these centers who had more than one year of experience in childhood cancer service provision (a universal sampling and 100% response rate).

Results: The perceived mean abandonment rate in Ethiopia is 34% (SE 2.5%). The risk of treatment abandonment is dependent on the type of cancer (high for bone sarcoma and brain tumor), the phase of treatment and treatment outcome. The highest risk is during maintenance and treatment failure or relapse for acute lymphoblastic leukemia, and during pre- or post-surgical phase for Wilms tumor and bone sarcoma. The major influencing risk factors in Ethiopia includes high cost of care, low economic status, long travel time to treatment centers, long waiting time, belief in the incurability of cancer and poor public awareness about childhood cancer.

Conclusions: The perceived abandonment rate in Ethiopia is high, and the risk of abandonment varies according to the type of cancer, phase of treatment or treatment outcome. Therefore, mitigation strategies to reduce the abandonment rate should include identifying specific risk factors and prioritizing strategies based on their level of influence, effectiveness, feasibility, and affordability.

Keywords: Childhood cancer, Treatment abandonment, Low-income countries, Sub-Saharan Africa, Ethiopia

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Background

Globally, close to 400,000 new cases of childhood (age range, 0–19 years) cancer are reported annually [1], and low- and middle-income countries (LMICs) account for

a large proportion (90%) of these cases [2–4]. The prognosis of childhood cancer varies from complete cure to near-certain death, depending on which part of the world the child is born in. The 5-year survival rate in high-income countries (HICs) is more than 80% [5–9], while it is 20% to 30% in LMICs [4, 10, 11] and can be as low as 10% in some East African Countries [12]. This drastic difference in survival can be explained by poor availability of and access to specialized pediatric oncology treatment centers and supportive care, diagnostic centers, drugs and other treatment supplies, trained human resources, social support, late presentation, and high treatment abandonment rate in LMICs [10, 13].

Treatment abandonment is one of the major factors for treatment failure and low survival rate in LMICs [14–20]. The International Society of Pediatric Oncology defines treatment abandonment as failure to start (refusal) or continue treatment for four or more consecutive weeks [16]. This does not include those with medical contraindications for the treatment or those who are transferred to other centers or lost to follow up after completion of treatment. A systematic literature review conducted in 2007 included nearly 50 studies conducted between 1992 and 2006 that examined the incidence of abandonment of childhood cancer treatment in LMICs [15]. The study showed abandonment of treatment was associated with all the major childhood cancer types and was found to be an issue across the LMICs. There was a high degree of variation in the incidence rate of abandonment reported by the reviewed studies: it fell within the 10%–25% range in most studies, but some studies reported as high as 50%–60% [15].

There have also been studies targeting health professionals as the source of understanding magnitude and reasons for abandonment. For example, a global study conducted in 2012 utilized online surveys to interview 602 health professionals from 101 countries distributed across all income categories, including 10 low-income countries (LICs) and 26 LMICs [14]. The study found large disparities in the magnitude of abandonment between HICs and LMICs: 91% of HICs reported a median abandonment rate of less than 5%, while only 37% of LMICs did so. This study included eight Sub-Saharan African LICs and LMICs, among which three reported a median abandonment rate of 6%–15%; two reported a median abandonment rate of 26%–50%; and three reported a median abandonment rate of > 50% [14]. Importantly, Ethiopia was one of the three countries that reported a median abandonment rate of more than 50% [14]. Further, studies conducted in Kenya found that 50%–54% of children diagnosed with malignant cancers abandoned treatment [21–24], and the corresponding abandonment rate was 45% in Zambia [25], 42% in Ghana [26], 35% in Sudan [27], 33% in Uganda [28], and 19% in Malawi [29].

A systematic review and metanalysis (published in 2017) conducted in Sub-Saharan Africa [30], as well as other country-specific studies, have found that the common reasons for treatment abandonment are supply-side barriers such as high cost of care (associated with therapy, diagnostics, food, and lodging), lack of insurance, long travel time, long waiting time, and lack of social support, and demand-side barriers such as low income, cost of transport, poor public awareness, and fear [14, 21, 23, 24, 31, 32]. Abandonment of treatment is observed as a major problem even in settings where treatment is provided for free. For example, in Zambia, where free healthcare is provided, data for the period 2008–2010 indicated a high treatment abandonment rate, 45% [25]. A study conducted in a Malawi hospital that also provides free treatment explored the common reasons for abandonment, apart from treatment fee [33]. The study found that even though the patients' families did not have to pay for treatment, they were deterred by other costs related to the treatment of their child, such as the cost of transport to and from the facility (which is a direct cost), as well as indirect costs such as the opportunity cost of labor income lost while being away from home. Another study on malignancies in patients below 16 years conducted between 2001 and 2003 in El Salvador found that low income and large household size were predictors of treatment abandonment [34], even when the cost of treatment was taken care of by relevant organizations. In addition to these factors, in Sub-Saharan African countries, preference for complementary and alternative medicine, strong faith and religious beliefs, competing priorities, and the notion that childhood cancer is an incurable illness highly influence abandonment [14].

According to the 2019–2023 Federal Ministry of Health of Ethiopia (FMoH)'s National Childhood and Adolescent Cancer Control Plan (NCACCP), addressing abandonment is one of the priority strategic objectives for improving the survival rate of children and adolescents with cancer [35]. The FMoH's plan is to reduce abandonment by 60% over the 5-year period of 2019 to 2023 [35], but there is a lack of baseline data. In addition, the intervention areas to be prioritized and addressed have not been clearly identified in the NCACCP because there is not enough contextualized evidence. Therefore, the rationale behind our research is to generate contextualized data on the magnitude of and reasons for abandonment of childhood cancer treatment in Ethiopia. We believe that our study will serve as a baseline to monitor progress over time and will shed light on the major contextual risk factors associated with treatment abandonment. Thus, our research could augment policy

making and the implementation of mitigation strategies to improve abandonment in Ethiopia and other closer settings.

Methods

Study setting

This study was conducted in Ethiopia—a country with a population of more than 100 million [36]. Ethiopia has a three-tier health delivery system that is composed of close to 300 public hospitals (including general and tertiary hospitals), 21,000 primary care public facilities (including health posts, health centers, and primary hospitals), 40,000 community health extension workers, 7,000 private clinics, and 70 private hospitals [37]. Ethiopia has made remarkable progress in the provision of primary health care, but access to specialty care, including pediatric oncology services, is poor. For example, there is a very limited number of pediatric oncology treatment and diagnostic centers, pediatric hematologist-oncologists (only seven as of 2021), oncology nurses, and pathologists [35]. The first pediatric oncology unit, located in Tikur Anbessa Specialized Hospital (TASH), was established in 2013, and recently, three additional centers, namely, Jimma University Hospital (JUH), Mekelle University Hospital (MUH), and Gondar University Hospital (GUH) have been added [35].

Study design and sampling

We used a cross-sectional study design and sampled three out of the four pediatric oncology centers (TASH, JUH, and GUH) in the country. The original design considered all four centers, but the pediatric oncology center in MUH was excluded at a later stage for security reasons. We interviewed all health care professionals (physicians, nurses, and social workers) working at these centers who had more than one year of experience in childhood cancer care service provision. The inclusion criteria were physicians, nurses, and social workers that have direct engagement on the management of a child with cancer. The exclusion criteria was less than one year of experience in childhood cancer care.

We had originally planned to include the perspectives of both the patients' caretakers (guardians) and healthcare providers. We had planned to use data from the Addis Ababa City Cancer Registry Unit (AACCRU), the only cancer registry in the country [38], for obtaining information from the patients' caretakers (guardians). Our strategy was to identify patients who had abandoned their treatment by telephonic screening and then conduct follow-up home visit interviews. Accordingly, the AACCRU tried to contact all the patients diagnosed with childhood cancer and registered (between 1 July 2019 and 30 June 2021) to understand their treatment status and ask them if they were willing to participate in the study. However, 70 out of the 186 eligible patients' caretakers (37.6%) were not accessible through the phone for various reasons: non-working lines, wrong numbers, or change in phone numbers. Among those who were accessible through calls, 58 stated that their child was currently receiving treatment, 47 reported that their child had died while on treatment, 2 reported completion of treatment (with the child having survived), and 9 stated that the patient had abandoned care. Seven out of the nine agreed to participate in the study. However, the number of inaccessible guardians was too high to obtain representative data. As a result, we decided to conduct the study by using the healthcare providers' perspective only.

Data collection and analysis

We used a validated, semi-structured questionnaire developed by the International Society of Pediatric Oncology Abandonment Technical Working Group, and previously used in a global abandonment estimate survey [14]. The questionnaire mainly covered incidence of childhood cancer treatment abandonment; influencing risk factors; availability of essential childhood cancer control interventions and strategies to reduce childhood cancer abandonment (Table S1). We administered the questionnaire in English, by using tablets and a central server. The field supervisors and the principal investigator had real-time access to de-identified data and provided feedback to data collectors whenever they identified gaps. Trained data collectors conducted in-depth face-to-face interviews from September 5 to 22, 2021. We conducted descriptive analysis using Stata/SE 17.0 version.

Results

Background characteristics of the study participants

Table 1 presents the background characteristics of the respondents. Thirty-eight healthcare providers from three out of four pediatric oncology centers in the country participated in our study. From the three pediatric oncology centers, all physicians ($n=7$) and social workers ($n=8$), and 23 out of 42 nurses were eligible for the study, and all of them agreed to participate (response rate, 100%). Most respondents (44%) were from TASH pediatric oncology center, and nurses comprised the highest proportion of participants (60%). Five out of the seven pediatric hematologist-oncologists in the country participated in the study. Further, 66% of the respondents were male. The average overall work experience in childhood cancer-related services was 3.2 years: TASH had the highest average work experience (4 years), and it was followed by JUH (3.2 years) and GUH (2.5 years). At an

Table 1 General background characteristics of the respondents

Variables		Name of the hospital			
		Tikur Anbessa Specialized Hospital, N (%)	Gondar University Hospital, N (%)	Jimma University Hospital, N (%)	Total, N (%)
Total healthcare professionals	Physician	3 (42.8)	3 (42.8)	1 (14.6)	7 (100.0)
	Nurse	23 (54.7)	10 (23.8)	9 (21.4)	42 (100.0)
	Social worker	3 (37.5)	3 (37.5)	2 (25.0)	8 (100.0)
	Total	29 (50.8)	16 (28.1)	12 (21)	57 (100.0)
Eligible participants	Physician	3 (42.8)	3 (42.8)	1 (14.6)	7 (100.0)
	Nurse	11 (47.8)	6 (26.1)	6 (26.1)	23 (100.0)
	Social worker	3 (37.5)	3 (37.5)	2 (25.0)	8 (100.0)
	Total number of participants	17 (44.7)	12 (31.58)	9 (23.7)	38 (100.0)
Physician	Pediatric hematologist-oncologist	3	1	1	5
	Pediatrician	0	1	0	1
	Resident	0	1	0	1
Sex: n (%) females, n (%) males		7 (41), 59 (10)	2 (17), 10 (83)	4 (44), 5 (56)	13 (34), 25 (66)
Work experience in childhood cancer care in years (mean, 95% confidence interval [CI])		4[2.4–5.6]	2.5[2.1–2.9]	3.2[2.1–4.3]	3.2[2.6–4.0]
Average annual number of cases (mean, 95% CI)		754[642–867]	119[104–134]	122[106–139]	426[294–559]

Table 2 Perceived estimate of abandonment

Pediatric oncology center	Mean	Standard error (S.E)	95% CI
Tikur Anbessa Specialized Hospital	28.3%	3.5%	21.2–35.5%
Gondar University Hospital	40.6%	3.7%	33–48%
Jimma University Hospital	40.7%	4.4%	31.4–49.8%
Overall	34.7%	2.5%	29.7–39.7%

individual level of observation, work experience ranged from 2 to 13 years. The average number of new cases per year, as estimated by the respondents since there were no robust cancer registries, was the highest in TASH (754 patients), and JUH and GUH had an estimated 119–122 new cases per year. Government financing is the major funding source at all centers, and this is followed by out-of-pocket payment by guardians. In addition, there are a few implementing partners and civil society organizations that provide social support for people in need. These organizations work closely with TASH and, to some extent, with JUH.

Incidence of treatment abandonment and associated risk factors

The mean perceived abandonment rate was 34% (standard error (S.E) 2.5) (Table 2). The estimate was the lowest for TASH 28.3% (S.E 3.5%), while it was 40.7% (S.E 4.4%) for JUH and 40.6% (S.E 3.7%) for GUH. On an individual level, 57% of the respondents perceived the abandonment rate to be higher than 35% (Table S2).

We asked physicians to report the risk of abandonment related to the commonly reported childhood cancers in Ethiopia by using the following categories: never, rarely, sometimes, often, always, don't know. The "don't know" responses were not included in the analysis, and the "often" and "always" responses were aggregated to indicate a high risk of abandonment. The perceived risk of abandonment was relatively higher for brain tumor and bone sarcoma (the most frequent response was "often"), and lower for non-Hodgkin's lymphoma and Hodgkin's lymphoma (Fig. 1).

We asked physicians to indicate the treatment phase or outcome (pre-treatment, induction/intensification, maintenance, no response to treatment/relapse, other) that carried the highest risk of abandonment for selected common childhood cancers (representing leukemia, lymphoma and solid tumor) in Ethiopia and allowed them to choose more than one option, if needed (Fig. 2). According to the physicians, patients with acute lymphoblastic leukemia (ALL) are highly likely to abandon care in the maintenance phase of the treatment cycle (46%). Children with Wilms tumor (38%) or bone sarcoma (58%) are highly likely to abandon treatment while waiting for surgery or in the post-surgery period. Additionally, failure to respond to treatment or relapse was estimated as a high-risk factor for treatment abandonment in cases of Wilms tumor and ALL. Further, close to 15% of ALL and non-Hodgkin's lymphoma patients abandoned care

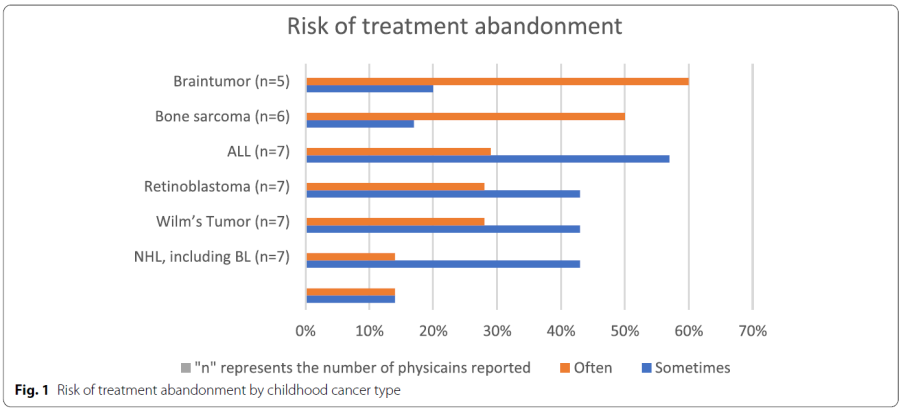

Fig. 1 Risk of treatment abandonment by childhood cancer type

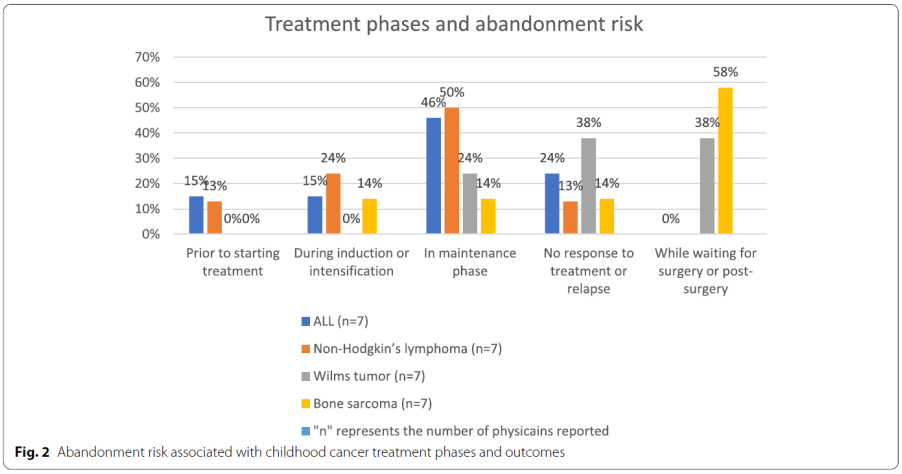

Fig. 2 Abandonment risk associated with childhood cancer treatment phases and outcomes

before the start of treatment (Fig. 2). Finally, 72% of the respondents reported that there is no routine practice for tracing defaulters as there is no contact tracing mechanism (Table S3).

We asked participants to indicate the level of influence of certain pre-identified risk factors on treatment abandonment at their center (Table S4). These risk factors were previously identified by the International Society of Pediatric Oncology Abandonment Technical Working Group [14]. We asked them to grade the factors based on their likelihood of leading to abandonment as follows: strongly decrease likelihood, decrease likelihood, no relation, increase likelihood, strongly increase likelihood. At the analysis stage, we developed five categories (major role, important role, moderate role, minor role, and no relation) based on a combination of reported responses on the likelihood of abandonment (Supplementary text S 1 summarizes how each category was constructed). The healthcare providers reported that low economic status, high cost of care

(related to diagnostics, chemotherapy, radiotherapy, surgery, supportive care, food, and lodging), long travel time to the treatment center, belief in the incurability of cancer, and low level of parental education played a major role in treatment abandonment (Fig. 3). Undernourishment, adverse effects and toxicity of treatment, painful diagnostic and therapeutic procedures, insufficient communication by healthcare professionals, preference for complementary and alternative medicine, and strongly held faith or religious beliefs were found to play an important role in influencing treatment abandonment, while HIV diagnosis and younger age of the child played a moderate and minor role, respectively. The sex of the child and older age of the child or adolescence were perceived as having no relationship with abandonment.

The likelihood of healthcare providers accepting a guardian's decision to abandon care was affected by the clinical prognosis of patients (see Table S3). Two out of seven (29%) physicians reported they would accept the decision of guardians to abandon care without further discussion, if the guardian of a child with a bad prognosis refused to start treatment. Four out of seven physicians (57%) reported that they would accept the decision under these circumstances if the guardian refused to continue treatment. On the other hand, in the case of children who had a good prognosis, all seven physicians reported they would either counsel guardians to convince them (to start or continue treatment) or connect them with social workers who could assist them (see Table S3).

Availability of essential interventions for the treatment of childhood cancer

We asked the physicians and nurses to evaluate the availability of essential childhood cancer treatment-related interventions at their centers (Table S5). The perceived availability of social support, free/subsidized food and blood product scored greater than 95% while availability of effective procedural sedation and analgesia, free or subsidized chemotherapy and surgery scored 75–80%; free/subsidized lodging 67%, and financial support for travel and availability of locally adopted treatment protocol 53%. Lodging and financial support for travel were not available at GUH. It is important to note that these perceived availability estimates only indicate the system-level willingness to address the barriers of childhood cancer treatment. However, it does not reflect the actual uninterrupted availability of these interventions. For example, frequent stockout of chemotherapy supplies was mentioned as one of the contributing factors for treatment abandonment in the open-ended questions, even though the system-level availability of subsidized chemotherapy was perceived as being high (77%).

Strategies to reduce the abandonment of childhood cancer treatment

We asked the healthcare providers to what extent the availability of globally recommended essential pediatric oncology treatment-related interventions might reduce abandonment in their setting, and we also asked an open-ended question so that they could suggest additional strategies or interventions to reduce abandonment.

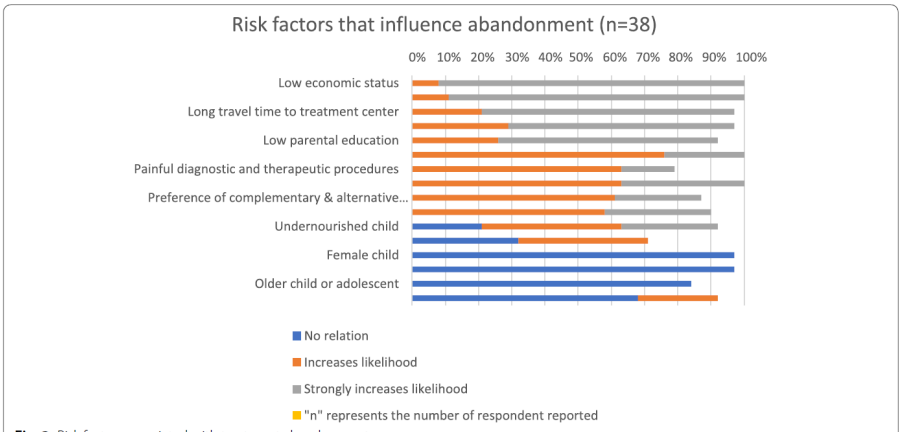

Fig. 3 Risk factors associated with treatment abandonment

According to their responses, the provision of free/subsidized surgery, blood products, chemotherapy and other supportive drugs and supplies, lodging, food, social support, financial support for travel, establishing satellite centers, and detailed and repeated counseling had a high likelihood of reducing the treatment abandonment rate. Additionally, effective procedural sedation and analgesia and locally adopted treatment protocols were moderately likely to reduce abandonment (Table 3).

Our of the 38 participants, 30 responded to the open-ended questions and reported that the following interventions would play an important role in reducing treatment abandonment: increasing government focus on the program, building human resource capacity (in terms of number of personnel and skill diversification such as hematologist-oncologists, oncology nurses, pharmacists, pathologists, and nutritionists) through short-term and long-term training, improving public awareness, improving diagnostic capacity and stockout of chemotherapy supplies, establishing a child-friendly environment (with engaging activities and motivation mechanisms), providing special foods to help children go through therapy, increasing senior physicians' (pediatric hematologist-oncologist) engagement with patients (most children were treated and followed up by a pediatric resident who has lesser training than the senior physician); providing health insurance coverage, establishing a multidisciplinary team, and establishing a contact tracing mechanism (Table 4).

Discussion

The estimated childhood cancer treatment abandonment rate in Ethiopia is 34% (S.E 2.5%). The estimate is lower for TASH (28.3%, S.E 3.5%) than for JUH (40.7%, S.E 4.4%) and GUH (40.6%, S.E 3.7%). This difference might be related to the relatively better availability of drugs, diagnostic services, beds, and trained personnel at TASH, as well as the social support (food and lodging, transport, and investigation and drug expenses) provided by civil society organizations. Although our estimate is based on health care providers' opinions and is not an actual estimate from the registry, our finding is similar to previous registry-based estimates reported for Uganda (32%), Sudan (35%), Ghana (42%) and Zambia (45.7%) [20, 22, 25–28]. However, it is higher than the estimate in Malawi (19%) [29] and lower than the estimate in Kenya (50%–54%) [21, 23].

The highest risk for treatment abandonment varies by type of cancer (high for bone sarcoma and brain tumor) and the phase and outcome of treatment. In the case of ALL, the highest risk is in the maintenance phase, or if the patient didn't respond to treatment or relapse. The high-risk time for Wilms tumor and bone sarcoma is while waiting for surgery or post-surgery. Similar findings have been reported in the global abandonment survey using healthcare providers' perspective [14] and a study in Sudan showed that close to 35% patients with Wilms tumor abandoned treatment prior to surgery [27]. The high risk of abandonment in the maintenance phase could be mainly related to misunderstanding of the early-stage improvement as a cured child (false sense of security) but also be related to prolonged treatment, computing household priorities, cost of care and financial hardship. The high risk of abandonment when there was no response to treatment or during relapse could be explained by loss of hope due to the poor prognosis communication, and associated preference to complementary and alternative medicines. It can also be related to cross cutting challenge like cost of care and financial hardship, computing social priorities. The high risk of

Table 3 Interventions to reduce the incidence of treatment abandonment

Interventions	High likelihood, n (%)	Moderate likelihood, n (%)	Minimal likelihood, n (%)	Total, N (%)
Free/subsidized surgery	38 (100)			38 (100)
Free/subsidized blood products	38 (100)			38 (100)
Free/subsidized chemotherapy	38 (100)			38 (100)
Free/subsidized lodging	38 (100)			38 (100)
Social support	37 (97)	1 (3)		38 (100)
Financial support for travel	37 (97)	1 (3)		38 (100)
Free/subsidized food	36 (94)	1 (3)	1 (3)	38 (100)
Free/subsidized supportive care drugs, e.g., antibiotics	36 (94)	2 (6)		38 (100)
Development of a satellite center	35 (92)	3 (8)		38 (100)
Detailed and repeated counseling	32 (84)	6 (16)		38 (100)
Effective procedural sedation and analgesia	25 (66)	9 (23)	1 (3)	38 (100)
Locally adopted treatment protocols	15 (39)	12 (32)	5 (13)	38 (100)

Table 4 Interventions proposed to decrease treatment abandonment (findings from the qualitative question)

Additional factors that could improve treatment abandonment	Frequency of reporting, n (%)
Improving government focus on the program[a]	13 (43%)
Short-term training and orientation for health professionals working at different levels, and increasing the number of pediatric hematologist-oncologists, oncology nurses, pharmacists, phycologists, pathologists, and nutritionists	13 (43%)
Creating public awareness about the curability of cancer and its early signs	11 (37%)
Improving diagnostic capacity to avoid delays in diagnosis, misdiagnosis, and mistreatment	9 (30%)
Providing special foods (that are different from that given to other patients) that could help patients go through therapy better	8 (27%)
Establishing a child-friendly environment	7 (23%)
Reducing stockout of chemotherapy supplies	6 (20%)
Improving senior physicians' (pediatric hematologist-oncologist) follow up and contact time with patients (most children are followed by a resident or pediatrician)	6 (20%)
Improving the linkage of childhood cancer services with health insurance	4 (13%)
Establishing a multidisciplinary team to improve service quality[b]	3 (10%)
Establishing a contact tracing mechanism	3 (10%)

[a] Allocating adequate budget, human resource training, establishing diagnostic centers, improving the availability of drugs and supplies, providing equipment such chemotherapy machines, and periodic monitoring

[b] Multidisciplinary team: includes (but is not limited to) pediatric oncologists, nurses, pharmacists, pathologists, surgeons, radiologists, respiratory therapists, anesthesiologists, social workers, and data clerks

abandonment while waiting for surgery or in the post-surgery period could be related to a long waiting time for surgery or radiotherapy, poor communication between departments, fear of the surgical outcome (e.g., fear of post-surgery functional impairment such as loss of vision and amputation) [29], and lack of a patient tracing mechanism. Overall, our findings indicate the need to understand and address cancer-specific abandonment-related factors, apart from general system-level risk factors indicated below.

The healthcare providers in the present study reported that the following health system (supply side) and community (demand side) barriers influence abandonment. The perceived supply-side barriers were as follows: high cost of care; limited physical and effective access to pediatric oncology services (reflected in long travel time, long waiting time for surgery and radiotherapy, interrupted supply of chemotherapy, and poor availability of diagnostic services); suboptimal human resource capacity, and suboptimal care by existing hematologist-oncologists; poor pain and toxicity management; poor prognosis at the time of diagnosis or treatment; poor rapport between the patient/guardian and clinician; lack of food that is tailored to the needs of children on cancer therapy, and lack of food and lodging support for guardians; lack of a child-friendly environment; low insurance coverage; and lack of contact tracing mechanisms. In particular, prediction of poor prognosis at the time of diagnosis or during treatment seems to highly influence the efforts of physicians in terms of providing counseling, convincing patients and their guardians, or connecting them to social workers for support. Such effort on the part of physicians might influence guardians to change their mind and continue with treatment, and this could have high impact in Ethiopia, given that most patients are diagnosed at a very late stage [27, 39]. The lack of contact tracing mechanisms is another key factor fueling treatment abandonment, as there is no way to counsel and return patients to care once they abandon care. The findings show there is a policy level attention and enabling situation to avail pediatric cancer services at affordable price (as most interventions are planned to be delivered as either free or subsidized cost) (Fig. 4 and Table 3) but the challenge is the low effective access related to suboptimal resource allocation that doesn't match the needs. The perceived demand-side barriers were as follows: low economic status, poor public awareness (about the curability of childhood cancer and its early signs), low level of parental education, preference for complementary and alternative medicine, and strong faith or religious beliefs.

The findings of this study are similar to reported risk factors influencing abandonment in other LMICs [14, 15, 21, 23–25, 30, 40], but the degree of influence differs. That is, even though our findings are consistent with the global survey findings for sub-Saharan Africa (which includes Ethiopia, Kenya, Tanzania, Rwanda, Mozambique, Mali, Malawi, South Africa, and Nigeria, for example) that were obtained using similar methods, the perceived risk of low economic status, cost of care, long travel time to treatment centers, belief in the incurability of cancer, and low level of parental education contributing to abandonment in Ethiopia is much higher according

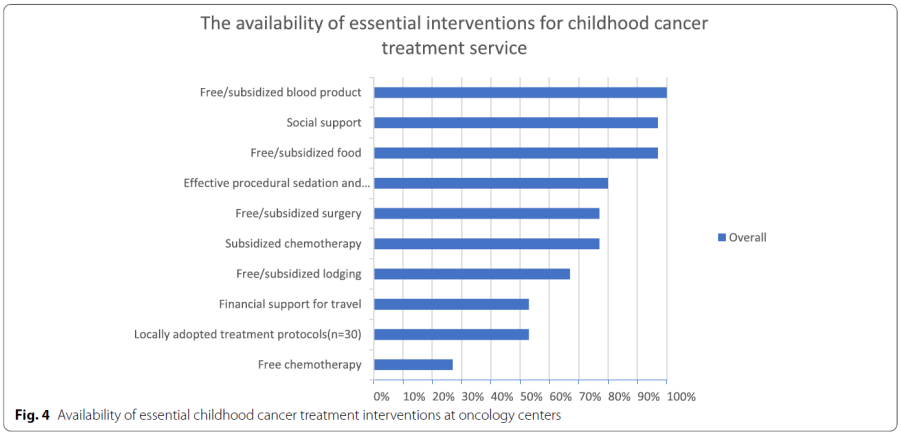

Fig. 4 Availability of essential childhood cancer treatment interventions at oncology centers

to our estimate. This could reflect the context-specific nature of the influencing risk factors and the need for context-specific prioritization of mitigation strategies.

Prioritizing the most influential risk factors is key, given that there are too many risk factors that are complex and require time to address. Importantly, mitigating some of these risk factors might even be beyond the scope of the health sector. Therefore, more emphasis should be placed on risk factors that play a major role, and mitigation strategies that are high-impact, affordable, and feasible for implementation should be prioritized. It is important to have a system in place that can progressively but substantially reduce the treatment abandonment rate. Thus, the development of high-impact, affordable, and feasible strategies to reduce the effect of the major risk factors (that is, low economic status and poor public awareness in terms of demand-side barriers, and high cost of care, long travel time, long waiting time, and interrupted availability of services in terms of supply-side barriers) is critical to achieving the ambitious goal set in the NCACCP (to reduce the rate of abandonment by 60% by 2023) [35]. To achieve this conducting a comprehensive situation analysis and system readiness assessment; identifying high impact and affordable interventions and developing short, medium, and long-term strategies to mitigate abandonment is critical.

There is growing evidence that public financing of childhood cancer control programs is cost effective, affordable, feasible, and sustainable [13], and the recently launched WHO Global Initiative for Childhood Cancer advises countries to prioritize these programs in their national health policies. Apart from the affordability, effectiveness, and feasibility of childhood cancer control programs, they are important from the viewpoint of equity, human rights, and social justice [13]. In the Ethiopian context, various options can be explored to address the major influential risk factors. Ethiopia has a long standing experience in exempting payment for high-priority health services [41]. Accordingly, the inclusion of childhood cancer control interventions in the exemption list and the allocation of additional funds towards it can be considered. This could have a strong impact on resolving the economic barriers that lead to abandonment such as high cost of care, low-income status, and limited access to care. Addressing the cost related barrier will be important since it is the highly reported influencing risk factor, and reducing cost of care (as an exemption or subsidy) is the most recommended strategy—by the health professionals in our study, to improve abandonment. In the long run, the health service exemption needs to be supplemented with sustainable forms of alternative financing, such as the Community-Based Health Insurance (CBHI) program. To achieve this, the population coverage of the CBHI program (which currently covers 56% of the population) needs to be expanded [42], and more importantly, a mechanism needs to be devised to cover the cost of care at pediatric oncology treatment centers for those who are already enrolled. Currently, even though tertiary-level care, including oncology treatment, is covered by the CBHI benefit package, in reality, CBHI is highly restricted to district-level primary healthcare services. That is, it does not cover tertiary care,

which requires patients to travel outside of their district or regions, as is true for almost all cases of children with cancer. Most CBHI schemes have contracts with health facilities in their district only, and there is no robust system, that allows the coverage of services are not available in the patients' district or regions [43] since there is no higher level fund pooling arrangement or alternative temporary mechanism to ensure continuity of service for CBHI beneficiaries. Mobilization of additional resources through development assistance (for example, advocacy for global partners to support childhood cancer control programs), twinning of local oncology centers with international centers (for drug and supply support, long- and short-term training of human resources, and standardization of care), and encouraging international and local civil society organizations to provide additional social support (such as support for food, lodging, and transport) are also important measures to tackle the issue of treatment abandonment. Given the promising high survival rate (> 80% in HICs) of childhood cancer to timely and quality therapy [13, 44] and the time-sensitive nature of treatment (better survival rate in the early cancer stage) [13], a potentially beneficial strategy might be to prioritize childhood cancer in diagnostic, radiotherapy, and surgical schedules, in contrast to the first-come-first-serve approach that is currently being practiced. To realize this, there is a need to develop clinical care prioritization guidelines through a participatory and transparent process. Such a measure could reduce the long waiting time to diagnosis and treatment and abandonment rate and, thereby, improve the survival rate of childhood cancer patients. To address the frequent stockout of drugs and supplies, childhood cancer drugs and supplies can be included in the national essential drug lists and follow-up lists of key procurement performance indicators; additionally, the long-term procurement framework and the financing source and mechanism need to be clarified. Another strategy is networking between pediatric oncology centers and other hospitals (based on geographical distribution) that can function as satellite sites, as this could address the barrier of limited physical access to treatment services.

Demand-side barriers, such as poor public awareness, preference for complementary and alternative medicine, and strong faith or religious beliefs, can be addressed through continuous awareness creation and the engagement and empowerment of community and other stakeholders. With regard to the perceived preference for complementary and alternative medicine and incurability of childhood cancer, some beneficial strategies are preparing a tool for community conversation, building the capacity of community health workers (health extension workers in the case of Ethiopia), and mapping and targeting key community influencers associated with abandonment (such as traditional healers, religious leaders, and village or clan leaders). In addition, continuous awareness creation using mass media, providing financial support for travel, and other community-driven social support initiatives could help reduce the treatment abandonment rate. These measures could be feasible and affordable given Ethiopia's extensive experience in health promotion and disease prevention at the primary healthcare level and the longstanding community structure and networking in place (for example, the Health Extension Program) [45]. Further, the growing access to media, such as radio, TV, mobile phone, and social media, in Ethiopia can facilitate the reachability of awareness creation activities [46, 47]. While placing emphasis on the highly influential risk factors, it is also important to work on improving the rapport between clinicians and patients/parents, pain management, human resource capacity (short- and long-term training), and senior physician engagement, creation of a child-friendly environment and adopting localized treatment protocols. Standardized treatment protocol can reduce treatment abandonment through minimizing the back-and-forth treatment trials and having a treatment aligned with available clinical supportive care (that can reduce associated treatment toxicity and toxicity related complications including death, cost, duration of treatment); improving patient trust and improving treatment outcome.

The key to successful implementation of the aforementioned interventions is improving government ownership (within and outside the health sector) of childhood cancer control programs; in addition, strategically planned and sustained advocacy work needs to be conducted at various levels of the government administration. This could help to translate the existing policy level attention for childhood cancer into a real commitment. Importantly, policy makers need to maximize the potential benefits of the new global movement for the support of childhood cancer control programs across the LMICs [13].

Our study has several limitations, but the major shortcoming is that we only captured the healthcare providers' side of the story, as our efforts to include patients' and guardians' perspectives failed. As a result, we may have missed some key influencing factors on demand-side barriers. A mixed-methods design that includes quantitative and qualitative study about the guardian's perspective (instead of a structured quantitative study only) would have been robust in terms of identifying risk factors, especially local context-specific risk factors. Another limitation is that the estimated abandonment rate is the perceived abandonment rate and not the actual estimate determined from the registry data; therefore, the

reported abandonment rate could be an over- or underestimation of the actual rate. Further, despite the use of a validated questionnaire and rigorous quality control of the data, there is a possibility of inter-respondent variation in understanding the questionnaire. However, our findings are still relevant in terms of informing national childhood cancer control programs and augmenting global knowledge about the incidence and risk factors of abandonment of childhood cancer treatment, given that the findings are consistent with those of other studies conducted in a similar setting.

Conclusions and recommendations

The present findings indicate that the perceived abandonment rate of childhood cancer treatment in Ethiopia is high, and is closely linked with the cancer type and phase of treatment or treatment outcome. Despite the similarity in the risk factors reported here and other studies, the level of influence varies across settings and context-specific prioritization is important.

Based on our results, we recommend that national childhood cancer programs prioritize and address the following supply- and demand-side barriers to improve the survival rate of children with cancer [1]. The proposed measures for addressing supply-side barriers are as follows: freeing/heavily subsidizing the high cost of care; ensuring uninterrupted availability of services; prioritizing children with cancer for shared hospital services (such as diagnostics, surgery, and radiotherapy) to decrease waiting time; and exploring options for establishing satellite sites. Along with addressing the high-priority risk factors, there is a need to improve the rapport between clinicians and patients/guardians and pain and toxicity management, as well as to provide special foods that can help patients tolerate the treatment process better and a child-friendly environment [2]. The following measures are proposed for addressing demand-side barriers: social support to guardians with low economic status and improving public awareness about childhood cancer. Identifying the type of cancer and treatment center-specific risk factors for abandonment, and developing specific mitigation plans are important. Establishing a contact tracing mechanism could help to identify defaulters on time and convince them to resume treatment. Increasing government and other stakeholders' focus on and engagement with childhood cancer care is also critical to addressing the identified risk factors and in translating the existing policy level priority attention into tangible actions. Further, strengthening the cancer registry in TASH and scaling it to the other centers could be instrumental for periodically monitoring treatment outcomes, including abandonment, and facilitating timely decision making. Future similar work using a robust registry and a prospective, mixed-methods design (qualitative and quantitative study) that includes guardians' perspective could provide a better understanding of the magnitude of the problem and the factors associated with it, especially in terms of identifying context-specific demand-side risk factors.

Supplementary information

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Additional file 1.

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Authors' contributions
MK led the entire study from planning to manuscript write up. OFN,MT,and SM provided supervisory support, reviewed study proposal, data collection tools, and analyzed results. DH and KA provided critical inputs in result interpretation and enriching of the manuscript. MP and ED contributed to study tool adaptation, data analysis, and results interpretation. All co-authors reviewed and endorsed the final manuscript. The author(s) read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
We obtained ethical approval for the study from the Regional Committee for Medical and Health Research Ethics (REC Western Norway, approval no. 64245), the Ethiopian Public Health Institute Scientific and Ethical Review Office (approval no. EPHI–IRB–268–2020), and the Pediatric and Child Health Department of the Research and Publication Committee of Addis Ababa University Medical Faculty (approval no. DRPC/011/13). The study was conducted in-line with guidelines in the Declaration of Helsinki [48]. Participation on the study was voluntary and written consent to participate in the study was obtained from all participants prior to the data collection using preapproved script by the IRB bodies stated above, and participants were informed that they could withdraw the consent at any point without any negative consequences. The consent and the data were documented confidentially in a de-identified file.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Supplementary Material

Table S1: Data collection tool for the study of childhood cancer treatment abandonment in Ethiopia

SECTION I: INTRODUCTION & CONSENT (IC)			
NO.	**QUESTION**	**RESPONSE**	**SKIP**
Facility name:			
SC1	ARE YOU A CLINICIAN, NURSE, SOCIAL WORKER INVOLVED IN THE CARE OF CHILDREN WITH CANCER?	Yes……1 No…….2	1 → SC2 2 → END
SC2	HOW LONG HAVE YOU BEEN CARING FOR CHILDREN WITH CANCER IN A PROFESSIONAL CAPACITY?	Less than 1 year……1 1–2 years…….....2 2–5 years…….....3 More than 5 years (est): [ ] years……..4	1 → END 2 → CONS 3 → CONS 4 → CONS
CONSENT FORM (CONS)			
You are invited to take part in a research study on abandonment of treatment in children with cancer. Abandonment of treatment is considered a major cause of treatment failure in children with cancer in Ethiopia, but the scientific evidence for it is limited. We (Addis Center for Ethics and Priority Setting) are, therefore, conducting this survey to study the extent of abandonment in Ethiopia, and to identify the related factors and mitigation strategies. You are invited to join this study if you are a **doctor**, **nurse**, or **social worker** involved in the care of children with cancer. The survey will take 30 minutes to complete and will ask questions about the setting in which you work, how abandonment may affect patients, the risk factors, and strategies that may be used in your facility. This survey is completely voluntary. Your work or relationship with any of the study's team members will not be affected by your participation in this study. We will also respect your privacy: the data collected is confidential, and your answers will not be linked to any details that could identify you in the final study report. By completing this survey, you consent to take part in this research study. We know of no harm that taking part in this study could cause you. You will not benefit directly from taking part in this study.			

Statement of Consent I have read the description of the research or have had it translated into a language I understand. I understand that my participation is voluntary. I know enough about the purpose, methods, risks, and benefits of the research study to judge that I want to take part in it. I understand that I may freely stop being part of this study at any time and I can ask to erase shared information. I understand that shared information will be stored in the University of Bergen server, Norway, for analysis. I have received a copy of this consent form to keep for myself.	
Date	*Signature of Participant*
Investigator's statement I, the undersigned, have explained to the volunteer in a language he/she understands the procedures to be followed in the study and the risks and benefits involved, and I have given a copy of the consent form to the participant.	
Address of chief investigator	*Email:* *Phone number:*
Date	*Signature of Participant*

SECTION II: INTERVIEW (IN)			
NO.	**QUESTION**	**RESPONSE**	**SKIP**
IN1	WHAT IS YOUR OCCUPATION?	Physician..……..……..…1 Nurse/nurse practitioner..…..…..….2 Social worker……3 Other: ……...4	
IN2	IF YOU ARE A PHYSICIAN, HOW WOULD YOU BEST DESCRIBE YOURSELF?	Pediatric hematologist and/or oncologist……1 Adult hematologist and/or oncologist……2 General pediatrician……..3 General physician…….4 Other: 5	
IN3	WHAT IS YOUR SEX?	Male……..1 Female……..2	
IN4	APPROXIMATELY HOW MANY CHILDREN NEWLY DIAGNOSED WITH CANCER (INCLUDING CHILDREN WITH LEUKEMIAS, LYMPHOMAS, SOLID TUMOURS AND BRAIN TUMOURS) ARE THERE IN YOUR CENTER OVER ONE YEAR?	[ ] patients per year Collect data from the register or ask their opinion if register is not available	
IN5	AT YOUR CENTER, APPROXIMATELY WHAT PROPORTION OF CHILDREN DIAGNOSED WITH CANCER DIE WITHIN THE FIRST YEAR OF DIAGNOSIS	20% or less……1 21% to 30%.....2 31% to 40%.....3 41% to 50%.....4 51% to 65%.....5 66% to 80%.....6 More than 81%.....7 Don't know……..……..9	
IN6	AT YOUR CENTER, APPROXIMATELY WHAT PROPORTION OF CHILDREN DIAGNOSED WITH CANCER DIE WITHIN THE FIRST TWO YEARS OF DIAGNOSIS	25% or less……1 26% to 40%.....2 41% to 50%.....3 51% to 60%.....4 61% to 70%.....5 71% to 80%.....6 More than 81%.....7 Don't know……..……..9	

IN7	AT YOUR CENTER, APPROXIMATELY WHAT PROPORTION OF CHILDREN DIAGNOSED WITH CANCER DIE WITHIN THE FIRST FIVE YEARS OF DIAGNOSIS	30% or less……1 31% to 45%.....2 46% to 55%.....3 56% to 65%.....4 66% to 75%.....5 76% to 85%.....6 More than 86%.....7 Don't know……..……..9	
IN8	WHAT ARE THE SOURCES OF FUNDING FOR THE CARE OF CHILDHOOD CANCER PATIENTS IN YOUR SETTING? [1] = Major source [2] = Minor source ***Circle all that apply***	Government (tax or insurance)……..[1]…[2] Private insurance……..[1]…[2] Out-of-pocket payment by patient/family……[1]…[2] National non-profit organization……..[1]…[2] International non-profit organization……..[1]…[2] Do not know……9	
IN9a	AT YOUR CENTER, APPROXIMATELY WHAT PROPORTION OF CHILDREN NEWLY DIAGNOSED WITH CANCER ABANDON TREATMENT (INCLUDING THOSE WHO ABANDON CARE EVEN BEFORE TREATMENT IS STARTED)?	15% or less……1 16% to 25%.....2 26% to 35%.....3 36% to 45%.....4 46% to 55%.....5 56% to 65%.....6 66% to 75%.....7 More than 75%.....8 Don't know……..9	
IN9b	From the categories you selected in IN9a, what is your average estimate for abandonment	_____ %	
IN10	WHERE DOES THIS ESTIMATE COME FROM? WE VALUE ALL RESPONSES EQUALLY, WHETHER THEY COME FROM A DATABASE OR FROM YOUR PERSONAL EXPERIENCE.	Personal opinion, I feel confident….1 Personal opinion, but not confident…2 Estimate comes from a database…….3	

IN11 — FOR EACH OF THE FOLLOWING CHILDHOOD CANCERS, HOW LIKELY IS TREATMENT ABANDONMENT IN YOUR FACILITY? (for physicians only)

Type of cancer	Never/Almost Never	Rarely	Some-times	Often	Always/ Almost always	Don't know
Acute lymphoblastic leukemia (ALL)						
Acute myeloid leukemia						
Hodgkin's lymphoma						
Non-Hodgkin's lymphoma (including Burkitt's lymphoma)						
Brain tumors						
Wilms Tumor						
Retinoblastoma						
Soft tissue sarcoma						
Bone sarcoma						

	HOW LIKELY IS CHILDHOOD CANCER TREATMENT	Never/Almost Never	Rarely	Some-times	Often	Always/ Almost always	Don't know

IN12	ABANDONMENT IN YOUR FACILITY? (Non-Physicians)						
IN13	IN YOUR CENTER, AT WHAT STAGE OF TREATMENT ARE CHILDREN WITH **ACUTE LYMPHOBLASTIC LEUKEMIA** HIGHLY LIKELY TO ABANDON TREATMENT? ***(SELECT UP TO 3 OPTIONS)***	Prior to starting treatment……..…1 During induction or intensification..2 In maintenance……...…3 If not responding to treatment or relapsing after treatment…….……..4 Other: _____ 5 Don't know….……..9					
IN14	IN YOUR CENTER, AT WHAT STAGE OF TREATMENT ARE CHILDREN WITH **NON-HODGKIN'S LYMPHOMA** HIGHLY LIKELY TO ABANDON TREATMENT? ***(SELECT UP TO 3 OPTIONS)***	Prior to starting treatment……..…1 During induction or intensification..2 In maintenance……...…3 If not responding to treatment or relapsing after treatment…….……..4 Other: _____ 5 Don't know….……..9					
IN15	IN YOUR CENTER, AT WHAT STAGE OF TREATMENT ARE CHILDREN WITH **WILMS TUMOR** HIGHLY LIKELY TO ABANDON TREATMENT? ***(SELECT UP TO 3 OPTIONS)***	Prior to starting treatment……..…1 During induction or intensification..2 In maintenance……...…3 If not responding to treatment or relapsing after treatment…….……..4 Other: _____ 5 Don't know….……..9					
IN16	IN YOUR CENTER, AT WHAT STAGE OF TREATMENT ARE CHILDREN WITH **BONE SARCOMAS** HIGHLY LIKELY TO ABANDON TREATMENT? ***(SELECT UP TO 3 OPTIONS)***	Prior to starting treatment……..…1 During induction or intensification..2 In maintenance……...…3 If not responding to treatment or relapsing after treatment…….……..4 Other: _____ 5 Don't know….……..9					

IN17 — HOW ARE THE FOLLOWING FACTORS RELATED TO THE LIKELIHOOD OF ABANDONMENT IN YOUR FACILTY ?

Factor	Strongly decreased likelihood	Decreased likelihood	No relation	Increased likelihood	Strongly increased likelihood	Don't know
Younger age of the child						
Older age of the child or adolescence						
Female sex						
Male sex						
Undernourishment						
HIV diagnosis of the child						
Low level of parental education						
Low socioeconomic status						
Long travel time to center						
Adverse effects and toxicity of treatment						
Painful diagnostic and therapeutic procedures						
Insufficient communication by healthcare professionals						
Preference for complementary and alternative medicine						

	Strong faith or religious beliefs						
	Belief in the "incurability" of cancer						

IN18	ARE THERE ANY OTHER FACTORS RELATED TO ABANDONMENT IN YOUR SETTING?	
	Factor 1:	
	Factor 2:	
	Factor 3:	

IN19	FOLLOWING DIAGNOSIS, IF A CHILD WITH A CANCER HAVING A GOOD PROGNOSIS (E.G., STANDARD-RISK ACUTE LYMPHOBLASTIC LEUKAEMIA OR HODGKIN'S LYMPHOMA) IS OFFERED TREATMENT AND FAMILY/CARERS REFUSE TO INITIATE IT, WHICH OF THE FOLLOWING WOULD OCCUR IN YOUR SETTING?	Decision accepted without discussion……1 Family would be counselled to investigate reason/convince decision maker to change decision……2 Connect with social worker……..3 Other: _____ 4 Don't know……9	
IN20	IN CASE OF REFUSAL TO INITIATE TREATMENT FOR A CHILD WITH CANCER HAVING A POOR PROGNOSIS (E.G., METASTATIC BONE OR SOFT TISSUE SARCOMAS, AND HIGH-RISK NEUROBLASTOMA) WHICH OF THE FOLLOWING WOULD OCCUR IN YOUR SETTING?	Decision accepted without discussion……1 Family would be counselled to investigate reason/convince decision maker to change decision……2 Connect with social worker……..3 Other: _____ 4 Don't know……...9	
IN21	IF THE FAMILY/CARER OF THE CHILD WITH A CANCER HAVING A GOOD PROGNOSIS (E.G., STANDARD-RISK ACUTE LYMPHOBLASTIC LEUKAEMIA AND HODGKIN'S LYMPHOMA) AND UNDERGOING TREATMENT REFUSES TO CONTINUE TREATMENT, WHICH OF THE FOLLOWING WOULD OCCUR IN YOUR SETTING?	Decision accepted without discussion……1 Family would be counselled to investigate reason/convince decision maker to change decision……2 Connect with social worker……..3 Other: _____ 4 Don't know……...9	
IN22	IN CASE OF REFUSAL TO CONTINUE TREATMENT FOR A CHILD WITH CANCER HAVING A POOR PROGNOSIS (E.G., METASTATIC BONE OR SOFT TISSUE SARCOMAS, AND HIGH-RISK NEUROBLASTOMA) WHICH OF THE FOLLOWING WOULD OCCUR IN YOUR SETTING?	Decision accepted without discussion……1 Family would be counselled to investigate reason/convince decision maker to change decision……2 Connect with social worker……..3 Other:…… 4 Don't know……...9	
IN23	DURING ONGOING TREATMENT, IF A CHILD MISSES A SCHEDULED APPOINTMENT FOR CHEMOTHERAPY, RADIOTHERAPY, OR SURGERY, WHICH OF THE FOLLOWING WOULD OCCUR IN YOUR	It is not routine practice to contact the child's family/caretaker……....1 Child's family/caretaker contacted only if they still don't turn up for the next few days…….……2 Child's family/caretaker contacted on the same/next day……..3 Other: …… 4 Don't know……..……...9	

	SETTING IN THE **FIRST INSTANCE**?		
IN 24	EVALUATE THE AVAILABILITY OF THE FOLLOWING INTERVENTIIONS/STRATEGIES 1 = Available 2 = Not available 9 = Don't know	Locally adopted treatment protocols ……[___] Effective procedural sedation and analgesia…..[___] Free chemotherapy……..……...[___] Subsidized chemotherapy ……...……..[___] Free/subsidized surgery…….....……..[___] Free/subsidized blood component therapy..……..[___] Financial support for travel……...…….[___] Free/subsidized food…….…….…..[___] Free/subsidized lodging……...……..[___] Social support……..…[___]	

IN25

HOW LIKELY ARE THE FOLLOWING STRATEGIES TO REDUCE ABANDONMENT IN YOUR CENTER?

Strategy	Very likely	Moderately likely	Minimally likely	Don't know
Locally adopted treatment protocols				
Effective procedural sedation and analgesia				
Free/subsidized chemotherapy				
Free/subsidized supportive care drugs, e.g., antibiotics				
Free/subsidized blood component therapy				
Free/subsidized surgery				
Development of a satellite center				
Money for travel				
Subsidy for food				
Support for lodging, e.g., guest house				
Patient/parent support group				
Patient/parent information sheets				
Detailed and repeated counselling				

IN26

ARE THERE **ANY OTHER** STRATEGIES WHICH COULD BE IMPLEMENTED IN YOUR SETTING IN THE **FUTURE** TO REDUCE ABANDONMENT?

Strategy 1	
Strategy 2	
Strategy 3	

IN27	WOULD YOU LIKE TO KNOW THE RESULTS OF THE SURVEY?	Yes (enter email below): [_____] No	

IN28	DO YOU HAVE ANY ADDITIONAL COMMENTS ABOUT ABANDONMENT OF TREATMENT IN CHILDREN WITH CANCER, OR ABOUT THIS SURVEY?		

Table S2. Perceived treatment abandonment rate by pediatric oncology treatment centers

Abandonment rate	Name of hospital			
	Tikur Anbessa Specialized Hospital , n (%)	Gondar University Hospital, n (%)	Jimma University Hospital, n (%)	Total, N (%)
15% or less	5 (29)	0 (0)	0 (0)	5 (13)
16% to 25%	2 (14)	3 (22)	1 (14)	6 (17)
26% to 35%	4 (21)	0 (0)	1 (14)	5 (13)
36% to 45%	5 (29)	4 (33)	3 (29)	11 (30)
46% to 55%	1 (7)	4 (33)	4 (43)	9 (23)
66% to 75%	0 (0)	1 (11)	0 (0)	1 (3)
Total	17 (100)	12 (100)	9 (100)	38 (100)

Table S3. Association between patients' clinical prognosis and physicians' action

Clinical condition	Decision accepted without discussion, n (%)	Family counselled to investigate reason/convince decision maker to change decision, n (%)	Connect with social worker, n (%)
A child with a good prognosis whose caretakers refuse to start treatment		7 (100)	
A child with a poor prognosis whose caretakers refuse to start treatment	2 (29)	5 (71)	
A child with a good prognosis undergoing treatment, whose caretakers refuse to continue treatment		6 (86)	1 (14)
A child with a poor prognosis undergoing treatment, whose caretakers refuse to continue treatment	4 (57)	3 (43)	
Contact tracing practice			
During ongoing treatment, what will happen if a child misses a scheduled appointment for chemotherapy or radiotherapy or surgery	Child's family/caretaker would be contacted	It is not routine practice to contact the child's family/caretaker	Total
	2 (28)	5 (72)	7(100)

Table S4. Pre-identified risk factors associated with treatment abandonment

Variable	Extremely low likelihood, n (%)	Low likelihood, n (%)	No relation, n (%)	High likelihood, n (%)	Extremely high likelihood, n (%)	Total, N (%)
Low economic status				3 (8)	35 (92)	38 (100)
Cost of care				4 (11)	34 (89)	38 (100)
Long travel time to treatment center			1 (3)	8 (21)	29 (76)	38 (100)
Belief in the incurability of cancer			1 (3)	11 (29)	26 (68)	38 (100)
Low level of parental education			3 (8)	10 (26)	25 (66)	38 (100)
Undernourishment of the child			8 (22.8)	16 (45.7)	11 (31.4)	38 (100)
Adverse effects and toxicity of treatment			3 (8)	22 (59.4)	12 (32)	38 (100)
Painful diagnostic and therapeutic procedures			5 (14)	24 (68.5)	6 (17)	38 (100)
Insufficient communication by healthcare professionals				24 (63)	14 (37)	38 (100)
Preference for complementary and alternative medicine			5 (13)	23 (61)	10 (26)	38 (100)
Strong faith or religious beliefs				29 (76)	9 (24)	38 (100)
HIV diagnosis of the child			12 (35.3)	15 (44)	7 (20)	38 (100)
Female sex			37 (97)	1 (3)		38 (100)
Male sex			37 (97)	1 (3)		38 (100)
Older age of the child or adolescence		3(8)	32 (89)	1 (3)		38 (100)
Younger age of the child			26 (72)	9 (25)	1 (3)	38 (100)

Supplementary text S1. Level of influence of pre-identified factors

The healthcare providers were asked to indicate the level of influence of pre-identified risk factors on treatment abandonment at their treatment center. These risk factors were identified by the International Society of Pediatric Oncology Abandonment Technical Working Group.

We asked them to indicate the perceived likelihood of a risk factor leading to treatment abandonment by using the following options: strongly decrease likelihood, decrease likelihood, no relation, increase likelihood, strongly increase likelihood. At the analysis stage, we developed five categories (major role, important role, moderate role, minor role, and no relation) based on a combination of responses about the level of influence.

i. A factor was considered to play a major role in influencing abandonment if more than 85% of the respondents indicated that it had a "strongly increase likelihood" or "increase likelihood", and provided that ≥65% of the respondents reported that it has a "strongly increase likelihood." We assigned more value to risk factors labeled as having a "strongly increase likelihood."
ii. A factor was considered to play an important role if the cumulative reported frequency was greater than 65%, and if more than 40% of the respondents reported an "increase likelihood" or 25% to 65% of the respondents reported a "strongly increase likelihood."
iii. A factor was considered to play a moderate role if 40% to 65% of the respondents reported a strongly increase likelihood" or an "increase likelihood."
iv. A factor was considered to play a minor role if 20% to 40% of the respondents reported a "strongly increase likelihood" or an "increase likelihood."
v. A factor was considered to not be related to abandonment if more than 80% of the respondents reported "no relation."

Table S5. Availability of essential interventions for childhood cancer treatment in the included healthcare centers

Interventions	Tikur Anbessa Specialized Hospital (n = 14)		Gondar University Hospital (n = 9)		Jimma University Hospital (n = 7)		Total (n= 30)	
	available	not available	available	not availabl e	available	not availab le	available	not availa ble
Locally adopted treatment protocols	47%	53%	58%	42%	86%	14%	53%	47%
Effective procedural sedation and analgesia	71%	29%	89%	11%	86%	14%	80%	20%
Free chemotherapy	14%	86%	0%	100%	86%	14%	27%	73%
Subsidized chemotherapy	100%	0%	17%	83%	100%	0%	77%	23%
Free/subsidized surgery	100%	0%	22%	78%	100%	0%	77%	23%
Free/subsidized blood products	100%	0%	100%	0%	100%	0%	100%	0%
Financial support for travel	57%	43%	11%	89%	100%	0%	53%	47%
Free/subsidized food	100%	0%	89%	11%	100%	0%	97%	3%
Free/subsidized lodging	93%	7%	0%	100%	100%	0%	67%	33%
Social support	100%	0%	89%	11%	100%	0%	97%	3%

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RESEARCH ARTICLE

Cost of childhood cancer treatment in Ethiopia

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Abstract

Background

Despite the recent interest in expanding pediatric oncology units in Ethiopia, reflected in the National Childhood and Adolescent Cancer Control Plan (NCACCP), little is known about the cost of running a pediatric oncology unit and treating childhood cancers.

Methods

We collected historical cost data and quantity of services provided for the pediatric oncology unit and all other departments in Tikur Anbessa Specialized Hospital (TASH) from 8 July 2018 to 7 July 2019, using a provider perspective and mixed (top-down and bottom-up) costing approaches. Direct costs (human resources, drugs, supplies, medical equipment) of the pediatric oncology unit, costs at other relevant clinical departments, and overhead cost share are summed up to estimate the total annual cost of running the unit. Further, unit costs were estimated at specific childhood cancer levels.

Results

The estimated annual total cost of running a pediatric oncology unit was USD 776,060 (equivalent to USD 577 per treated child). The cost of running a pediatric oncology unit per treated child ranged from USD 469 to USD 1,085, on the scenario-based sensitivity analysis. Drugs and supplies, and human resources accounted for 33% and 27% of the total cost, respectively. Outpatient department and inpatient department shared 37% and 63% of the cost, respectively. For the pediatric oncology unit, the cost per OPD visit, cost per bed day, and cost per episode of hospital admission were USD 36.9, 39.9, and 373.3, respectively. The annual cost per treated child ranged from USD 322 to USD 1,313 for the specific childhood cancers.

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Conclusion

Running a pediatric oncology unit in Ethiopia is likely to be affordable. Further analysis of cost effectiveness, equity, and financial risk protection impacts of investing in childhood cancer programs could better inform the prioritization of childhood cancer control interventions in the Ethiopia Essential Health Service Package.

Background

High-income countries have achieved remarkable progress in the survival rates of children with cancer from a low starting point (around 30%) in the 1960s to above 80% in the 2020s, even higher (90–95%) for some cancer types, such as acute lymphoblastic leukemia (ALL) and Wilms' tumor [1–5]. This achievement is mainly related to the tremendous progress made in improving access to care, timely detection, and prompt treatment; an improvement in the safety of treatment and supportive care; and a large reduction in the treatment abandonment rate [3,6,7]. On the contrary, the survival rate in low-income countries (LICs), where more than 90% of the childhood cancer burden occurs [3], is around 20–30% [3,6,8–10]. In LICs, only a small portion of children with cancer are diagnosed and treated [11]. Even if they have access to treatment, the survival rate is low due to late diagnosis (treatment initiated at an advanced stage), misdiagnosis, high abandonment rate, poor quality of care (lack of standard protocol, suboptimal trained human resources, unavailability of essential medicines, frequent stockout of drugs and supplies), high treatment-related toxicity, and poor supportive care facilities [3,11,12].

The situation in Ethiopia is similar to those of other LICs. Children with cancer are often not detected and diagnosed promptly in the country [13,14]. Those who made it through are highly likely to receive delayed, incomplete, or no care [15]. Children in the incurable disease stage (a common situation in Ethiopia) are often sent home without palliative care [13]. For many years, the country has only had one pediatric oncology unit located at Tikur Anbessa Specialized Hospital (TASH) [16] in the capital city of Addis Ababa. Recently, three additional units have opened at Jimma, Mekelle, and Gondar University Hospitals. There are critical gaps in trained human resources, the availability of diagnostic centers, and essential medicines [15]. This could generally indicate the low priority given to childhood cancer programs in Ethiopia. In 2019, the health sector recognized these critical gaps and launched a five-year strategic plan (the National Childhood and Adolescent Cancer Control Plan (NCACCP), 2019– 2023) and set a target of achieving a 40% cure rate for common and curable childhood and adolescent cancers [15]. One of the major targets set in the NCACCP to achieve this goal is increasing the number of equipped and staffed pediatric oncology units from three to eight before the end of 2023 [15]. However, the availability of evidence on the cost of running and scaling pediatric oncology units and disease (specific childhood cancer types) level cost estimates is scarce and unavailable in Ethiopia. The available estimates in LICs highly varied across study reports for several reasons, such as differences in the quality of care, cancer patterns, treatment protocols, and costing methods applied. A systematic review conducted in 2019 on the cost and cost-effectiveness of childhood cancer treatment in low—and middle-income countries (based on 18 studies that met their costing study criteria) reported an annual cost per treated child of USD 1,401 in Uganda, USD 1,638–1,913 in Rwanda, and USD 10,540 in Ghana [17]. These studies were classified as comprehensive—considering the key cost inputs assessed—and had scored $>$ 20 out of 24 on the consolidated health economic evaluation reporting standards

(CHEERS) criteria [17]. The cost per treated child ranged from USD 2,400 to USD 31,000 in another study that examined the cost-effectiveness of treating childhood cancer in four centers in sub-Saharan African countries (Kenya, Nigeria, Tanzania, and Zimbabwe) [18].

In the recently revised Ethiopia Essential Health Service Package (EEHSP), most of the childhood cancer interventions were given low priority, as prioritization of childhood cancer interventions is mainly conducted based on experts' judgement due to the lack of local evidence on the cost and cost-effectiveness of childhood cancer interventions [19]. Therefore, the rationale behind the present costing study was to generate the evidence needed for the EEHSP and to better inform the NCACCP strategy.

Methods

Study setting

This study explored treatment costs at the pediatric oncology unit in TASH in Addis Ababa, Ethiopia, which was established in 2013 [16]. TASH is the largest specialized hospital in Ethiopia, with 81 clinical departments. In 2019, it had a 735 bed capacity and served close to 500,000 OPD visits (20). The pediatric oncology unit in TASH had a capacity of 42 beds and was located both within the main compound and had a satellite center around 1 km away from the hospital. The pediatric oncology unit within the TASH compound served inpatient services, while the satellite center provided both inpatient and outpatient services for regular follow-up and short cycles of chemotherapy. The pediatric oncology unit shared various services with other departments in TASH, such as pharmacy, laboratory, pathology, radiology, emergency, intensive care, and surgery. The unit was staffed with pediatric oncologists, trained oncology nurses, pharmacists, social workers in pediatric oncology services, and pediatric residents who work on a rotation basis. At the time of the study, TASH was the only hospital in Ethiopia that provided radiotherapy treatment. The pediatric oncology unit was mainly publicly funded and aimed to provide services with large subsidies, but interrupted availability of supply was a big challenge (mainly due to budget gap), and cost of care is one of the major drivers of treatment abandonment in TASH (Kiros et al.–submitted for publication). Childhood cancer treatment-related medical products were procured and distributed through the national public medical supply procuring body, Ethiopia Pharmaceutical Supply Agency (EPSA).

Data collection and analysis

General TASH costing study approach. This study was conducted as part of a costing exercise carried out in TASH by the Ethiopia Health Insurance Agency (EHIA) to estimate the community health insurance premium rate (period 8 July 2018 to 7 July 2019) [20]. The additional costing elements specific to this study were collected simultaneously with data collected for the broader hospital-level costing, and the three authors of this paper had the role of guiding and coordinating the entire costing exercise (from design to analysis). The data collection was conducted October 5–28, 2020.

The annual cost of running TASH in general as well as of running the pediatric oncology department was estimated from the health system (provider) perspective using historical data. The historical costing exercise collected annual data from the period 8 July 2018 to 7 July 2019 (EFY 2011), and therefore avoided any cost distortion due to seasonal utilization differences. The exercise was structured through a mixed costing approach with predominantly top-down estimation in which aggregate costs at the hospital level were collected and allocated out to departments. This was supplemented by a bottom-up approach in estimating staff time and, to some extent, in estimating the relative consumption of certain drugs and supplies at the department level for the overall TASH costing and at the disease (childhood cancer specific)

level in the case of pediatric oncology care costing. Patient chart review was conducted to estimate the annual consumption of drugs, laboratory, radiology, and surgery supplies, and blood products for specific childhood cancers. Direct cost inputs—costs directly attributable to a specific department or service output, that is, costs of human resources, medical equipment depreciation and drugs and other supplies—were computed by estimating amounts consumed by the unit in a year (consumed quantity) multiplied by their unit costs.

Staffing inventory. We collected a list of all staff that was active during the study period from each department. Staff was categorized by cadre and qualification (e.g., nurse, BSc). Time allocation of each cadre of staff to each department, including patient and non-patient facing time, was collected from interviewed heads of departments for allocation. Then, for each cadre and qualification category, the total number of full-time equivalents (FTE) was calculated. This measurement considered the part-time work of staff members who shared their time across several departments. For example, if a department had two BSc nurses working 30% and one BSc nurse working 100%, the department would be recorded as having 1.6 FTE BSc nurses (2*0.3 + 1*1 = 1.6). Average personnel cost per cadre (including salaries, benefits, and allowances) was calculated for clinical and administrative staff employed from 8 July 2018 to 7 July 2019 based on data from the human resources and/or finance department. Staff costs were assigned based on the staff mix of the department, as defined during key informant interviews with the department head. The average annual salary plus allowances for each cadre, as defined by human resource (HR) data, were used to build up the cost of staff in each department.

Drugs, lab reagents, and supplies purchase costs and the volume of internal distribution of drugs, lab reagents, and supplies among departments were collected from the central pharmacy unit using the facility's Health Commodities Management Information System (HCMIS). For items where the unit cost was not found in the HCMIS, the unit cost was obtained from the EPSA. For donated items with no unit cost at EPSA, we used international unit prices such as Management Sciences for Health (MSH) [21], and The National Institute for Health and Care Excellence (NICE) [22].

Medical equipment. An inventory of all functional medical equipment available at the time of the visit was collected for all departments. This study included only costs related to functional clinical equipment (excluding administrative equipment such as desks, chairs, and communication equipment, for example). The value of equipment was estimated using procurement data for the study period obtained from the EPSA (3 years average), considering the equipment replacement cost regardless of whether the equipment was purchased by the facilities through EPSA, through the private sector, or was donated. A straight-line depreciation rate of 10%, which is in line with government capital item accounting standards [23], was used to amortize equipment over 10 years and to estimate the yearly cost of equipment.

Intermediate departments and overhead services. Shared services or departmental costs such as radiation, imaging, pathology, surgical operating room (OR), intensive care unit (ICU), pediatric emergency services (ER), inpatient food services, laundry, utilities (rent, electricity, telecommunication, water, and other utility charges) and other overhead costs (operating expenses such as office supplies, printing, educational supplies, fuel, per diem, training cost, etc.), were costed by allocating the share of each of those services used by the pediatric oncology unit using different allocation bases as appropriate in each case (for further details, see S1 Table).

Service statistics. Utilization data were collected from department-specific registers and service statistics reports. For cases in which this information was unavailable, we used hospital-level health management information system reports. This included total patient visits, bed days, visits by service/procedures (lab, pathology, imaging tests, surgeries), and length of stay information. The surface area of each department (in square meters) was also measured

manually. Service statistics were collected for the overall departments, as well as those specific to childhood cancer services. These service statistics were used to allocate shared costs to various departments and to compute department unit costs. For example, laundry and food were allocated to inpatient departments based on the share of total bed days; utilities, such as rent, electricity, and water, were allocated based on the square meter size of the department; other overhead costs were allocated based on the department's share of total hospital staff; and costs for administration (e.g., HR, finance, and liaison) were allocated based on the department's share of personnel and bed days, respectively. The costs of intermediate (clinical support) departments, such as the operating room, laboratory, and radiology, were allocated out to other OPD and IPD departments in the final step of the cost allocation (see S1 Fig).

We computed the total cost of the unit by adding 1) the direct costs (HR, drug, and supplies, medical equipment), 2) the share of indirect costs (food services, laundry, utilities, and other overhead cost), 3) the cost share from cross-cutting departments (such as administrative offices, liaison office), 4) the cost share from intermediate clinical support departments such as laboratory, pathology, radiology, triage, OR, pediatric emergency department, pediatric ICU, radiotherapy department) (see S1 Fig). The final cost estimate in Ethiopia Birr is converted to USD using the 2019 exchange rate [24].

To further disaggregate the costs for each specific childhood cancer, we applied different approaches. To allocate the estimated fixed costs (such as HR, medical equipment, and overhead costs) at the pediatric oncology unit level to the specific cancer types, we used the disease-level service utilization share at each department among the childhood cancer types. For intermediate clinical support departments such as laboratory, pathology, radiology, triage, ER, ICU, and surgery, we used department-specific childhood cancers' disease-specific utilization rates. Where available and reliable, each department's registry book was transcribed to find out the relative patient load for different cancer types. Accordingly, we found childhood cancer disease-specific utilization data for surgery, ER, ICU, pathology, and X-ray services. Costs for these departments were then allocated to each cancer type according to its relative share of total utilization (assuming one visit or bed day required equal resource use for all cancer types). For cases in which registry data were not available (in the case of the lab and radiology department except for X-ray), the relative consumption share among the childhood cancer types on the chart review (described below) was used as the source to determine cost distribution.

To distribute the cost of drugs and supplies from the pediatric oncology unit to specific childhood cancers, we applied the following techniques. First, with the help of a senior pediatric oncologist, we matched the drugs and supplies consumed at the pediatric oncology unit (collected from the hospital's HCMIS database) to specific disease types. This helped to identify which items belonged to which cancer types. We did one-to-one matching for medicine that was only utilized by a single cancer type, with 100% of the cost transferred to that specific cancer type. For items that were matched with two or more cancer types, we used the relative prescription rate share for that specific item (among the childhood cancer types) in the chart review to allocate the total cost of a specific drug or supply to childhood cancer types. For example, if the relative prescription rate for "x" item on the chart review was 60% acute lymphoblastic leukemia, 30% acute myeloid leukemia, and 10% Hodgkin's lymphoma, then the total cost allocated for "x" item at the pediatric oncology unit level was distributed by applying these proportions (60%, 30%, 10%, respectively).

Patient chart review. Since historical costing only included actual expenditures (associated with the level of quality of care) at the facility in a given period, it may not capture the full cost of treating patients. In Ethiopia, overall drug availability in public health facilities is suboptimal. The average essential drug availability estimate in 2018 was 28% [25], which might be

even lower for pediatric oncology drugs, given their high cost and low attention. The same gap in service readiness is true for lab, radiology, and pathology services. To account for such gaps, we embedded a patient's chart review in the study together with the top-down costing that considered the same study period (8 July 2018 to 7 July 2019). To obtain a representative patient's chart number for that given year, we divided the year into four quarters and selected a random month in each quarter (a total of four months selected) through an Excel-based lottery system. Then, we randomly selected a week in each selected month, a total of four weeks selected in the four quarters. This yielded 345 patients registered for the selected weeks, and all patients' charts were reviewed for a full month of clinicians' prescription order. The month was defined as 30 or 31 days, starting from the specific date they utilized care in the sampled weeks. We collected four months' prescription orders (including drugs and supplies, lab, pathology, radiology, and surgeries) and were then annualized by multiplying by 3. The annualized data were expected to be representative, given the large random sample and by assuming a similar pattern of patient flow and prescription practice in a year. The chart review was carried out October 12–23, 2020.

As indicated above, while detailed service statistics at the diagnosis level were collected for pediatric cancer departments and associated departments, data availability and quality varied and were not available at the diagnosis level in some instances. The chart review therefore afforded the secondary benefit of enabling more precise cost estimates at the disease level by providing indicative data on the distribution of services between cancer types for those departments with service statistic data gaps.

Data collection process and data quality control. Data collection was undertaken by experienced costing data collectors. We identified data collectors who performed well in the previously conducted costing study (in 2017) for secondary and primary hospitals by the Ethiopian Health Insurance Agency and the Clinton Health Access Initiative. The team was given a one-day training session in which the study objective, data collection tools, and guidelines and routines for data collection were covered. Data collection tools were paper-based and were derived from the Simple Cost Analysis Tool for Hospitals (SCAT) developed by Abt Associates and previously used by EHIA [20]. The team was closely managed on-site (by three of the authors in this paper), with daily check-ins at the beginning and end of each day.

Once the data collection was finalized and entered into the Excel-based tool (from the paper-based data collection templates), an iterative process of data validation was conducted. First, collected data were compiled, and preliminary analysis was performed. Gaps and suspicious values in the data were identified, and follow-up was undertaken with hospital staff in person. Follow-up was done with particularly high frequency in the weeks immediately after data collection but continued ad hoc over several months as the data were compiled and analyzed. The cost analysis was conducted using an Excel-based model adopted from the Joint Learning Network for Universal Health Coverage [26], which was previously used by EHIA for a similar exercise.

Results

There were 42 staff members (corresponding to 32 FTE, full-time equivalent) working in the pediatric oncology unit: 3 FTE oncologists, 11 FTE residents, and 18 FTE nurses. During the study period, the unit served 1,345 patients with 7,842 OPD visits, 1,302 IPD admissions, 9.4 days of average length of stay per episode of admission, and 12,180 bed days (Table 1). Seventy percent of the bed days were in the inpatient ward within the TASH compound, and 30% were in the satellite clinic. The annual OPD visits per patient and bed days per patient were 5.8 and 9.1, respectively (Table 1).

Table 1. Childhood cancer incident and service utilization distribution in TASH, 2018–2019.

Diagnosis	Share, N (%)	OPD visits, N (%)	Bed-days, N (%)	Annual OPD visits / patient	Annual bed days /patient
Acute lymphoblastic leukemia	378 (28.1%)	2,259 (28.8)	2,706 (22.2)	6.0	7.2
Wilms' tumor	197 (14.6%)	967 (12.3)	803 (6.6)	4.9	4.1
Hodgkin's lymphoma	161 (12.0%)	851(10.9)	540 (4.4)	5.3	3.4
Rhabdomyosarcoma	117 (8.7%)	897 (11.4)	1,366 (11.2)	7.7	11.7
Retinoblastoma	90 (6.7%)	801 (10.2)	928 (7.6)	8.9	10.4
Neuroblastoma	76 (5.7%)	313 (4.0)	1,081(8.9)	4.1	14.2
Non-Hodgkin's lymphoma	70 (5.2%)	400 (5.1)	1,769 (14.5)	5.7	25.5$^{\Delta}$
Acute myeloid leukemia	48 (3.5%)	180 (2.3)	1,306 (10.7)	3.8	27.5$^{\Delta}$
Osteosarcoma	47 (3.5%)	130 (1.7)	412 (3.4)	2.8	8.8
Ewing sarcoma	31 (2.3%)	178 (2.3)	507 (4.2)	5.7	16.3
Nasopharyngeal cancer	27 (2.0%)	697 (8.9)	295 (2.4)	25.6$^{\Delta\Delta}$	10.8
Other cancers*	104 (7.7%)	169 (2.2)	467 (3.8)	1.2	3.3
Total** or Average ***	1345 (100)**	7 842 (100)**	12 180 (100)**	5.8***	9.1***

* Angiosarcoma, germ cell tumor, sacrococcygeal teratoma, yolk sack tumor, Burkitt's Lymphoma, Hemangioma, soft tissue sarcoma, Kaposi sarcoma, neuroblastoma, chronic myeloid leukemia› thymoma.

** Total.

*** Average.

Δ Radiotherapy services were given as outpatient care and each day's visit was counted as a separate OPD visit. It might also be a data quality gap.

ΔΔ Can be partly explained by the high risk of treatment related prolonged neutropenia that leads to longer admission period but can also be a data quality gap.

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The top seven pediatric cancer types in TASH during the study period were acute lymphoblastic leukemia, Wilms' tumor, Hodgkin's lymphoma, rhabdomyosarcoma, retinoblastoma, neuroblastoma, and non-Hodgkin's lymphoma (Table 1).

Table 2 summarizes the annual costs of running a pediatric oncology unit in TASH. The estimated annual total cost was USD 776,060 (equivalent to USD 577 per treated child). Seventy-eight percent of total costs consisted of direct and indirect (overhead) costs from the pediatric cancer OPD and IPD departments (Table 2). From this share, drugs and supplies made up the major component (33%), followed by personnel costs (27%). The remaining 22% of total costs were evenly split between other clinical department services (ER, ICU, and surgery), which represented 11% of total costs, and intermediate department services (lab, pathology, radiology, and triage), which represented 11% of total costs. Among intermediate departments, radiology services accounted for the largest cost, while the ER accounted for the largest cost share among the clinical departments.

Thirty-seven percent (USD 289,953) of the total cost was attributable to OPD services, and the remaining 63% (USD 486,108) was attributable to IPD services. For the pediatric oncology unit, the cost per OPD visit, cost per bed day, and cost per episode of hospital admission was USD 36.9, 39.9, and 373.3, respectively.

The cost of running a pediatric oncology unit per treated child ranged from USD 469 to USD 1,085 on the scenario-based sensitivity analysis (S2 Table), which accounted for the potential cost underestimation due to under-provision of services, using the cost estimation results from the patients' chart review.

Table 3 presents costs for the most prevalent cancer types per patient, per OPD visit and per bed day. Overall, the annual cost per patient ranged from USD 322 to USD 1,313, but the estimate for the top six cancer types was in the range of USD 433 to USD 676.

Table 4 presents cost drivers for the different cancer types. Drugs and supplies were the largest cost contributors to pediatric cancer treatment at TASH. Acute lymphoblastic leukemia, Wilms' tumor and Hodgkin's lymphoma had a cost share of drugs and supplies that was

Table 2. Annual costs of treating childhood cancers in TASH July 2018–July 2019.

Pediatric oncology OPD (including radiotherapy) and IPD	Annual total cost, USD (%)	Annual cost/patient (USD)
Personnel	212,367 (27)	157.9
Drugs & Supplies	258,391 (33)	192.1
Equipment depreciation	11,649 (2)	8.7
Overhead	121,642 (16)	90.4
Intermediate		
Lab	21,112 (3)	15.7
Pathology	14,231 (2)	10.6
Radiology	43,885 (5)	32.6
Triage	5,733 (1)	4.3
Other clinical departments		
Pediatric ER	65,875 (8)	49.0
Pediatric ICU	15,509 (2)	11.5
Pediatric Surgery	5,667 (1)	4.2
Total	766 060 (100)	577.0
Distribution by departments		
Department	Cost (%)	Cost per service utilization
Out-Patient Department (OPD)	289,953 (37%)	USD 36.9 per OPD visit
In-Patient Department (IPD)	486,108 (63%)	USD 39.9 per bed day
		USD 373.3 per episode of admission

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above the pediatric oncology unit level estimate (33%). However, non-Hodgkin's lymphoma, acute myeloid leukemia and nasopharyngeal cancer had low drugs and supplies and high HR share.

Discussion and conclusions

The total annual cost of running a pediatric oncology unit in TASH was USD 776,060. The cost increased to USD 1,122,802 (a 45% increase from the base case scenario) when the potential under-provision of services due to interrupted availability of drugs and supplies, lab,

Table 3. Disease-level childhood cancers unit costs in TASH July 2018–July 2019.

Pediatric cancer diagnosis	Total cost	Cost share (%)	Annual cost per patient (USD)
Acute lymphoblastic leukemia	219 481	28.3	581
Wilms' tumor	90 383	11.6	459
Hodgkin's lymphoma	69 733	9.0	433
Rhabdomyosarcoma	67 174	8.7	575
Retinoblastoma	47 960	6.2	535
Neuroblastoma	51 357	6.6	676
Non-Hodgkin's lymphoma	65 778	8.5	940
Acute myeloid leukemia	62 443	8.0	1313
Osteosarcoma	18 510	2.4	396
Ewing sarcoma	20 084	2.6	644
Nasopharyngeal cancer	32 390	4.2	1 187
Other cancers	30 766	4	322

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Table 4. Disease-level cost drivers for childhood cancers in TASH, 2018–2019.

Pediatric cancer diagnosis	Cost category share (in %)						
	Human resources	Drugs & supplies	Equipment	Overhead	Clinical Support	Intermediate	Total
Acute lymphoblastic leukemia	24	45	1	13	12	5	100
Wilms' tumor	20	39	1	11	11	18	100
Hodgkin's lymphoma	21	37	1	10	16	14	100
Rhabdomyosarcoma	30	29	3	20	9	10	100
Retinoblastoma	33	28	5	20	5*	9	100
Neuroblastoma	30	24	2	20	13	12	100
Non-Hodgkin's lymphoma	42	18	1	25	10	5	100
Acute myeloid leukemia	32	12	1	19	31	5	100
Osteosarcoma	29	40	2	20	0*	9	100
Ewing sarcoma	32	24	3	23	9	9	100
Nasopharyngeal cancer	43	25	6	15	3*	9	100
Other cancers	19	43	1	12	10	15	100

Clinical Support includes ER, ICU, surgery.

Intermediate includes X-ray, CT scan, ultrasound, pathology, lab, MRI, ECO.

* A zero or a small number of patients were reported from the clinical support departments.

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pathology, and radiological investigation were accounted for using chart review. The annual cost of running a pediatric oncology unit per patient (for the base case scenario) was USD 577 and ranged from USD 469 to USD 1,085 (S2 Table) on the scenario-based sensitivity analysis. The major drivers (78%) of the costs were drugs, supplies, and personnel. The true cost of running a pediatric oncology unit could be higher than our estimate if we included the start-up investment costs (such as building and training costs), and it could even increase further as the availability of quality care (advanced diagnostic services, continuous availability of primary and supportive treatment, palliative care) improves.

Overall, the cost composition of the pediatric oncology unit was comparable to the adult oncology unit but markedly differed from the hospital-level (TASH) cost [20]. HR was the main cost driver at TASH, whereas drugs and supplies took the largest share at the pediatric and adult oncology unit level (S3 Table). This can mainly be explained by the heavy dependence of oncology units on expensive chemotherapies. This pattern is also similar for the common childhood cancer types (Table 4) but particularly marked in the case of ALL, and Wilms' tumor which can be partly explained by the longer duration of chemotherapy, the high number of chemotherapy drugs used per cycle in the case of ALL, and the relatively expensive drug types (treatment protocol) in the case of Wilms' tumor. Non-Hodgkin's lymphoma, acute myeloid leukemia and nasopharyngeal cancer had low drugs and high HR cost share, and this could be related to a smaller number of drugs needed per cycle in the case of AML and nasopharyngeal cancer.

For the pediatric oncology unit, the cost per OPD visit, cost per bed day, and cost per episode of hospital admission were USD 36.9, 39.9, and 373.3, respectively. The cost per pediatric cancer unit OPD visit, excluding clinical support departments such as the ER, was USD 27. This is significantly higher than the hospital-level average of USD 15.7 [20]. One explanation is that expensive chemotherapy treatment is commonly administered as outpatient care. A second explanation is that radiotherapy treatment has been included in this estimate (since radiotherapy was delivered as outpatient care for children), which is a more advanced form of OPD treatment than the average visit.

The cost per pediatric cancer unit IPD bed day, again excluding clinical support departments such as ICU, was USD 37.3. This is significantly lower than the hospital average of USD 61.3 [20]. At the hospital level, nearly one-third of IPD costs came from intermediate departments, whereas the cost share of intermediate departments for pediatric cancer treatment was found to be around 11%. This discrepancy may be one explanation for the difference in the cost of IPD per bed day. The second reason is the higher service utilization in the pediatric oncology unit (12,180 bed days), lowering the cost per bed day estimate. This could be an economy of scale but could also be related to suboptimal provision of services due to an imbalance between patient flow (volume of services needed) and facility preparedness.

For specific childhood cancer types, the annual cost per patient ranged from USD 322 to USD 1,313, but the estimate for the top six cancer types was in the range of USD 433 to USD 676. The less commonly reported childhood cancer types had higher annual unit cost estimates, which can partly be explained by the low volume of service utilization that exaggerated the unit cost estimate or could be related to the data quality gap.

Generally, it was difficult to perform a one-to-one comparison of our study with reports from similar settings, mainly due to the inconsistency in costing approach and methods, differing cancer patterns, treatment protocols, and quality of care. Our estimate is smaller compared to study reports from Uganda and Rwanda, which applied a relatively similar costing approach [27,28]. We adjusted the estimate from both countries (which was in 2014) to match our study period (2018–2019) using the inflation rate [29,30]. In Uganda, the annual cost of treating a child with Burkitt's lymphoma in 2019 was US$1,479 (28). In Rwanda (in 2019), the cost per treated child for Hodgkin's lymphoma and Wilms' tumor was USD 1,757 and USD 1,345, respectively [27]. Beyond service quality differences, differing disease patterns (heterogeneity), and treatment protocols, costing methods explain part of the variation in the unit cost estimate. The cost of providing health services in Ethiopia is generally low since the HR salary wage is low, and most utilities (such as water and electricity) are subsidized by the government. For example, the average doctor's salary per month in 2022 is USD 408 in Ethiopia, USD 1,600 in Rwanda, and USD 1,740 in Uganda [31–33]. Similarly, the cost of electricity per kWh is USD 0.007, 0.19, and 0.25 in Ethiopia, Uganda, and Rwanda, respectively [34].

Our cost estimate could help the government and other stakeholders in Ethiopia make informed investment decisions. For an annual cost of USD 577 (which could be as high as 1,085 when adjusted for suboptimal care) per treated child, the budget impact of financing the childhood cancer program—combined with prioritizing high-impact interventions—could be low as the population in need of care is small (annual incidence of childhood cancer is around 3,800) [35], hence it could be affordable in Ethiopia. Of course, the cost of running a pediatric oncology unit and the cost per treated child could increase as more centers, beds, trained staff, advanced diagnostics, and safer treatment are made available, which could also significantly improve the survival rate of children with cancer. Cost must also be compared to expected health outcomes (but no cost-effectiveness analysis has been conducted to date in Ethiopia). There is growing evidence that investing in childhood cancer programs could be cost-effective in LMICs [6,17,18,36,37] and the incremental cost-effectiveness ratio estimate ranged from USD 22 to USD 4,475 per DALY averted [17]. One of the key pillars of universal health coverage is addressing equity (through prioritizing the worst off) and financial risk protection [38]. Children with cancer fall under the worst-off categories as they face a large individual-level disease burden, and their guardians are at high risk of encountering impoverishing health expenditure, as the cost of cancer care (direct and indirect medical and indirect non-medical costs) is high [38–41]. The high share of drugs and supplies costs in our study could also indicate the potential cost burden to affected households, if not made continuously available with a large subsidy or cost exemption through public funding. This is critical given that around 23.5% of

Ethiopians live below the poverty line [42]; the nation's health insurance system is in its infancy [43,44] and does not provide effective coverage for specialty services such as childhood cancer treatment.

Our study has many limitations that warrant cautious interpretation of its results. First, key costing elements, such as building costs and long-term specialty training to produce pediatric oncologists, oncology nurses, pharmacists, and pathologists, were not captured. Second, despite the effort we made to address the underestimation of costs due to suboptimal provision of services, the prescription practices of clinicians could be influenced by the perceived availability of services in TASH. As a result, clinicians might prescribe less effective (less costly) alternatives or avoid prescribing such items to patients. Further, poor chart documentation of the clinician's order might affect our cost estimate. Third, non-medical costs, such as transport, lodging, and productivity loss of guardian's, were not included. Fourth, despite the rigorous efforts made to improve the data quality (related to the poor hospital recording), there is a chance that our results could be biased, most likely in the direction of underestimating cost.

In conclusion, running a pediatric oncology unit in Ethiopia is likely to be affordable. Further analysis of the cost effectiveness, equity, and financial risk protection impacts of investing in childhood cancer could strengthen our findings and better inform the national essential health service package. An integrated and robust health, human resource, supply, lab, and financial information management system, and a cancer incidence and survival registry are highly needed for a better cost and health outcomes estimate and monitoring of progress and, more importantly, to enhance day-to-day decisions in TASH and the pediatric oncology unit.

Supporting information

S1 Fig. Cost aggregation at pediatric oncology unit level in TASH July 2018–July 2019.
(PDF)

S1 Table. Allocation statistics used for costing analysis.
(DOCX)

S2 Table. Scenario-based cost sensitivity analysis in TASH July 2018- July 2019.
(DOCX)

S3 Table. Cost categories share for TASH overall, adult oncology and pediatric oncology units in TASH, 2018–2019.
(DOCX)

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Ethical approval

We obtained ethical approval for the study from the Regional Committee for Medical and Health Research Ethics (REC Western Norway, approval no. 64245), and data use approval for the fully anonymized cost dataset from the Ethiopia Health Insurance Agency (አጤ ም ኤ/ሰጉ./999/014)

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Supplementary Material

Table S1: Allocation statistics used for costing analysis

Cost components	**Allocation Base**	**Allocated to**
Overhead cost		
Utilities	M2 (AREA)	
		To all departments
Patient Food	Bed days	To IPDs
Laundry	Weighting factor across ER, OR IPD	To IPDs, ER and OR
	[1 * # surgeries] + [(1/5) * # procedures] + [(1/10) * # bed days] + [(1/5) * 365 * # ER beds]	Tailored approach. A subset of departments was assumed to be the main consumers of laundry services (mapped by the hospital staff): Major OR, Minor OR, IPD wards, and ER. Then, the team, together with the hospital staff, estimated relative consumption of laundry for the four categories, which is given as 1 Major OR surgery = 5 Minor OR surgeries = 10 IPD bed days = 5 ER bed days. That is to say that one major surgery uses 5–10 times more laundry services
Other overheads (like office supplies, printing, educational supplies, fuel, per diem, training cost, etc.)	Personnel	All departments
Cross cutting departments		
Cost component (department)	**Allocation Base**	**Allocated to**
Administrative departments (Human resources, Finance, General Service, legal etc.) cost	Personnel	All departments except Admin

Cost of running the Pharmacy department a) Personnel (Direct cost)	Visits and Admission	OPD[a] and IPD[b] only
Cost of running the Pharmacy department b) overhead cost (Indirect cost)	Personnel	All departments except Admin and Pharmacy
Liaison	Bed days	All IPDs
Clinical support departments		
Cost component (department)	**Allocation Base**	**Allocation to**
Minor OR[c]	Visits	Relevant OPDs mapped by clinicians
Major OR	Admission	Relevant IPDs
Laboratory	Patient load*	Relevant OPDs and IPDs
	∑ (All OPD visits*3, All IPD visits*1, Number of deliveries*2, All ER[d] visits*3)	Patient load is calculated using 1Bed day = 3 OPD visits = 3 ER visits = 2Deliveries (50)
Radiology	Patient load	Relevant OPDs and IPDs
Endoscopy	Patient load	Relevant OPDs and IPDs
Pathology	Patient load	Relevant OPDs and IPDs
Triage	Visits	Relevant OPDs

[a] Outpatient department
[b] Inpatient department
[c] Operation theatre
[d] Emergency room

Figure S1:cost aggregation at pediatric oncology unit level in TASH July 2018–July 2019

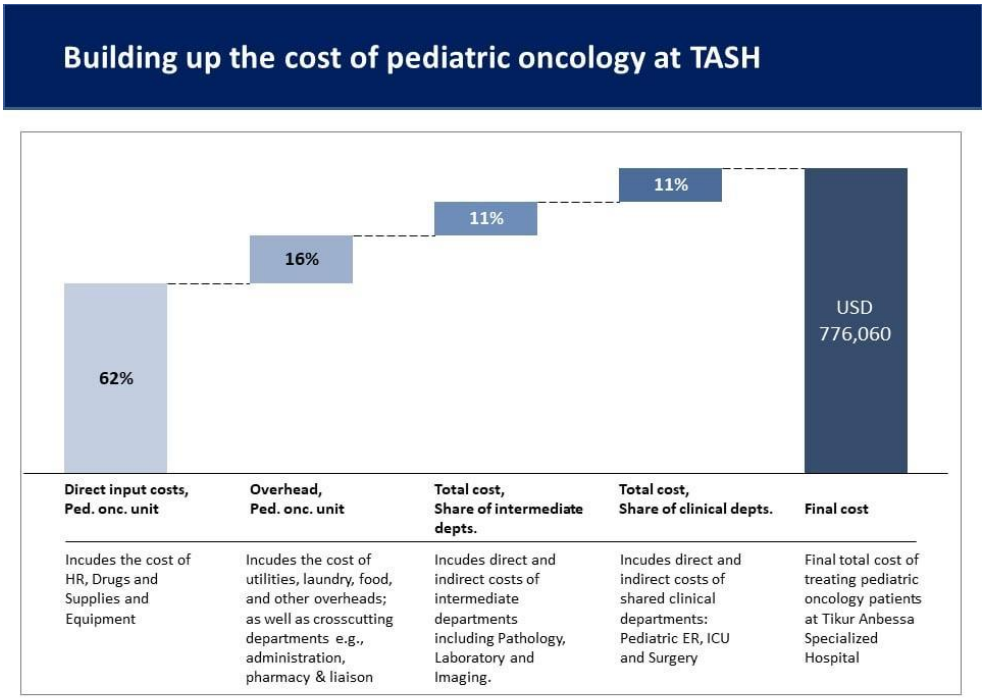

Table S2: Scenario-based cost sensitivity analysis in TASH July 2018- July 2019

Scenario	***cost (USD)***
base case (costing result from the top-down	577
low case (baseline unit cost adjusted taking incident case from the registry, 1,654)	469
high case scenario (taking cost estimate and incident number of cases (1,035) from chart review)	1 085

The estimated number of annual patients was 1,035 from the chart review and 1,654 from the department register. Since there was a problem with data quality in the pediatric oncology unit register (mainly double counting), we used the midpoint value (1,345 patients) in the base case costing analysis to account for potential underestimation in the chart review due to sampling effects and a potential overestimation of the department registry. We used the number of patients from the chart review (1,035) for the high-cost scenario and the data from the pediatric oncology unit (1,654) for the low-cost scenario estimate.

Table S3: cost categories share for TASH overall, adult oncology and pediatric oncology units in TASH, 2018-2019

Cost category	***Cost category share***		
	Pediatric oncology	**Adult oncology**	**TASH overall**
Human resource	31%	24%	35%
Drugs & supplies	38%	42%	18%
Equipment depreciation	2%	4%	4%
Overhead	18%	16%	15%
Intermediate departments	12%	14%	29%

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Cost--effectiveness of running a paediatric oncology unit in Ethiopia

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ABSTRACT

Objective To estimate the cost--effectiveness of running a paediatric oncology unit in Ethiopia to inform the revision of the Ethiopia Essential Health Service Package (EEHSP), which ranks the treatment of childhood cancers at a low and medium priority.
Methods We built a decision analytical model—a decision tree—to estimate the cost--effectiveness of running a paediatric oncology unit compared with a do-- nothing scenario (no paediatric oncology care) from a healthcare provider perspective. We used the recently (2018–2019) conducted costing estimate for running the paediatric oncology unit at Tikur Anbessa Specialized Hospital (TASH) and employed a mixed costing approach (top--down and bottom--up). We used data on health outcomes from other studies in similar settings to estimate the disability--adjusted life years (DALYs) averted of running a paediatric oncology unit compared with a do--nothing scenario over a lifetime horizon. Both costs and effects were discounted (3%) to the present value. The primary outcome was incremental cost in US dollars (USDs) per DALY averted, and we used a willingness--to--pay (WTP) threshold of 50% of the Ethiopian gross domestic product per capita (USD 477 in 2019). Uncertainty was tested using one--way and probabilistic sensitivity analyses.
Results The incremental cost and DALYs averted per child treated in the paediatric oncology unit at TASH were USD 876 and 2.4, respectively, compared with no paediatric oncology care. The incremental cost--effectiveness ratio of running a paediatric oncology unit was USD 361 per DALY averted, and it was cost--effective in 90% of 100 000 Monte Carlo iterations at a USD 477 WTP threshold.
Conclusions The provision of paediatric cancer services using a specialised oncology unit is most likely cost--effective in Ethiopia, at least for easily treatable cancer types in centres with minimal to moderate capability. We recommend reassessing the priority--level decision of childhood cancer treatment in the current EEHSP.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The cost--effectiveness analysis was informed by robust primary costing data from Tikur Anbessa Specialized Hospital.
- We mitigated the lack of local data on childhood cancer survival rates by conducting a scoping review.
- The model does not capture the heterogeneity of childhood cancers, such as variation in cost of care, treatment duration and diverse clinical scenarios, including survival rate.

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BACKGROUND

Globally, childhood cancer (age 0–19 years) represents 0.5%–4.6% of the total cancer burden in a population,[1–4] and nearly 90% of this burden falls on low and middle-- income countries (LMICs).[5–7] In 2017, child-hood cancer represented a disease burden of 11.5 million disability--adjusted life years (DALYs) globally and ranked as the sixth and ninth leading causes of disease burden in total cancer and childhood disease, respectively.[8] Over the past few decades, high--income countries have dramatically improved the treatment outcomes of childhood cancers. In the UK, for example, the 5--year survival rate has increased from less than 30% in the 1960s to almost 80% on average in the 2000s.[9–13] By contrast, survival rates in Africa generally remain lower than 20%,[7 14–16] and these avoid-able deaths are largely due to late diagnosis, misdiagnosis, lack of access to quality thera-peutic and supportive care, high treatment abandonment rate, treatment adverse effects and avoidable high rate of relapse.[14 17]

In general, there is a significant lack of reli-able data on the disease burden of childhood cancers in Ethiopia. The latest estimates from GLOBOCAN 2018 put the incidence of cancer among children aged 0–14 at 3800 cases annually, or 8.9 per 100 000 children.[2 3] Another study on cancer incidence in Ethi-opia estimated 3707 annual cases as of 2015.[18] The most common childhood cancers in Ethiopia are acute lymphoblastic leukaemia (25.7%), non--Hodgkin's lymphoma (8.9%), rhabdomyosarcoma (8.9%), Wilms tumour (8%) and neuroblastoma (7.8%).[19 20]

Sadly, as in other low--income countries (LICs), most childhood cancers in Ethiopia are not successfully treated. One Ethiopian study examined all children below 15 years of age admitted to the paediatric wards of Gondar University Hospital due to cancer in

2010–2013[21] and found that only 20% improved, while 65% were discharged without improvement and 7% died in the hospital. The main reason for discharge was the unavailability and unaffordability of chemotherapeutic drugs. In addition to the challenge of obtaining supplies and the unaffordability of treatment, there is also a large gap in the availability of equipped facilities and trained staff. As of 2019, Ethiopia had only six qualified paediatric hemato--oncologists for the entire nation,[19] and access to diagnostic or treatment centres is very limited. Until recently, Tikur Anbessa Specialized Hospital (TASH) had the country's only paediatric oncology unit.

Cognizant of these factors, the Ethiopian Federal Ministry of Health (FMoH) recently developed a National Childhood and Adolescent Cancer Control Plan (NCACCP) for the years 2019–2023 with the aim of improving survival rates through early detection and diag-nosis, quality treatment and supportive care.[19] The overall goal is to achieve at least a 40% cure rate for common and curable childhood and adolescent cancers. The timing of the NCACCP plan aligns with the WHO Global Initiative for Childhood Cancer, launched in 2018, which aims to improve survival to at least 60% and to decrease cancer--related suffering for all children with cancer by 2030.[22] One means by which the FMoH aims to achieve these targets is by increasing the number of fully equipped and functional paediatric oncology centres in the country from three in 2019 to eight before the end of 2023.[19]

In general, there is limited evidence on the cost, cost--effectiveness and affordability of paediatric cancer units in LMICs, but a few studies have found that treatment of certain paediatric cancers can be highly cost--effective in such settings. A 2019 systematic review of childhood cancer treatment in LMICs indicates that the cost per DALY averted could range from US dollars (USD) 22 to 4475, which is less than one time the gross domestic product (GDP) per capita of the studied countries, indi-cating that selected interventions are cost--effective[23]; the wide range of the result is explained by the difference in cost--component accounting among studies. Simi-larly, a study conducted in 2021 in four African coun-tries (Kenya, Zambia, Nigeria and Tanzania) found that costs per DALY averted were less than 0.3 times the GDP per capita of Tanzania and Zambia.[24] A 2013 study on the cost--effectiveness of acute lymphoblastic leukaemia and Burkitt's lymphoma treatment in Brazil and Malawi concluded that running a paediatric oncology unit in LMICs would be highly cost--effective by the standard of the WHO--CHOICE cost--effectiveness threshold.[25] Other studies conducted at paediatric oncology units in El Salvador and Ghana support these findings, with cost per DALY averted estimates of USD 1624 and USD 1034, respectively,[26 27] which is very cost--effective according to the countries' cost--effectiveness thresholds as determined by the WHO--CHOICE framework.

Despite this promising evidence from other LMICs, a need remains for more country--level evidence because of differing disease burdens, patients' survival rates, cost of care profiles and willingness to pay (WTP) in Ethiopia compared with other LMICs. Furthermore, local cost--effectiveness evidence could enhance advocacy, trust and policy prioritisation for childhood cancer programmes in the national priority--setting process. As an example, the Ethiopia Essential Health Service Package (EEHSP)[28] classifies most childhood cancer diagnostic and treat-ment services as either low or medium priority despite the aspirational goals of the NCACCP and the recent global attention and advocacy for countries to invest in childhood cancer control; this represents a setback in Ethiopia's childhood cancer control efforts, which will continue to be underfinanced and out of the leadership's attention. These priority rankings were partly influenced by a lack of contextualised cost--effectiveness evidence, and the decision was based on experts' judgement. Therefore, this research aimed to fill the local evidence gap regarding the cost--effectiveness of childhood cancer treatment (specialised paediatric oncology care delivery) to inform the revision of the EEHSP and harmonise the conflicting priority level of childhood cancer treatment between the NCACCP and the EEHSP.

METHODS

Study setting

Ethiopia, a country with a population close to 110 million in 2019,[29] formerly had only one paediatric oncology unit nationally, located at TASH in Addis Ababa, Ethiopia's capital. Recently, three additional paediatric oncology centres (in Jimma, Gondar and Mekelle University Hospitals) were added. The costing part of this study was conducted at TASH, which has 81 clinical depart-ments, a 735--bed capacity and close to 500 000 outpa-tient department (OPD) visits per year in 2019. TASH's paediatric oncology centre has a capacity of 42 beds, and most suspected cases of childhood cancer (age <15 years) across the country have until recently been referred to this centre. The paediatric oncology unit is financed mainly by the government. The unit has an inpatient depart-ment embedded in the main compound of TASH and a satellite clinic proximal to TASH (around 1 km away). The satellite clinic not only serves mainly as an OPD but also provides inpatient services for short admissions to administer chemotherapy. Although the paediatric oncology unit is far from ideally staffed and equipped,[7] it has paediatric oncologists, nurses trained in paediatric oncology services, social workers and dedicated pharma-cists. Some clinical support services are shared with other departments, such as the laboratory, pharmacy, imaging, pathology, surgery, intensive care unit (ICU), emer-gency, radiotherapy, blood bank and non--medical central services, such as food, laundry, utilities (eg, electricity and water) and other operational costs.

Decision analytic model

We built a decision analytic model—a decision tree—to estimate the cost--effectiveness of running a paediatric

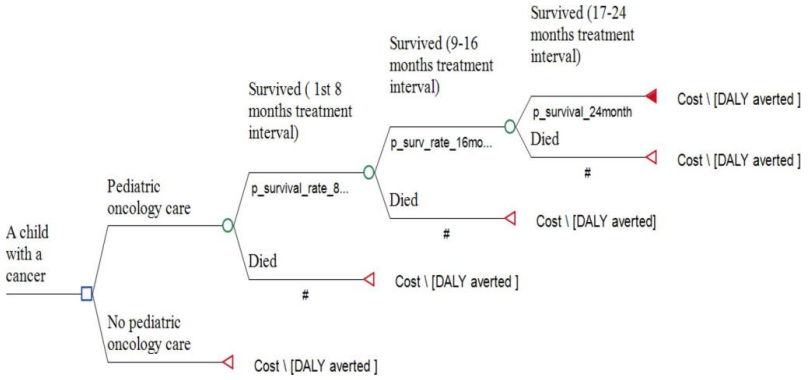

Figure 1 A decision--analytic model structure (decision tree) with an average 2--year childhood cancer treatment duration divided into 8--month treatment intervals. The model compares a simulated child with cancer (without a specific diagnosis) who receives services from the paediatric oncology unit to a do--nothing scenario (defined as no paediatric oncology care). The p_survival_rate_8 represents the probability of survival in the first 8 months of treatment. Similarly, p_survival_rate_16 is the probability of survival in 9–16 months of treatment, and p_survival_rate_24 is the probability of survival in 17–24 months of treatment. DALYs, disability--adjusted life years.

oncology unit compared with a do--nothing scenario from a provider perspective (figure 1). As time and recurrence are important considerations in shaping the natural course of cancer patients, state transition models (a cohort--level or individual--level microsimulation) applied to specific childhood cancer types would have been an ideal approach but that would require very detailed epidemiology and effectiveness data for each cancer type from Ethiopia or at least from similar settings to properly map the various clinical scenarios of patients over time (eg, remission, disease progression, recurrence, death) and justifiably populate the state transition models. Lacking such data, we used a decision analytic model and limited the scope of the study to providing only a gross overview of the cost--effectiveness of paediatric oncology care (at a service--platform level) compared with no paedi-atric oncology care to inform the national--level policy dialogue. The cancer--specific cost--effectiveness will be incorporated and addressed as more data become avail-able in the future.

We created a generic model simulating a child with cancer (without specifying the diagnosis) who receives services from the paediatric oncology unit (labelled as paediatric oncology care in figure 1) compared with a do--nothing scenario (labelled as no paediatric oncology care). To estimate costs and effects, the model depicts 2 years of treatment (considering an average cancer treat-ment duration) divided into 8--month treatment inter-vals. We considered the average treatment duration to be around 2 years, as acute lymphoblastic leukaemia (which can take more than 3 years of treatment) was the domi-nant type of cancer at TASH, and we took estimates from other centres with comparable cancer patterns.[30 31] An 8--month treatment interval was chosen, as the reported median time for events to occur (abandonment or death related to relapse, disease progression, treatment toxicity or background death) is around 8 months.[30 31] For the no paediatric oncology care scenario, we assumed that all patients would die at the end of 6 months. For cured chil-dren, our model assumes that some survivors will develop late--treatment chronic complications that will affect their quality of life and shorten their life expectancy compared with other children with background mortality. Two outcomes—survival (event--free survival (EFS)) and death (non--survival)—were used to estimate cost and effects at the end of each 8--month treatment interval, and the probabilities for EFS and death were taken from a litera-ture review in similar settings (table 1 and online supple-mental text S1 and tables S2 and S3). Abandonment, a significant problem in Ethiopia (around 34%),[32] was taken as an event and captured as equivalent to death in our model for the following reasons: (1) most childhood cancer patients in Ethiopia and LICs are diagnosed at a late stage (stage 3–4), and most patients abandon care at an early stage of the treatment phase (due to refusal to start or early discontinuation)[21 31 33 34]; thus, the chance of survival after abandonment is likely very low[35]; (2) TASH was the only oncology centre in Addis Ababa, making it unlikely that children would find alternative better treat-ment elsewhere in the country after abandoning care at the oncology unit unless they travelled abroad; (3) if chil-dren accessed treatment in private health facilities (in the country or abroad), the cost would fall on the patients' guardians and could not be captured in our model, which is from the provider perspective.

The disability of surviving patients was assumed to be better than non--surviving in each treatment interval (table 1). Surviving patients in each treatment interval

Table 1 Model parameters, value ranges and type of distribution used in the probabilistic sensitivity analysis (PSA)

Model parameters, value ranges and distribution type					
Name	**Value**	**Low***	**High***	**Distribution type used in PSA**	**Source**
Average age at diagnosis	7 years				21
Annual case incidence at TASH	1345	1035	1654	Normal	TASH costing study
Average duration of treatment	2 years				30 31
Duration in years of each treatment interval	0.66 (8 months)				
Median duration of events to occur	8 months				30 31
Average survival duration in years of patients on no paediatric oncology care	0.50 (6 months)				Assumed
Life expectancy gap of cured patient compared with children with background mortality	25%	20%	30%	Normal	40
Life expectancy at age 9 years	58.90				52
OPD visits per patient	5.8	5.32	6.88		Estimate from the TASH costing study
OPD visits per patient in the no paediatric oncology care scenario	0.90				53
Bed days per patient	9.10	7.51	10.69		Estimate from the TASH costing study
Bed days per patient in the no paediatric oncology care scenario	1.4†				
Discount rate	3%				38
WTP threshold for Ethiopia in 2019 (USD): 50% of GDP	477				54
Cost (in USD)					
Cost per bed day of paediatric oncology care	39.90‡	28.10	53.70	Gamma	Estimate from the TASH costing study
Cost per OPD visit of paediatric oncology care	37.0	24.30	52.30	Gamma	Estimate from the TASH costing study
Cost per OPD visit in paediatric medical OPDs	14.20				Estimate from the TASH costing study
Adjustment factor for cost of inpatient department (IPD) for non--surviving patient compared with surviving	2.00	1.75	2.25	Normal	Estimated from the TASH costing study
Adjustment factor for cost of OPD for non--surviving patient compared with surviving	1.50	1.3	1.7	Normal	Estimated from the TASH costing study
Event--free survival rate					
Probability of 2--year EFS rate	0.25	0.15	0.35	Beta	4 30 31 41–46 55
Probability of EFS rate in the first 8 months	0.55	0.40	0.70	Beta	30 31
Probability of EFS rate, 9–16 months	0.64	0.59	0.68	Beta	30 31
Probability of EFS rate, 17–24 months	0.71	0.669	0.759	Beta	30 31
Utility					
Disability weight for cured patients	0.07	0.05	0.09	Beta	36
Disability weight for patients with no paediatric oncology care	0.55	0.39	0.71	Beta	36
Disability weight for survived patients in the 9–16 months treatment interval	0.29	0.19	0.38	Beta	36
Disability weight for survived patients in the 17–24 months treatment interval	0.20	0.11	0.29	Beta	36
Disability weight for survived patients in the first 8 months treatment interval	0.37	0.22	0.52	Beta	36
Disability weight of patients with death outcome (across all treatment intervals)	0.54	0.39	0.69	Beta	36

*The low and high values are the range of values for a given variable tested in the one--way and probabilistic sensitivity analyses.
†Taking the proportion of OPD visits between the no paediatric oncology care scenario versus paediatric oncology care (which is 0.155 times that of paediatric oncology care) and using that adjustment factor (0.155 times) to downscale the bed days per capita of the paediatric oncology care scenario to that of the no paediatric oncology care scenario. ‡The unusual cost estimate difference between the cost per OPD visit and cost per bed day is partly explained by how TASH's paediatric oncology unit was structured (radiation therapy was given as an outpatient service) and by the higher IPD service utilisation in the paediatric oncology unit (12 180 bed days compared with 7842 OPD visits), lowering the cost--per--bed--day estimate, even though the IPD accounted for 67% of the oncology unit.
EFS, event--free survival; OPD, outpatient department; TASH, Tikur Anbessa Specialized Hospital.

were assumed to have a better utility compared with their earlier treatment interval status to account for response to treatment and reduced risk of treatment--associated toxicity. Hence, the disability weight progressively fell as they moved from the first 8--month interval to the second (9–16 months), third (17–24 months), and once cured. The disability weight at the first 8 month treatment interval was 0.37, while it was 0.29 at 9–16 months, 0.20 at 17–24 months and 0.07 for cured. The disability weights are taken from the 2019 Institute for Health Metrics and Evaluation estimate for childhood cancer[36] and are measured on a

scale of 0–1, in which 0 equals perfect health and 1 equals death (table 1).

Model parameter inputs and assumptions

The cost--related model parameters were generated through primary data collection (described below), and the health benefit parameters were taken from a literature review of comparable settings, as no local data were avail-able (table 1 and online supplemental text S1 and tables S2 and S3). We conducted a scoping literature review to identify studies documenting the effectiveness of child-hood cancer treatment in African LICs. The literature search was done in six electronic databases, including PubMed, Embase, ScienceDirect, Scopus, Web of Science and African Journals OnLine by combining terminologies covering the spectrum of childhood cancer types, country names (LICs in Africa) and treatment outcomes (survival or mortality). We identified 14 studies fulfilling our criteria and prioritised the evidence based on systematic review or meta--analysis, followed by prospective studies based on cancer registries, multicountry/multicentre studies, and those with large sample sizes, broad cancers coverage, long survival periods and recently conducted studies. We substantiated the survival rate findings from the scoping review using experts' judgements and local evidence on treatment abandonment and survival rates drawn from expert opinion (online supplemental text S1). We set a modest survival rate in our model to avoid biased cost--effectiveness conclusions. We assumed the 2--year childhood cancer survival rate at TASH to be 25%, with a 95% CI of 15% to 35%, despite commonly reported overall survival rates ranging from 35% to 45% in paedi-atric oncology centres in LICs in Africa. Further details on the scoping review process, key findings and transfer-ring approach are provided in the online supplemental text S1 and tables S2 and S3.

Estimation of cost

We conducted a costing study (8 July 2018–7 July 2019) to estimate the annual cost of running the paediatric oncology unit at TASH from a provider perspective, using a mixed (top--down and bottom--up) costing approach (for further details, see, Mirutse MK, Palm MT, Tolla MT, Memirie ST, Kefyalew ES, Hailu D, Norheim OF. Cost of childhood cancer treatment in Ethiopia, submitted for publication). We identified, measured and valued the cost inputs used in running the unit. Direct cost inputs— costs directly attributable to a specific department or service output, such as costs of human resources, drugs/ supplies and medical equipment—were computed by estimating the amounts consumed by the unit in a year (consumed quantity) multiplied by their unit costs. The costs of shared departments or services—including labo-ratory, radiation, imaging, pathology, surgical operating room, ICU, paediatric emergency services, inpatient food services, laundry, utilities (rent, electricity, tele-communication, water and other utility charges) and other overhead costs (operating expenses such as office supplies, printing, educational supplies, fuel, per diems and training costs)—were costed by allocating the share of those services used by the paediatric oncology unit; we used various allocation bases appropriate to each case (for further details, see, Mirutse MK, Palm MT, Tolla MT, Memirie ST, Kefyalew ES, Hailu D, Norheim OF. Cost of childhood cancer treatment in Ethiopia, submitted for publication).

Finally, the total cost of the unit was computed by adding the direct cost, the indirect costs from the interme-diate departments and the overhead cost. We converted the total cost to USD using the mean exchange rate for 2019. We computed the number of OPD visits per patient during the 8 months, cost per OPD visit, 8--month bed days per patient and cost per bed day. The 8--month OPD visits per patient were computed by dividing the total annual OPD visits of the paediatric oncology unit (7842) by the annual number of patients (1345), and this annual estimate was adjusted for 8 months (taking an 8 month share). The same techniques were used for the 8--month bed days per patient by using the total annual bed days (12 180) and annual number of patients. The costs per OPD visit and per bed day were calculated by integrating the annual OPD and IPD cost estimate and the annual OPD and IPD utilisation statistics report. Then, for each 8--month treatment interval, we estimated the cost of OPD and IPD in each arm and aggregated the total cost. We used the costs of OPD and IPD of non--surviving patients as 1.5 and 2 times the costs of OPD and IPD of surviving patients, respectively, as they are likely to use more and/or expensive services. These estimates were derived from the costing study at TASH, taking into account the cost distri-bution between regular OPDs and departments related to critical patients and the anticipated service utilisation patterns between surviving and non--surviving patients. However, it is also possible the cost of non--surviving patient to be lower than surviving patient given the high rate of treatment abandonment in Ethiopia, which affects the non--surviving arm in our model and such assump-tion lowers the cost of running the paediatric oncology unit at TASH (as the model assumes the overall survival rate at TASH to be 25%); hence, it will shift the conclu-sion towards cost--effective and vice versa in the case of surviving patient cost more than non--surviving patient assumption. We chose a more conservative assumption (the non--surviving patient costing more than surviving patient) so as not to bias the results towards overstating cost--effectiveness and as the alternative assumption will not change the conclusion.

We discounted costs using the global discounting rate (3%)[37] for 1 year, as cost was captured only over a 2--year treatment period.

Estimation of health benefits

We used the number of DALYs averted as the effective-ness measurement metric.[38 39] The following formula was used to compute the DALYs:

DALYs = years of life lost (YLL) + years lived with disability (YLD)

For the no paediatric oncology scenario, we estimated the YLD by assuming that patients would survive for only 6 months without treatment (we multiplied the disability weight without treatment by the average survival dura-tion) (table 1), and we computed the YLL by taking the difference between the age of death and life expec-tancy at that specific age. We compared both scenarios to a theoretical worst--case situation in which a child dies immediately after cancer diagnosis.

To estimate DALYs averted, we used combinations of model variables (table 1): annual number of new cases, average age at diagnosis, average duration of treatment, EFS rate at end of treatment intervals, life expectancy at specific age, life expectancy gap related to late recurrence or late treatment adverse effects and disability weight. Table 1 gives further details on the model variables, range of values and assumptions. As there is no cancer survival registry or previously conducted childhood cancer health outcome studies in Ethiopia, treatment outcome--related data were taken from evidence in similar settings.[4 30–32 40–46] We did not use treatment outcome data from high and middle--income countries, as such outcomes would require further investments in quality improvements that were not captured in our costing esti-mate. We discounted DALYs averted by 3% using a life-time horizon to bring future benefits to present value.

Cost-effectiveness analysis

Cost--effectiveness in this generic model was expressed as the incremental cost--effectiveness ratio (ICER) and computed by dividing the incremental costs of intro-ducing a specialised oncology unit by the incremental DALYs averted, that is, due to interventions.

$$ICER = IC/IE.$$

An intervention was considered cost--effective if the ICER was less than 50% of the Ethiopian GDP per capita, and not cost--effective if otherwise.[43] We used TreeAge software to build the decision model and run the cost-- effectiveness analysis.

Uncertainty

We varied cost, EFS, life expectancy gap after treatment and disability weights using the 95% CI reports from the literature review to estimate the effect of the model variables' uncertainty on the estimated result (table 1). We conducted a one--way sensitivity analysis and probabi-listic sensitivity analysis (PSA) with 100 000 Monte Carlo simulations using various distributions (table 1).

Patient and public involvement

This project did not include patients or the public in developing the research questions or designing and conducting the study. There is a plan to disseminate the results of the study to various stakeholders, including asso-ciations and civil societies working on childhood cancer control programmes in Ethiopia.

RESULTS

A total of 1345 children with cancer were treated at TASH from 8 July 2018 to 7 July 2019. The most common cancer types were acute lymphoblastic leukaemia (28%), Wilms tumour (15%) and Hodgkin's lymphoma (12%), followed by rhabdomyosarcoma, retinoblastoma, neuro-blastoma and non--Hodgkin's lymphoma (further details included in online supplemental table S1). The total cost of a running paediatric oncology unit per treated child (for 2 years) was USD 901, while it was USD 18 for the no paediatric oncology care scenario (6 months). The IC was USD 876 per treated child. The DALYs averted per treated child for an operating paediatric oncology unit were 2.49, whereas the figure was 0.06 for no paediatric oncology care, and the IE per treated child was 2.43. The ICER was USD 361 per DALY averted (table 2).

The tornado diagram (figure 2) presents the variables and range of values tested in the one--way sensitivity anal-ysis. The length of the horizontal bar indicates an indi-vidual variable's potential level of parameter--impact uncertainty on the ICER estimate. The longer the bar, the greater the impact in the direction of the bar (to the left or right). Accordingly, the five parameters with the greatest potential influence on the ICER estimate were cost per bed day, EFS rate in the first 8 months, cost per OPD visit, EFS rate at 17–24 months and life expectancy gap. In the one--way sensitivity analysis, the uncertainty of individual parameters did not alter the cost--effectiveness conclusion, as the level of impact was lower than the WTP threshold for all individual parameters. We varied the cost of the no paediatric oncology scenario down to zero,

Table 2 ICER of running a paediatric oncology unit compared with no paediatric oncology care at TASH in 2019

Strategy	Cost (USD)	Incremental cost	Effectiveness (DALYs averted)*	Incremental effectiveness	ICER (USD/DALYs averted)	WTP for Ethiopia (2019), USD/DALYs averted
No paediatric oncology care	1907		0.06			477
Paediatric oncology care (unit)	894.95	875.89	2.49	2.43	360.76	

*The DALYs averted were computed in comparison to a theoretical worst--case situation in which a child dies immediately after cancer diagnosis.
DALYs, disability--adjusted life years; ICER, incremental cost--effectiveness ratio; TASH, Tikur Anbessa Specialized Hospital.

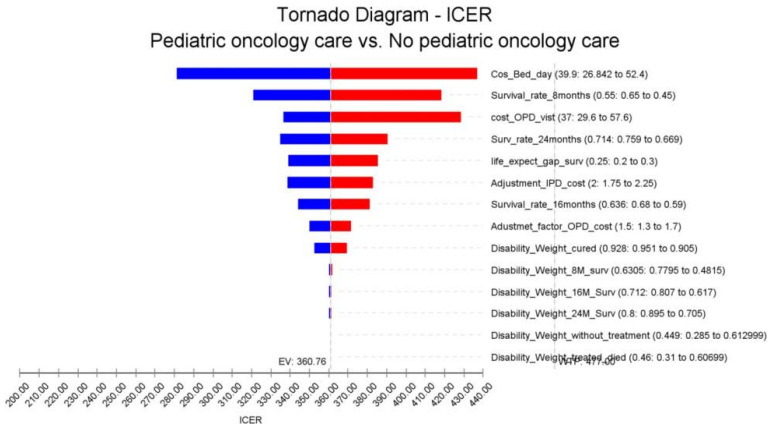

Figure 2 Tornado diagram of the results of the one--way sensitivity analysis of the cost--effectiveness analysis of running a paediatric oncology unit in Ethiopia, summarising the key variables tested for one--way sensitivity analysis, the ranges of values tested and their impacts on the ICER estimate. The longer the horizontal bar, the greater the impact in the direction of the bar (to the left or right). ICER, incremental cost--effectiveness ratio.

but it had a minimal effect, slightly increasing the ICER from USD 362 per DALY averted in the base case to USD 370 per DALY averted.

Figure 3 presents the PSA results. At a WTP of <USD 361, the no paediatric oncology care scenario had a higher probability of being cost--effective. At a WTP of USD 361, the two scenarios had an equal probability of being cost--effective (where the red and blue lines cross in figure 3), and the probability of cost--effectiveness was higher for paediatric oncology care at a WTP of >USD 361. The probability of paediatric oncology care being cost--effective was 100% at a WTP of >USD 600.

In our model, running a paediatric oncology unit was cost--effective compared with a no paediatric oncology

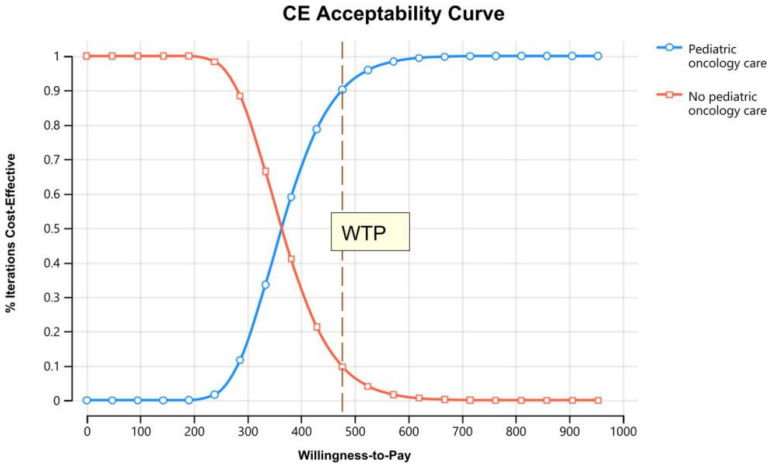

Figure 3 Probabilistic sensitivity analysis for the cost--effectiveness of running a paediatric oncology in Ethiopia. The figure depicts the range of WTP thresholds in which the no paediatric oncology care scenario will have higher probability of being cost--effective compared with paediatric oncology care (WTP<USD 361), indicates when two scenarios reach equilibrium (WTP=USD 361), and shows when the probability of cost--effectiveness of paediatric oncology care will be higher (WTP>USD 361). WTP, willingness-to-pay.

care scenario in 90% of the Monte Carlo simulations (100 000 simulations) at a WTP of USD 477 (based on 50% of GDP per capita for Ethiopia in 2019) as indicated by the broken brown line in figure 3. The highest ICER estimate from the PSA was around USD 600 per DALY averted.

DISCUSSION

Running a paediatric oncology unit is more effective (2.43 DALYs averted per child treated) than a no paediatric oncology care scenario, but it also costs more (USD 876 per child treated). The ICER of running a paediatric oncology unit compared with the no paediatric oncology care scenario is USD 361 per DALY averted, and it is cost--effective using a USD 477 WTP threshold (50% of Ethiopia's 2019 GDP per capita), which is a lower threshold than the commonly used WHO--CHOICE--recommended threshold for very cost-- effective interventions (lower than the 1 x GDP per capita (USD 953) for Ethiopia).[37 47] The results of the Monte Carlo simulation (100 000 iterations) indicate a 90% chance that the ICER will be below the WTP threshold (being cost-- effective). As indicated by the one--way sensitivity analysis, the chance of being cost--effective increases with an improvement in survival rate, which is currently very low in Ethiopia.[21] The WHO Global Initiative for Childhood Cancer and the Disease Control and Priority Cancer module indicate that investing in childhood cancer control programmes will improve survival and is highly cost--effective, affordable and feasible in LMICs[7 22] with prioritisation of certain cancer types, such as acute lymphoblastic leukaemia, Hodgkin's lymphoma, Burkitt's lymphoma, retinoblastoma, Wilms tumour and low--grade glioma (brain tumour). Our ICER finding in the generic model is similar to estimates from Tanzania (USD 323 per DALY averted), higher than reports from Uganda (USD 97 per DALY averted)[48] and lower than reports from Zimbabwe (USD 537 per DALY averted), Ghana (USD 1034 per DALY averted) and Nigeria (USD 2940 per DALY averted).[24 27] The lower ICER estimate in Ethiopia may be related mainly to the low annual cost estimate, which is possibly explained by Ethiopia's low human resource payment scale, heavily subsidised utility costs (eg, water, electricity), service quality differences, unconsidered cost inputs (explained in the limitations discussion), differences in volume of service provided (the high patient volume in TASH compared with that in the other countries could reduce the cost per treated patient) and differences in treatment protocols, childhood cancer patterns and cost--effectiveness analysis approach.

With an annual cost of USD 577 per treated child (which could be as high as USD 1085 when adjusted for suboptimal care), the budget impact of investing in child-hood oncology care may be optimistic, as the population in need of care is small (an annual incidence of childhood cancer of around 3800). Beyond its high potential for cost--effectiveness and low budget impact (hence afford-ability), investing in paediatric oncology treatment could contribute to reducing financial hardship and improving equity. According to a 2014 WHO report, *Making Fair Choices on the Path to Universal Health Coverage*, one defi-nition of the worst off is those with the largest individual disease burden, and children with cancer qualify for that definition, as they face high premature death.[49] Further-more, the Ethiopia Health Sector Transformation Plan and Health Equity Strategic Plan place due emphasis on addressing inequity, and children are among the priori-tised groups.[50 51]

In the current EEHSP,[28] childhood cancer services are less prioritised; for example, three of the six high-- priority childhood cancers identified in the WHO Global Initiative for Childhood Cancers and the Disease Control Priorities—Burkitt's lymphoma, retinoblas-toma and Wilms tumour—are classified as low priority, and two (acute lymphoblastic leukaemia and Hodgkin's lymphoma)[7 22] are classified as medium priority. This may be due to various factors, including a lack of local cost and cost--effectiveness data (leading to a decision based on expert judgement), limitations related to transferring evidence from other countries to Ethiopia's context and the general perception of a high cost of cancer care and of non--affordability in Ethiopia. Suboptimal engagement and alignment with key stakeholders (within and outside the sector) in the childhood cancer programme may also contribute to this; for example, the goals and target set in the NCACCP contradict the EEHSP revision's priority results, although both were developed by the same organ-isation and the EEHSP was endorsed soon after the NCACCP. Our results support recent calls by WHO to emphasise childhood cancer, and they provide evidence for the NCACCP strategy to expand paediatric oncology units in Ethiopia.

Our study has many limitations in terms of cost and effect estimation. The true cost of running a paediatric oncology unit may be larger than our estimate for the following reasons: (1) our estimate did not capture the start--up capital investment, such as building costs and the cost of training specialists (eg, oncologists, specialised nurses and pathologists); (2) the availability of critical diagnostic service, imaging, drugs and supportive care may be suboptimal; (3) direct non--medical costs (eg, transport, lodging) and indirect costs were not captured in our costing exercise; (4) the cost of late treatment adverse effects was not captured; (5) cancers that require advanced and costly diagnosis and treatment such as radiotherapy may not be well represented in our study as such treatment was not readily available in TASH and
(6) despite the rigorous data validation conducted, data quality concerns persist in regards to hospital records in general, and it is almost certain that it was not possible to correct all data errors; this may have introduced bias in the form of both overestimation and underestimation of costs, but underestimation is the highly likely case. Since the cost--effectiveness analysis was conducted for a service delivery platform using average costs and average health outcomes, our model does not capture the clinical scenarios a patient might encounter during the treatment period, and the heterogeneity of childhood cancers could

present differences in unit costs and health outcomes and, consequently, differences in ICER values. As we lacked a survival registry and previous local health outcome esti-mates, our model relied on reports from similar settings, which may not be as comparable as assumed. However, we tried to mitigate the limitation by adopting cautious survival values. Furthermore, the potential impact of these limitations on the ICER estimate was explored in the sensitivity analysis, which considered a reasonable range of input parameters and found minimal to no effect on the final conclusions. Around 90% of the ICER itera-tion results were below the WTP threshold, indicating the relevance of our results. The highest ICER estimate in the PSA is USD 600 per DALY averted, which is fairly close to the WTP.

CONCLUSIONS AND RECOMMENDATIONS

The provision of paediatric cancer services using a special-ised oncology unit is most likely cost--effective in Ethiopia, at least for easily treatable cancer types in centres with minimal to moderate capability. Our findings support Ethiopia's NCACCP strategy to expand childhood oncology units in the country. We recommend reassessing the priority--level decision regarding childhood cancer treatment in the current EEHSP. Childhood cancers' specific cost--effectiveness estimates, along with budget, financial risk protection and equity impact analysis (which can indicate heterogeneity), could better inform priori-tisation among childhood cancers. Improving the child-hood cancer information system, including establishing a cancer registry in Ethiopia, is crucial to informing the childhood cancer control programme with robust evidence.

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Contributors MK led the entire study (study planning, design, data collection and analysis, results interpretation and manuscript write--up) and he is the guarantor of the study. MTP provided critical inputs in the study design, data collection, analysis and manuscript write--up. OFN, MTT and STM provided supervisory support, reviewed, and provided critical inputs to the study proposal, data collection tools, results, and manuscript. DH provided critical inputs in data collection, results interpretation, and enriching of the manuscript. All the coauthors reviewed and endorsed the final manuscript.

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Supplementary material

Table S1. Childhood cancer incidence distribution in Tikur Anbessa Specialized Hospital (TASH), 2018–2019

Diagnosis	**Share: N (%)***
Acute lymphoblastic leukemia	378 (28.1%)
Wilms tumor	197 (14.6%)
Hodgkin's lymphoma	161 (12.0%)
Rhabdomyosarcoma	117 (8.7%)
Retinoblastoma	90 (6.7%)
Neuroblastoma	76 (5.7%)
Non-Hodgkin's lymphoma	70 (5.2%)
Acute myeloid leukemia	48 (3.5%)
Osteosarcoma	47 (3.5%)
Ewing sarcoma	31 (2.3%)
Nasopharyngeal cancer	27 (2.0%)
Other cancers**	104 (7.7%)
Total	1,345 (100%)

* There may be under representation of certain cancer types that require advanced diagnosis and treatment modalities such as radiotherapy, as it is not readily available in TASH.

**Angiosarcoma, germ cell tumor, sacrococcygeal teratoma, yolk sack tumor, Burkitt lymphoma, hemangioma, soft tissue sarcoma, Kaposi sarcoma, neuroblastoma, chronic myeloid leukemia, thymoma

Supplementary text S1

Scoping review of childhood cancer survival rates in low-income countries in Africa

We conducted a scoping literature review to identify studies documenting the effectiveness of childhood cancer treatment in low-income countries (LICs) in Africa. The literature search was done in six electronic databases, including PubMed, Embase, ScienceDirect, Scopus, Web of Science, and African Journals OnLine by combining terms covering the spectrum of childhood cancer types, country names (LICs in Africa), and treatment outcomes (survival or mortality). The searches were not restricted by publication type, but priority was given to randomized control trials, systematic reviews, and meta-analysis papers summarizing important findings related to the purpose of this study. References reported in English, published in 2000–2019, and focusing on the treatment of childhood cancer (age 0–19 years) were included.

Following a review of titles, abstracts, and full texts, 14 studies were identified that met the eligibility criteria. Table S2 summarizes the basic characteristics of the reviewed papers. Overall, the studies varied greatly in scope, including in the number of centers and cancers covered, in sample sizes, and in duration of follow-up. Similarly, the estimated survival years reported in the studies were heterogeneous, with some estimating the 5-year event-free survival (EFS) rate while others used a 4-, 3-, 2-, or 1-year EFS rate. The estimated EFS rate for a given cancer also differed among pediatric oncology centers, which may be explained mainly by differences in access to care, quality of service, and available social support. We prioritized evidence from systematic reviews or meta-analyses, followed by that from prospective studies based on cancer registries, multicountry/multicenter studies, and those with large sample sizes, broad cancer coverage, long survival periods, and recently conducted studies. Generally, most of the mean EFS rate estimates (for two years and beyond) fell in the range of 35%–45%, some in 25%–35%, and very few above 50% (Table S2).

To assess the comparability of pediatric oncology centers, we reviewed available evidence on the basic characteristics of the pediatric oncology units in which the survival estimates were conducted. It was not possible to obtain adequate, detailed published data for most of the centers, however, so it was difficult to reach a conclusion on their comparability with high certainty given the limited availability of detailed information on medical infrastructure, human resource (number, mix, skill), consistent availability of diagnostics, therapeutic and clinical supportive care, and the comprehensiveness of social support. However, we found little difference among the centers when assessing them using gross level parameters (Table S3).

Generally, it was difficult to adopt a single EFS rate value in our model; this was because the EFS rate estimates were disease specific (rather than overall EFS rates for all childhood cancers in a given oncology unit), because of differences in the pattern of cancers admitted to the centers, because of methodological difference in the EFS estimates, and because of the difficulty of ascertaining the comparability between TASH and the other centers. We used the scoping review to guide our EFS rate assumption in TASH rather than transferring a specific value from the studies. Even though most of the authors of the present study believed that the overall EFS rate at TASH ranged from 30% to 40%, we adopted 25% in our model to be on the safe side in avoiding biased cost-effectiveness conclusions. The 25% EFS rate assumption in our model was further triangulated with a treatment-abandonment rate study based on experts' judgments in three of the four pediatric oncology units in Ethiopia, in which the centers' nurses and pediatric oncologists were asked to describe the magnitude of and risk factors influencing treatment abandonment in their center (1). They were also asked about the overall survival rate of children with cancer in their center as follows: "At your center, what proportion of children diagnosed with cancer die within the first five years from diagnosis?" The perceived mean treatment abandonment rate in Ethiopia was high at 34%, with a 95% CI of 29.7%–39.7%. The mean perceived five-year EFS rate as judged by nurses and pediatric oncologists (N=27) was 37.5% (95% CI: 31.5%–44.0%), and the estimate by pediatric oncologists (N=3) was 25% (95% CI: 10%–40%). These findings were accounted for adopting a modest survival assumption in TASH.

We tested the robustness of our modeling by taking a low (15%) and high (35%) EFS rate. We used the 15% EFS rate to account for low estimates by some studies, such as a modeling-based survival rate prediction in LICs by Ward et al. and Atun et al. (2, 3), who used the global cancer registry to estimate the overall survival rate for Eastern African countries at 8.4% (95% CI: 4.4%–14.0%). However, this estimate was at the national level rather than at a specialized oncology center, so it will obviously be lower than the rate in a specialized center, which is the main interest of our study. Hence, we used the EFS rate of 15% as a lower bound in our

sensitivity analysis, as almost all the scoping review findings from pediatric oncology centers are above 20%.

Table S2. Characteristics of the studies included in the literature review.

Cancer type	Author	Country	Title	Study type	Follow-up duration/ estimated survival period	Number of patients	Findings
Acute lymphoblastic leukemia (ALL)	Rubagumya et al. (2017) (4)	Rwanda	Outcomes of Low-Intensity Treatment of Acute Lymphoblastic Leukemia at Butaro Cancer Center of Excellence in Rwanda	A retrospective study of ALL patients enrolled in care, July 1, 2012–June 30, 2014	2 years	42	The 2-year event-free survival (EFS) rate was 26% (95% CI: 13%–41%).
ALL	Kersten et al. (2013) (5)	Tanzania	Current Treatment and Outcome for Childhood Acute Leukemia in Tanzania	Retrospective study of patients enrolled January 1, 2008–December 31, 2010 at Ocean Road Cancer Institute; based on chart review	3 years	81	The 2-year EFS rate was 33% (95% CI: 15.9%–37.5%).
ALL	Joko-Fru et al. (2018) (6)	Kenya, Uganda,	Survival from Childhood	Prospective study of children	5 years	527 total patients, 52 with ALL	The mean 5-year survival rate for

		Zimbabwe	Cancers in Eastern Africa: A Population-Based Registry Study	diagnosed with cancers in 1998–2009 who were followed for 5 years from date of diagnosis using a population-based cancer registry in Harari, Kampala, and Nairobi			ALL was 57.8% (95% CI: 32.8%–77.6%) in Nairobi. The 3-year survival in Harare was 29% (95% CI: 10.5%–51.0%).
ALL	Liu et al. (2020) (7)	Uganda	Survival from Childhood Cancer in Kampala, Uganda	A prospective survival study of children diagnosed with cancer in 2010–2014 to estimate survival at 1 and 3 years after diagnosis using the Kampala Cancer Registry	3 years	221 total patients, 19 with ALL	The 3-year EFS rate was 46% (95% CI: 23%–67%).
Non-Hodgkin's lymphoma (NHL), excluding Burkitt's lymphoma	Joko-Fru et al. (2018) (6)	Kenya, Uganda, Zimbabwe	Survival from Childhood Cancers in Eastern Africa: A Populati	Prospective study of children diagnosed with cancers in 1998–2009 who	5 years	527 total patients, 49 with NHL	The mean 5-year survival rate for NHL in Harare was 31% (95% CI: 17%–46%).

			on-Based Registry Study	were followed for 5 years from date of diagnosis using a population-based cancer registry in Harari, Kampala, and Nairobi			
NHL, excluding Burkitt's lymphoma	Liu et al. (2020) (7)	Uganda	Survival from Childhood Cancer in Kampala, Uganda	A prospective survival study of children diagnosed with cancer in 2010–2014 to estimate survival at 1 and 3 years after diagnosis using the Kampala Cancer Registry	3 years	221 total patients, 18 with NHL	The 3-year EFS rate was 42% (95% CI: 17%–65%).
NHL, excluding Burkitt's lymphoma	Mutyaba et al. (2019) (8)	Uganda	Presentation and Outcomes of Childhood Cancer Patients at Uganda Cancer Institute	A retrospective survival study of children diagnosed with cancer in 2006–2009	1 year	310 total patients, 32 with NHL	The 1-year EFS rate was 43% (95% CI: 23%–61%).
Hodgkin's lymphoma (HL)	Mutyaba et al. (2019) (8)	Uganda	Presentation and Outcomes of	A retrospective survival study of	1 year	310 total patients, 20 with HL	The 1-year EFS rate was 68%.

			Childhood Cancer Patients at Uganda Cancer Institute	children diagnosed with cancer in 2006–2009			
HL	Ekenze et al. (2020) (9)		Wilms Tumor in Africa: A Systematic Review of Management Challenges and Outcome in Two Decades (2000–2019)	A systematic review of the outcome of Wilms tumor in Africa in 2000–2019; 27 studies involving 2,250 patients were analyzed.			The overall survival rate in Africa was 56.5%. The 2010–2019 overall survival rate in East Africa was 46.1% (95% CI: 25.0%–63.2%).
Wilms tumor	Paintsil et al. (2014) (10)	Malawi, Uganda	The Collaborative Wilms Tumor Africa Project: Baseline Evaluation of Wilms Tumor Treatment and Outcome in Eight Institutes in Sub-Saharan Africa	A retrospective study using a chart review of children diagnosed with Wilms tumor in 2011–2013	End of treatment (not clearly specified)	244 total Wilms tumor patients, 57 from Malawi and 54 from Uganda	The mean survival at end of treatment for the six centers in sub-Saharan Africa was 39%; it was 61% in Malawi and 11% in Uganda. Long-term survival (adjusted for relapse) in the six centers was 25%.
Wilms tumor	Joko-Fru et al. (2018) (6)	Kenya, Uganda, Zimbabwe	Survival from Childhood Cancers in	Prospective study of children diagnosed with cancers	5 years	527 total patients, 108 with Wilms tumor	The mean 5-year survival rate for Wilms tumor was 36% (95%

			Eastern Africa: A Population-Based Registry Study	in 1998–2009 who were followed for 5 years from date of diagnosis using a population-based cancer registry in Harari, Kampala, and Nairobi			CI: 22%–51%) in Harare and 8.6% (95% CI: 0.6%–32%) in Kampala.
Wilms tumor	Axt et al. (2013) (11)	Kenya	Wilms Tumor Survival in Kenya	A retrospective study using a chart review of patients diagnosed with Wilms tumor from January 1, 2008–2012	2 years	133	The 2-year EFS rate was 52.7%
Wilms tumor	Lui et al. (2020) (7)	Uganda	Survival from Childhood Cancer in Kampala, Uganda	A prospective survival study of children diagnosed with cancer in 2010–2014 to estimate survival at 1 and 3 years after diagnosis using the	3 years	221 total patients, 35 with Wilms tumor	The 3-year EFS rate was 30% (95% CI: 15%–47%).

				Kampala Cancer Registry			
Wilms tumor	Mutyaba et al. (2019) (8)	Uganda	Presentation and Outcomes of Childhood Cancer Patients at Uganda Cancer Institute	A retrospective survival study of children diagnosed with cancer in 2006–2009	1 year	310 total patients, 28 with Wilms tumor	The 1-year EFS rate was 44% (95% CI: 22.5%–63.0%).
Retinoblastoma	Joko-Fru et al. (2018) (6)	Kenya, Uganda, Zimbabwe	Survival from Childhood Cancers in Eastern Africa: A Population-Based Registry Study	Prospective study of children diagnosed with cancers in 1998–2009 who were followed for 5 years from date of diagnosis using a population-based cancer registry in Harari, Kampala, and Nairobi	5 years	527 total patients, 88 with retinoblastoma	The mean 5-year survival rate for retinoblastoma in Harare was 23% (95% CI: 9.7%–40.5%), and it was 65% in Nairobi.
Retinoblastoma	Lui et al. (2020) (7)	Uganda	Survival from Childhood Cancer in Kampala, Uganda	A prospective survival study of children diagnosed with cancer in 2010–2014 to estimate survival	3 years	221 total patients, 21 with retinoblastoma	The 3-year EFS rate was 57% (95% CI: 31%–76%).

				at 1 and 3 years after diagnosis using the Kampala Cancer Registry			
Retinoblastoma	Waddell et al. (2014) (12)	Uganda	Improving Survival of Retinoblastoma in Uganda	Eighty-nine patients were prospectively followed in 2009–2013 after treatment with surgery and neoadjuvant chemotherapy at Ruharo Eye Hospital in Uganda			The 2-year EFS rate was 65%.
Retinoblastoma	Waddell et al. (2015) (13)	Uganda	Clinical Features and Survival among Children with Retinoblastoma in Uganda	A national prospective cohort study of children diagnosed with retinoblastoma in 2006–2011, before the introduction of neoadjuvant chemotherapy in Uganda	3 years	282	The 3-year EFS rate was 45% (95% CI: 37%–53%).

Retinoblastoma	Sankara et al. (2020) (14)	Burkina Faso	Epidemio-clinical Features of Retinoblastoma at the Yalgado Ouedraogo University Hospital Center in Burkina Faso: About 32 Cases	A retrospective study of patients diagnosed with retinoblastoma at Yalgado Ouedraogo University Hospital Center, January 2013–2017	5 years	32	The 5-year EFS rate was 34.37%.
Retinoblastoma	Traoré et al. (2018) (15)	Mali	Treatment of Retinoblastoma in Sub-Saharan Africa: Experience of the Pediatric Oncology Unit at Gabriel Toure Teaching Hospital and the Institute of African Tropical Ophthalmology, Bamako, Mali	A prospective study of children diagnosed with retinoblastoma in November 1, 2011–December 31, 2015	4 years and 2 months	88	The 4-year EFS rate was 59% (95% CI: 47.9%–69.5%).
Burkitt's lymphoma	McGoldrick et al. (2019) (16)	Uganda	Survival of Children with Endemic Burkitt's Lymphoma in a	A prospective study of children diagnosed with Burkitt's	4 years	181	The 4-year survival rate was 44% (95% CI: 36%–53%).

			Prospective Clinical Care Project in Uganda	lymphoma in 2012–2017			
Burkitt's lymphoma	Joko-Fru et al. (2018) (6)	Kenya, Uganda, Zimbabwe	Survival from Childhood Cancers in Eastern Africa: A Population-Based Registry Study	Prospective study of children diagnosed with cancers in 1998–2009 who were followed for 5 years from date of diagnosis using a population-based cancer registry in Harari, Kampala, and Nairobi	5 years	527 total patients, 53 with Burkitt's lymphoma	The mean 5-year survival rate for Burkitt's lymphoma in Kampala was 45% (95% CI: 27.5%–61.5%).
Burkitt's lymphoma	Lui et al. (2020) (7)	Uganda	Survival from Childhood Cancer in Kampala, Uganda	A prospective survival study of children diagnosed with cancer in 2010–2014 to estimate survival at 1 and 3 years after diagnosis using the Kampala	3 years	221 total patients, 35 with Burkitt's lymphoma	The 3-year EFS rate was 54% (95% CI: 33%–71%).

				Cancer Registry			
Burkitt's lymphoma	Mutyaba et al. (2019) (8)	Uganda	Presentation and Outcomes of Childhood Cancer Patients at Uganda Cancer Institute	A retrospective survival study of children diagnosed with cancer in 2006–2009	1 year	310 total patients, 87 with Burkitt's lymphoma	The 1-year EFS rate was 55% (95% CI: 42%–67%).
Miscellaneous	Lui et al. (2020) (7)	Uganda	Survival from Childhood Cancer in Kampala, Uganda	A prospective survival study of children diagnosed with cancer in 2010–2014 to estimate survival at 1 and 3 years after diagnosis using the Kampala Cancer Registry	3 years	221 total patients, 42 with Kaposi sarcoma, 19 with rhabdomyosarcoma, and 14 with osteosarcoma	The 3-year EFS rate was 34% (95% CI: 20%–49%) for Kaposi sarcoma, 49% (95% CI: 12%–79%) for osteosarcoma, and 54% for rhabdomyosarcoma.
	Mutyaba et al. (2019) (8)	Uganda	Presentation and Outcomes of Childhood Cancer Patients at Uganda Cancer Institute	A retrospective survival study of children diagnosed with cancer in 2006–2009	1 year	310 total patients, 68 with Kaposi sarcoma	The 1-year EFS rate was 67% (95% CI: 52%–78%).
Overall LIC survival estimate (2, 3)*	Ward et al. (2019) (2); Atun et al. (2020) (3)	Global	Global Childhood Cancer Survival Estimates and Priority-Setting:	Micro-simulation of the 5-year survival rate for close to	5 years		The 5-year survival rate for Eastern African countries was 8% (95% CI:

			A Simulation-Based Analysis	200 countries			4.4%–14.0%).

* The estimate by Ward et al. (2019), Atun et al. (2020) were an average survival rate for all childhood cancers and at a national level while the other study reports were cancer specific and at a specialized pediatric oncology unit level. This may explain the large survival rate estimate difference among the reports.

Table S3. Basic characteristics of the pediatric oncology centers included in the scoping review

Parameters	TASH[a] (1, 10)	QECH[b] (10, 17)	ORCI[c] (5)	UCI[d] (10)	BCER[e] (4, 18)
LIC	Yes	Yes	Yes	Yes	Yes
Dedicated pediatric oncology center	Yes since 2013	Yes since 1997	Yes since 1996	Yes since 2011	Yes since 2011
Patient volume	500–600 (in 2013)	200 (in 2013)	230 (in 2010)	450 (in 2013)	169 (in 2014)
Inpatient beds	40 (in 2013)	24	17 (2010)	23 (in 2013)	
Nurse: patient ratio	1:4 in daytime and 1:10 at night	1:15 in daytime and 1:30 at night	1:15 in daytime and 1:30 at night	1:20 in daytime and 1:40 at night	1:15 in daytime and 1:30 at night
Pediatric oncologist	Trained pediatric oncologists available	Experienced pediatrician	Trained pediatric oncologists available	Trained pediatric oncologists available	Experienced pediatrician
Diagnostics	Chemistry, X-ray, computerized tomography (CT) , pathology, and ultrasound services were available at subsidized cost but mostly inconsistent. Magnetic resonance imaging (MRI) was	X-ray, ultrasound CT, MRI, and pathology were available for free.	X-ray, CT, MRI, pathology, and chemistry were mostly consistently available for free.	X-ray, CT, pathology, and chemistry were available but not MRI.	X-ray, ultrasound, and pathology services were available. Imaging services, such as CT and MRI were provided through referral to another hospital (in 2014).

	not available at the time of the study (2019).				
Therapeutics	Chemotherapy was available at a subsidized cost but inconsistent. Radiotherapy was available but with a long waiting time.	Chemotherapy was available for free.	Most chemotherapy was consistently available for free; radiotherapy was also available.	Chemotherapy was available. Radiotherapy was available in another referral hospital (Mulago National Referral Hospital).	Chemotherapy was available. Radiotherapy was not available in 2014.
Clinical supportive care (ER, ICU, blood service, surgery)	Pediatric ER, ICU, surgery, and blood service were available within the hospital.		ICU was not available.	Surgery was available in another referral hospital (Mulago National Referral Hospital).	ICU and surgery service were provided through referral.
Twinning partnership	Yes	Yes	Yes	Yes	
Social supports	Yes	Yes	Yes	Yes	Yes

[a] TASH: Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia
[b] QECH: Queen Elizabeth Central Hospital, Blantyre, Malawi
[c] ORCI: Ocean Road Cancer Institute, Dar es Salaam, Tanzania
[d] UCI: Uganda Cancer Institute, Kampala, Uganda
[e] BCER: Butaro Center of Excellence in Rwanda

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Appendix 2. Ethical approval

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK vest	Ingvild Haaland		08.09.2020	64245
			Deres referanse:	

Ole Frithjof Norheim

64245 Prioritering av kreft hos barn i Etiopia

Forskningsansvarlig: Universitetet i Bergen

Søker: Ole Frithjof Norheim

Søkers beskrivelse av formål:

This research project will generate new evidence on magnitude and reasons for abandonment, cost-effectiveness of running a specialized paedriatic oncology unit, and cost-effectiveness of treating the most common form of cancer in Ethiopia, acute lymphoblastic leukemia which are prioritized in the national cancer control plan. Such evidence will inform priority setting and resource allocation exercise and help to address barrier to treatment adherence in Ethiopia .

REKs vurdering

With reference to your revised project application received 24.6.2020. The Regional Committee for Medical and Health Research Ethics (REC Western Norway) reviewed the revised application in the meeting 19.08.2020, pursuant to The Health Research Act § 10.

Ethical review

The Committee previously asked for a revised protocol (including questionnaire) on identifying and approaching caretakers, more experienced reviewers, and revision regarding relevance and link between different substudies. The project leader has sent a response letter addressing these issues, with revised protocol, questionnaire and informed consent.

The committee finds that the investigators have answered all the questions satisfactorily. First, they have provided a clearer justification for the project (although one may still

disagree). Second, they have provided a much better informed consent form where it is made clear that the parents are not to be blamed for the non-treatment of their children. Third, they will use more highly trained interviewers that will deal with these sensitive issues.

Decision: Approved

Vedtak

REK vest

Besøksadresse: Armauer Hansens Hus, nordre fløy, 2. etasje, Haukelandsveien 28, Bergen

Telefon: 55 97 50 00 | E-**post**: rek-vest@uib.no

Web: https://rekportalen.no

Godkjent

REC Western Norway approves the project in accordance with the submitted application and revision.

Sincerely

Marit
Grønning
Prof. Dr.med
Committee Chairman

Ingvild Haaland
Committee Secretary

Sluttmelding

Søker skal sende sluttmelding til REK vest på eget skjema senest seks måneder etter godkjenningsperioden er utløpt, jf. hfl. § 12.

Søknad om å foreta vesentlige endringer

Dersom man ønsker å foreta vesentlige endringer i forhold til formål, metode, tidsløp eller organisering, skal søknad sendes til den regionale komiteen for medisinsk og helsefaglig forskningsetikk som har gitt forhåndsgodkjenning. Søknaden skal beskrive hvilke endringer som ønskes foretatt og begrunnelsen for disse, jf. hfl. § 11.

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ቁጥር Ref. No EPHI 6.13/927
ቀን Date 19 NOV. 2020

EPHI-IRB Certificate of Approval

EPHI-IRB MM No.: 072
Protocol Number: EPHI-IRB-268-2020

Protocol Title: Magnitude and Reasons for Childhood Cancer Treatment Abandonment in Ethiopia.		
Primary Investigator	Dr Mizan Kiros	
Institute:	University of Bergen, Norway	
Study site/s	Addis Ababa	
Elements Reviewed (EPHI-IRB AF 01-008/02.0):	☐ Attached	✔ Not attached
Mode of Review	☐ Expedited	✔ Full Board
Decision of the meeting	✔ Approved	

I. Elements approved:
1. Protocol Version No.: 02
2. Protocol Version Date: 11 Nov 2020
3. ICF Version No.: 02
4. ICF Version Date: 11 Nov 2020

II. . Obligations of the PI:
1. Should comply with the standard international & national scientific and ethical guidelines
2. All amendments and changes made in protocol and consent form needs IRB approval
3. The PI should report SAE within 48 hours of the event
4. This approval certificate is valid for only one year (specified below). The PI should Submit continuation request before expire date of approval, if project is to continue.
5. Final report/Thesis should be submitted to the IRB secretariat office (SERO) within two months following completion of the study, and Articles as soon as published

Institutional Review Board Approval Date: **07 Nov 2020**
Approval Period: **From 07 Nov 2020 to 06 Nov 2021**
Follow up report expected in:
6 months ____ 9 months ____ one year ✔

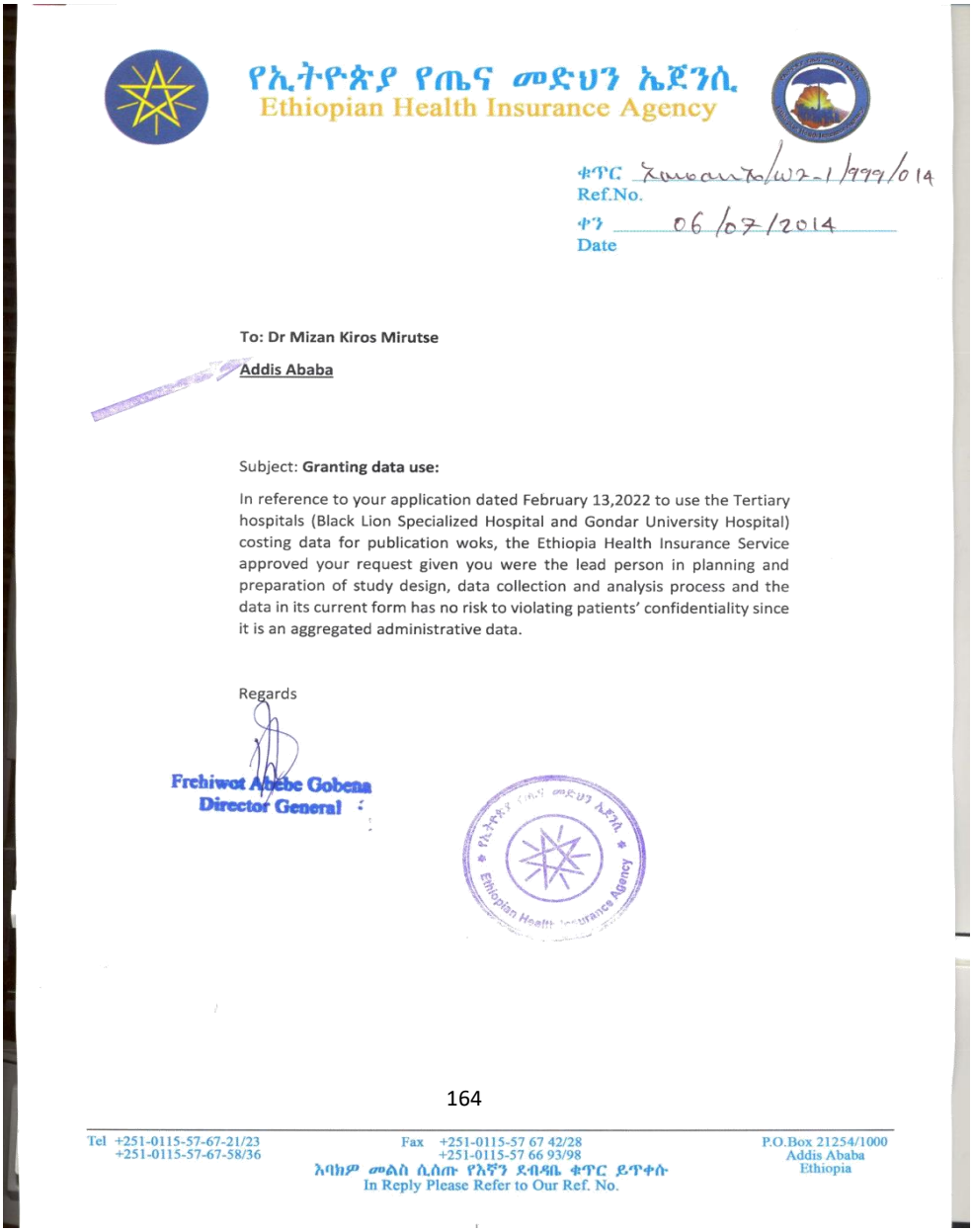
EPHI-IRB Chairperson Name &Signature ____ Date: 19/11/2020

EPHI Director General Name &Signature ____ Date: 18/11/20

The Federal Democratic Republic of Ethiopia * Ethiopian Public Health Institute *

Ebba Abate (Dr)
Director General

Data use approval



የኢትዮጵያ የጤና መድህን ኤጀንሲ
Ethiopian Health Insurance Agency

ቁጥር Ref.No. ጽሕፈቤ/ሠ2-1/999/014

ቀን Date 06/07/2014

To: Dr Mizan Kiros Mirutse

Addis Ababa

Subject: **Granting data use:**

In reference to your application dated February 13,2022 to use the Tertiary hospitals (Black Lion Specialized Hospital and Gondar University Hospital) costing data for publication woks, the Ethiopia Health Insurance Service approved your request given you were the lead person in planning and preparation of study design, data collection and analysis process and the data in its current form has no risk to violating patients' confidentiality since it is an aggregated administrative data.

Regards

Frehiwot Adebe Gobena
Director General

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Ethiopia

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In Reply Please Refer to Our Ref. No.

September 09, 2021

Department of Pediatrics and Child Health

Department Research and Publication Committee (DRPC) Regular Meeting

Minute Number: DRPC/011/13

Date: September 09, 2021 **Time:** 9:00 AM **Place:** DPCH Library (7th Floor)

Present: 1. Dr. Ayalew Moges – Chairperson

2. Dr. Bezaye Abebe – Secretary

3. Dr. Henok Tadele - Member

Excused: Dr. Abdulkadir Mohamedseid – Member, Dr. Rahel Argaw – Member

1. Magnetite of and reasons for childhood cancer treatment abandonment in Ethiopia

   PI- Dr. Mizan Kiros

   Advisors- Professor Ole Frithjof Norheim, Mieraf Tadesse Tolla (MD, PhD, Solomom Tessema Memirie (MD, PhD) and Daniel Hailu Kefenie (MD, Pediatric Oncologist)

   - **Accepted with Minor Comments**

2. Impact of mobile clinical decision support tool on prescription behavior and patient outcome in low resource settings; a pilot trial of self-stewardship in Ethiopia.

   Dr. Workeabeba Abebe (Site PI for TASH)

   PI- Makeda Semret, Nicole Basta, Solomie Jebessa Deribessa (Site PI for SPHMMC) Co-investigators- Cedric Yansouni, Tinsae Alemayehu

   - **Accepted with Major Comments**

Dr. Ayalew Moges

Dr. Bezaye Abebe

1. Dr. Henok Tadele :
2. Dr. Rahel Argaw :
3. Dr. Abdulkadir Mohamedseid :

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