Title: Financial toxicity of cancer care in low and middle-income countries: a systematic review and meta-analysis

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Abstract

Introduction: The costs associated with cancer diagnosis, treatment and care present enormous financial toxicity. However, evidence of financial toxicity associated with cancer in low and middle-income countries (LMICs) is scarce.

Aim: To determine the prevalence, determinants and how financial toxicity has been measured among cancer patients in LMICs.

Methods: Four electronic databases were searched to identify studies of any design that reported financial toxicity among cancer patients in LMICs. Random-effects meta-analysis was used to derive the pooled prevalence of financial toxicity. Sub-group analyses were performed according to: costs; and determinants of financial toxicity.

Results: A total of 31 studies were included in this systematic review and meta-analysis. The pooled prevalence of objective financial toxicity was 56.96% [95% CI, 30.51, 106.32]. In sub-group meta-analyses, the objective financial toxicity was higher among cancer patients with household size of more than four (1.17% [95% CI, 1.03, 1.32]; $p = 0.02$; $I^2 = 0\%$), multiple cycles of chemotherapy (1.94% [95% CI, 1.00, 3.75]; $p = 0.05$; $I^2 = 43\%$) and private health facilities (2.87% [95% CI, 1.89, 4.35]; $p < 0.00001$; $I^2 = 26\%$). Included studies hardly focused primarily on subjective measures of financial toxicity, such as material, behavioural and psychosocial. One study reported that 35.4% (n = 152 of 429) of cancer patients experienced high subjective financial toxicity.

Conclusions: This study indicates that cancer diagnosis, treatment and care impose high financial toxicity on cancer patients in LMICs. Further rigorous research on cancer-related financial toxicity is needed.

Keywords: Cancer, Treatment, Financial Toxicity, Low and Middle-Income Countries,

Introduction

New cases and deaths from cancer continue to increase in low and middle-income countries (LMICs). During the period 2012-18, the annual new cancer cases increased by from 8 million to 9.9 million and cancer deaths increased from 5.3 million to 6.7 million in LMICs (1, 2). Governments have a responsibility of providing appropriate, accessible and affordable services to the increasing number of cancer patients. However, multiple influential factors, such as: unpredictable political climate; inadequately trained cancer care providers; poor coordination; and the increasing cost of cancer care make it difficult to achieve high-quality prevention, early detection, diagnosis, treatment, survivorship and palliative care services (3).

The cost of care is an important barrier to many cancer patients seeking treatment and care. Several LMICs spend about 4% to 7% of their gross domestic product (GDP) on health, with regional differences in patients' ability and willingness to pay for medical and non-medical care (4). In most LMICs, there is little or lack of widespread health insurance coverage. Even among patients with health insurance, many are inadequately protected against the costly demands of cancer care because of high costs of insurance, including higher co-payments and increased deductibles. Cancer patients often spend relatively high out-of-pocket for cancer care (5). The financial support of informal carers is substantial; yet estimates of informal caregiving costs in cancer care have been neglected. Cancer patients and informal caregivers who are often, but not always, family members are vulnerable to losing employment and have a greater risk of personal bankruptcy (6, 7).

There remains a lack of a uniform terminology in the literature to describe the medical and non-medical cancer care costs that result in financial burden for cancer patients and their informal caregivers. A broad definition of financial toxicity was recently proposed as: "the possible outcome of perceived subjective financial distress resulting from objective financial burden" (8). Objective financial burden refers to direct costs and indirect care-related costs while subjective financial distress include material, psychosocial stress, negative emotions and behavioural reactions to cancer care (7, 8). Terms commonly used interchangeably with financial toxicity include financial or economic difficulty, financial hardship, financial risk and economic stress (9). Efforts have been made to develop tools for measuring cancer patients risk of experiencing financial toxicity, which include: COmprehensive Score for Financial Toxicity (COST) (10); Personal Financial Wellness (PFW) Scale (11); and Cancer Survivors' Unmet Needs (CaSUN) measure (12). These tools were developed and/or validated with cancer patients from high-income countries (HICs) in mind. The lack of practical guidance and tools that are psychometrically acceptable across settings in LMICs for identifying cancer patients at risk of developing financial toxicity hinder cancer care providers from implementing policies.

A recent systematic review with included studies mostly from HICs identified that cancer patients who were younger, non-white, unmarried, living with dependents and residing in non-metropolitan service areas are more at risk of financial toxicity (13). There has been proliferation of studies using quantitative design to investigate financial toxicity among cancer patients in LMICs. Hence, it seems

timely to conduct a systematic review and meta-analysis to objectively summarise the results to address significant gaps in terms of designing and implementing innovative strategies in LMICs. The study aimed to determine the prevalence, determinants and how financial toxicity has been measured among cancer patients in LMICs, which will be helpful in future studies of financial toxicity.

Methods

This systematic review followed the preferred reporting items for systematic review and meta-analysis (PRISMA) guideline (14). It was registered with the international Prospective Register of Systematic Reviews (PROSPERO) [CRD42020207205] (15).

Eligibility criteria

The inclusion criteria were as follows: primary studies of any design that reported financial toxicity experienced by cancer patients; studies conducted in any country classified as LMIC by the World Bank Group in 2020 (i.e LMICs are categorised into: low-income countries [$1,045 or less]; low-middle income [$1,046 to $4,095]; and upper-middle-income [$4,096 to $12,695]); studies that focused on people with any type of cancer; studies published in peer-reviewed journals; and in the English language to capture the current complexity of financial toxicity. Editorials, opinion pieces, comments, letters, reviews and studies focused on high-income settings were excluded.

Information sources

Four electronic databases were searched, namely: Ovid Embase; Ovid MEDLINE(R) and In-Process & Other Non-Indexed Citations; Cumulative Index of Nursing and Allied Health Literature (CINAHL); and Cochrane Library. A hand search of the reference lists of included studies was performed to supplement the database search.

Search strategy

Databases were searched on September 7, 2020. The search strategy included terms relating to the following concepts: cancer; cancer patients; delivery of health care; cost of illness; cancer survivors; and LMICs. Medical subject headings, keywords and free text terms were combined using “AND” or “OR” Boolean operators. The initial search strategy was developed in MEDLINE (Ovid) (Supplementary Table 1).

Study selection

Two authors independently screened titles and abstracts of citations retrieved by the search for relevance against the inclusion criteria, and full texts of articles were obtained. Ten per cent of the articles were independently screened by a third author. Disagreements were resolved through discussion.

Data extraction

An electronic data extraction form was developed, and full-text data extraction was performed by three authors. The extracted data was reviewed, discussed in a team meeting and disagreements were resolved through consensus. Data extracted included: general information; study eligibility; setting; cancer type; study design; data collection; participants; outcome measures; and results.

Quality assessment

Two reviewers assessed the quality of the included studies. Qualitative studies were assessed by using the Joanna Briggs Institute Critical Appraisal Checklist for Qualitative Research (16). Quantitative studies were assessed according to the appropriate Joanna Briggs Institute Critical Appraisal Checklist, such as cross-sectional studies (17) and cohort studies (18). Disagreements were resolved by discussion. To enable comparison, each item in the appraisal checklist was rated using a three-point scale, with: “1 = yes; -1 = no; and 0 = not applicable”. The sum was divided by the number of items in the appraisal checklist and multiplied by 100%. The risk of bias scores were categorised as: ≥ 80% (low); 60% to 80% (moderate); and < 60% (high).

Data synthesis and analysis

We used quantitative data to determine the prevalence and determinants of financial toxicity. Meta-analysis was employed for studies that reported quantitative data. A random-effects meta-analysis of odds ratio (OR) was used to calculate pooled data with 95% confidence intervals (CI). Heterogeneity among studies was estimated using the I^2 index, with values classified as: “low heterogeneity” (less than or equal to 25%); “moderate heterogeneity” (26% - 50%); and “high heterogeneity” (greater than 50%) (19, 20). Leave-one-out sensitivity analysis was performed to examine whether single studies had a disproportionally excessive influence. Sub-group meta-analyses were conducted to determine the potential sources of heterogeneity. Forest plots were generated. Probability values below 0.05 were considered statistically significant. Data were analysed using Review Manager 5.3.

Qualitative data investigates how certain coping strategies were adopted to address financial toxicity. A narrative synthesis was undertaken for studies that reported qualitative data by comparing similarities and differences across studies (21). Studies were independently coded by two authors by applying the socio-ecological framework to determine the coping strategies adopted to reduce financial toxicity. Emerging themes were explored, refined and any discrepancies resolved through discussion. The socio-ecological framework is suitable to provide a multi-level perspective and structured approach to understanding coping strategies for reducing financial toxicity among cancer patients in LMICs. It is a four-tier framework for organising factors, which then inform corresponding coping strategies (22). The four levels are: individual; relational; community; and societal levels. Individual level factors relate to person characteristics such as age, gender and health conditions. Relational level factors are defined by direct person-to-person interaction such as family, peer and social support or withdrawal. Community level factors pertain to workplaces, neighbourhoods,

churches and non-governmental/charity organisations. Social level factors include policies, laws, social and cultural norms (22).

Results

The electronic databases searches yielded 4,798 articles, with another two identified through hand search. A total of 324 articles were excluded due to duplication. The title and abstract of remaining articles were screened and 4,398 articles were excluded because they did not meet the inclusion criteria. The full-text of the remaining 78 articles were then reviewed for eligibility, of which 31 were found to be eligible for inclusion. The PRISMA flow diagram provides detail of the screening process (Figure 1).

[Insert Figure 1]

Characteristics of included studies

Table 1 presents the characteristics of included studies. The 31 studies (30 quantitative and one qualitative) were conducted in four different regions, including Asia (China, n = 10; Iran, n = 3; Thailand, n = 3; Turkey, n = 3; Vietnam, n = 2; and Malaysia, n = 2); Africa (Kenya, n = 2; Ethiopia, n = 1; and Morocco, n = 1); Middle East (Jordan, n = 1); South America (Brazil, n = 1); and Europe (Serbia, n = 1), with a multinational study exploring financial toxicity across Malaysia, Thailand, Indonesia, Philippines, Vietnam, Laos, Cambodia and Myanmar (23). The quantitative data were based on 14 retrospective cohort studies, 11 cross-sectional studies, four prospective longitudinal and one observational cohort study. One-third of the studies (n = 10) were published in 2018 and one-fifth (n = 7) in 2019. The total sample size was 120,883, which ranged from 30 to 45692 participants. Majority of the participants were females (n = 65,564). The mean age of the participants was 57.7±7.8 years and ranged from 42 to 72 years. The majority of the studies focused on specific cancer types, such as: lung (24-28); breast (29-31); colorectal (32, 33); liver (34); ovarian (35); prostate (36); and stomach (37).

[Insert Table 1]

Prevalence of objective financial toxicity

Three studies provided the prevalence estimates of objective financial toxicity (38-40) enabling a meta-analysis. The pooled prevalence of objective financial toxicity was 56.96% [95% CI, 30.51, 106.32] (see Figure 2). The random-effects meta-analysis showed that the pooled prevalence of objective financial toxicity among cancer patients varied from 17.73% [95% CI, 15.76, 19.94] to 93.38% [95% CI, 87.21, 99.99] in any cancer type after separating the data on rural and urban in one study (40). Rural dwellers had a substantially higher prevalence of objective financial toxicity estimates (93.38% [95% CI, 87.21, 99.99]). However, the heterogeneity in the ratio of prevalence was extremely high (I^2 = 100%). Objective financial toxicity was categorised into direct medical costs, direct non-medical costs and indirect costs.

[Insert Figure 2]

Direct medical costs

Table 2 presents the results of the mean estimates of cancer care costs using random-effects meta-analysis and sub-group meta-analysis. Direct medical costs were categorised into seven cost items: consultation; diagnosis; treatment, including surgery, radiotherapy, chemotherapy, hormone therapy, combined modalities and palliative/supportive care; inpatient care; outpatient care; and follow-up care. In total, 11 studies presented data on mean direct medical costs (25, 27-29, 31, 36, 37, 39, 41-43). Overall mean direct medical costs were $2,740.18, which ranged from $1,953.62 to $3,526.74 per cancer patient. Components of the overall mean direct medical costs included: $2,366.00 [95% CI, 1920.76, 2811.24] in any cancer type; $1,902.95 [95% CI, $-655.85, $4,461.74] in lung cancer; $4,961.80 [95% CI, $4,892.80, $5,030.80] in stomach cancer; $91.60 [95% CI, $72.87, 110.33] in breast cancer; and $6,141.30 [95% CI, $5,717.88, $6,564.72] in prostate cancer, with GDP per capita ranging from $858 in Ethiopia to $10,262 in China.

Three studies reported data on diagnostic costs (31, 36, 41). Expressed as random-effect estimates, mean diagnosis costs were higher for any cancer type ($138.90 [95% CI, $126.59, $151.21]; $p < 0.00001$), as well as breast cancer in women ($16.02 [95% CI, $15.12, $16.92]; $p < 0.00001$) and prostate cancer in men ($205.80 [95% CI, $168.32, $243.28]; $p < 0.00001$). Consultation costs significantly favoured higher medical costs ($p < 0.00001$) (41). The ratio of consultation costs to GDP per capita ranged from 1.77 to 2.16 in Kenya.

Costs of surgery were measured in three studies from Kenya (41), Vietnam (31) and Iran (36) with GDP per capita ranging from $1,817 to $5,506. The pooled mean costs of surgery were $1,678.80 [95% CI, $62.39, $3,295.20]; $p = 0.04$; $I^2 = 100\%$), which varied greatly from breast cancer ($82.35 [95% CI, $76.86, $87.84]; $p < 0.00001$) to prostate cancer ($3,709.50 [95% CI, $3,396.01, $4,022.99]; $p < 0.00001$). On the other hand, data regarding overall mean costs of radiotherapy were available in two studies (31, 36). A non-significant increase in total mean costs of radiotherapy favouring low costs burden was observed ($4,131.50 [95% CI, $-3,923.69, $12,186.69]; $p = 0.31$; $I^2 = 100\%$), with higher heterogeneity. The ratio of radiotherapy costs to GDP per capita ranged from 0.59 in Vietnam to 154.78 in Iran.

The sub-group meta-analysis of the total costs of chemotherapy favouring high financial toxicity were observed ($6,555.98 [95% CI, $-97.19, $13,014.76]; $p = 0.05$; $I^2 = 100\%$), showing increase mean costs of: $476.48 per breast cancer patients; $1,372.50 per any cancer type; $10,540.00 per lung cancer patient; to $14,181.30 per prostate cancer patient. Two studies presented data on mean costs of combined surgery, chemotherapy and radiotherapy (27, 41), with total costs of $9,888.14 [95% CI, $-4,480.83, $24,257.12] and a substantial heterogeneity ($I^2 = 100\%$). One study reported that combined surgery and radiotherapy for any cancer type resulted in even higher associated direct medical costs ($1,749.35 [95% CI, $1,257.90, $2,240.80]; $p < 0.00001$) (41).

Mean costs of palliative care were measured in four studies from Kenya (41), Vietnam (31), Brazil (43) and Turkey (27) with GDP per capita ranging from $1,817 to $9,042. The random-effects meta-analysis estimated direct medical costs attributed to palliative care as $3,741.28 [95% CI, $2,241.19, $5,241.37]. Also, two studies conducted in Ethiopia (39) and Turkey (29) reported data on costs of outpatient care, which was significantly associated with higher financial burden ($673.03 [95% CI, $488.40, $857.66]; $p < 0.00001$; $I^2 = 85\%$). One study from Vietnam (31) with GDP per capita of $2,715 reported costs of follow-up care in breast cancer patients as $356.24 ranging between $311.36 to $401.12 per patient.

Direct non-medical costs

The total direct non-medical costs as reported by one study from Turkey were $334.00 [95% CI, $333.74, $334.26] per lung cancer patient (28). Direct non-medical costs were observed to be significant ($p < 0.00001$). Components of the direct non-medical costs included disease-related transfer, accommodation, informal and transportation costs. It was observed that mean transportation costs ($162.00 [95% CI, $125.307, $198.693]; $p < 0.00001$) were responsible for 48% of the total direct non-medical costs incurred by lung cancer patients (28). Also, informal costs were associated with significantly higher direct non-medical costs among prostate cancer patients, with mean costs of $2,454.70 ranging between $2,171.84 and $2,737.56 ($p < 0.0001$) (36). The ratio of informal costs to GDP per capita ranged from 39.44 to 49.72 in Iran.

Indirect costs

Two studies conducted in Iran and Turkey with GDP per capita ranging from $5,506 to $9,042 reported quantitative data on indirect non-medical costs (28, 36). The overall pooled mean indirect costs were $2,402.47 [95% CI, $-2,356.15, $7,161.09], with $17.34 [95% CI, $11.87, $22.80] per lung cancer patient and $4,873.93 [95% CI, $3,604.88, $6,142.98] per prostate cancer patient. However, there was high heterogeneity ($I^2 = 98\%$).

[Insert Table 2]

Prevalence of subjective financial toxicity

Included studies hardly focused primarily on subjective measures of financial toxicity, such as material, behavioural and psychosocial. We were unable to provide pooled prevalence of subjective financial toxicity because only one study provided prevalence estimate. The study reported that 35.4% (n = 152 of 429), 11.9% (n = 51 of 429) and 52.7% (n = 226 of 429) of cancer patients experienced high, average and low subjective financial toxicity respectively (44).

One study assessed the psychosocial impact of cancer in 150 family caregivers using the Diagnostic and Statistical Manual of Mental Disorders (45). Depression was more common, with 62.7% (n = 94 of 150) of caregivers reporting at least one depressive signs. Other psychosocial issues identified in one qualitative study were anxiety and social relationships disruption through conflict and criticism (46).

Three studies highlighted coping behaviours at the individual level, which included: using personal savings; selling assets; skipping bill payments; borrowing or incurring bank debt; and delaying/forgoing treatment (39, 47, 48). Two studies identified coping behaviours at the relational level, such as: receiving financial support from family and friends; and emotional support from partners, friends and family members (39, 46). The major coping behaviour at the community level was seeking financial assistance from workplaces, neighbourhoods, churches and non-governmental/charity organisations to cover the financial toxicity imposed on cancer patients and their household (39, 49). There were two main coping behaviours at the social level, which included: creating supportive policies (e.g. a waiver to help cancer patients offset their medical bills); and promoting a pleasant social support environment, such as food, accommodation and transport for treatment programme (46, 49) (see Figure 4).

Determinants of objective financial toxicity

It was challenging to perform a meta-analysis of the factors associated with subjective financial toxicity because the instruments and domains differed across studies. Figure 3 presents pooled estimates of the determinants of objective financial toxicity. The sub-group meta-analyses showed that cancer patients with a household size of more than four were associated with a significant increase in objective financial toxicity (1.17% [95% CI, 1.03, 1.32]; p = 0.02; I^2 = 0%). There was no significant heterogeneity among the three included studies (44, 50, 51). The meta-analysis revealed that cancer patients who received more than six cycles of chemotherapy were almost two times more likely to experience high financial toxicity (1.94% [95% CI, 1.00, 3.75]; p = 0.05; I^2 = 43%). In three of the included studies (38, 39, 51), it was observed that cancer patients who attended private health facilities during the course of their disease were statistically associated with high-level financial toxicity (2.87% [95% CI, 1.89, 4.35]; p < 0.00001; I^2 = 26%). One study indicated that prolonged length of hospital stay was significantly related to cancer patients encountering higher objective financial toxicity (1.88% [95% CI, 1.68, 2.11]; p < 0.00001) (51).

Using data from six studies (23, 38, 40, 44, 50, 51), the pooled estimate for health insurance as a determinant of objective financial toxicity among cancer patients was not a significant factor (1.19% [95% CI, 1.00, 1.42]; p = 0.06; I^2 = 33%). However, according to the leave-one-out sensitivity analysis, the random-effects meta-analysis showed that not having health insurance was a significant risk factor for exposure to objective financial toxicity (1.29% [95% CI, 1.03, 1.61]; p < 0.03; I^2 = 42%) when removing one study from China (40) from the pooled analysis. The sub-group meta-analyses indicate no statistically significant association with cancer-related objective financial toxicity by gender (0.97% [95% CI, 0.65, 1.45]; p = 0.89; I^2 = 70%), stage at diagnosis (1.16% [95% CI, 0.79, 1.70]; p = 0.46; I^2 = 32%), level of education (0.73% [95% CI, 0.27, 2.03]; p = 0.55; I^2 = 97%) or income level (1.74% [95% CI, 0.68, 4.47]; p = 0.25; I^2 = 97%).

[Insert Figure 3]

Measuring financial toxicity

Over one-third of the studies used unvalidated questionnaires to measure the financial toxicity related to cancer care (23, 25, 26, 30, 35, 36, 38, 40, 45, 49, 53). Answers to questions, such as: “How much did you pay for the medical expense last month?”’; and “How much did you spend on the disease-related expenses other than medical expenses?” were often used to measure the objective financial toxicity during cancer treatment and care (25). Catastrophic health expenditure was defined as “when previous one year patient households’ out-of-pocket expenditure for cancer care exceeded 10% of total annual household income” (39). One study applied a pre-existing generic financial assessment instrument, namely the PFW scale, which consists of: five items on the psychosocial; two items on financial resources; and one item on coping strategies (44). One study utilised the Chinese version of the cancer-specific Comprehensive Needs Assessment Tool (CNAT) (52). One-fifth of the studies obtained financial information through hospital billing systems (27-29, 31, 33, 42, 43).

Three instruments were used in six studies to measure the health-related quality of life (HRQoL) of cancer patients in general and disease-specific aspects of life (23, 25, 26, 35, 36, 44). The most frequently used HRQoL instrument was the Functional Assessment of Cancer Therapy (FACT). In particular, the FACT is a two-part instrument that assesses general HRQoL related to cancer and cancer therapy (FACT-G) and tumour-specific measures, such as prostate (FACT-P).

Another instrument that was often used in the assessment of HRQoL in cancer patients was the European Quality of Life Five Dimension (EuroQol/EQ-5D), which measured well-being in five dimensions: usual activities; self-care; pain/discomfort; anxiety/depression; and mobility (23, 26). The EuroQol/EQ-5D combines self-assessment with a valuation of quality of life in which full health is scored at “one” and death is “zero”. Two studies used the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), which consists of 30 core items with five functional scales (cognitive, emotional, physical, role and social), three symptom scales (fatigue, pain and vomiting/nausea) and a global health and quality-of-life scale (26, 35).

Quality assessment

Supplementary Figure 1 presents the results of the quality assessment of the included quantitative studies. Sixteen studies achieved an overall low risk of bias. Fifteen of the quantitative studies were mainly rated low on overall quality. Thirteen of the quantitative studies were rated as a moderate risk of bias often because there were no: identification of potential confounders; evidence of strategies to deal with effects of confounding factors; and/or description of statistical adjustment in data. Overall, two of the quantitative studies were rated as high risk of bias because of: outcome measurement; and statistical analysis issues. Outcome measurement issues were due to the use of unvalidated instruments and lack of clear definition and documentation of outcomes. The qualitative study demonstrated low risk of bias. It showed sufficient quality in terms of underlying research method, data collection and analysis (46).

Discussion

This systematic review and meta-analysis describes the prevalence of cancer-related financial toxicity, its determinants and how it has been measured in LMICs based on available data published from 2007 to 2020. The prevalence of objective financial toxicity among cancer patients in LMICs varied significantly, ranging from 17.73% to 93.38%. There are several direct medical costs, direct non-medical costs and indirect costs that impact on cancer patients, their families and friends. For instance, the mean direct medical costs per cancer patients were $2,740.18 and the costs attributable to surgery, radiotherapy, chemotherapy, hormone therapy and palliative care were $1,678.80, $4,131.50, $6,555.98, $1,471.27 and $3,741.28 respectively. Direct non-medical costs, which included disease-related transfer, accommodation, informal and transportation costs were hardly measured in the studies reviewed. Similarly, there is limited knowledge when it comes to measuring subjective financial toxicity and included studies scarcely focused on it. This finding confirms previous observation that there is a lack of accepted definition of subjective financial toxicity (54).

The review shows the frequent use of unvalidated or unreliable instruments for measuring financial toxicity among cancer patients in LMICs. Unvalidated instruments may generate data that do not contribute to a better understanding of cancer patients' financial difficulties because that data cannot be interpreted effectively. Similar results have been reported by a previous systematic review, which synthesised methods for measuring financial toxicity after cancer diagnosis with most of the included studies conducted in HICs, such as United States and United Kingdom (8). Few standardised instruments have been developed and validated in an attempt to quantify financial toxicity in cancer patients. Examples of such instruments include Breast Cancer Finances Survey Inventory (55), PFW Scale (11) and COST (10, 56). These tools were developed in HICs and available mostly in these countries where cancer patients' experience of financial toxicity differ from their counterparts in LMICs. Thus, there is a need to develop a simple and cost-effective instrument that is applicable to LMICs.

The limited data in this study does not show clear evidence that health insurance is a determinant of financial toxicity. Data from six studies did not reach statistical significance (23, 38, 40, 44, 50, 51). However, the inclusion of data from China may in part explain this (40). A recent study has demonstrated that government's health insurance coverage significantly increased utilisation of expensive targeted anti-cancer medicines and improved patient's affordability (57). Despite the insufficient data to examine the relationship between health insurance and financial toxicity, it is critical to implement strategies to make health insurance systems sustainable and facilitate access to affordable cancer treatment and care. Previous studies have also highlighted that rural dwellers are less likely to access cancer treatment and care due to the lack of health insurance, travel distance and financial burden (58, 59). Innovative strategies, such as tele-consultation and cancer patient assisted travel schemes can be implemented to reduce rural-urban health inequities by decreasing out-of-pocket costs.

The review shows that household size of more than four, multiple cycles of chemotherapy and private health facilities are significantly associated with objective financial toxicity. It is well known that cancer drugs remain unaffordable in most LMICs, with large number of cancer patients delaying or skipping treatment resulting in decreased quality of life. To prevent the potential financial and clinical harms, it is critical to provide cost effective cancer care by reducing overuse of anti-neoplastic medication (60). Also, cancer patient groups, health professionals and governments can engage pharmaceutical companies to implement policies or interventions to lower the cost of cancer drugs. The association between large household size and objective financial toxicity is consistent with the literature on financial toxicity in traumatic injury (61). Large household size in most LMICs can be explained by the high infant mortality that translates into insecurity in families about the survival of their children (62). Previous studies have indicated that large number of children results in the decline of parents' participation in the labour force (63). It also reduces household savings which exposes larger families to income shortfalls. Long-term, community ownership, community-led partnership and results-based interventions must be considered to ensure sustainable development, poverty and child mortality reduction in LMICs.

The results from this systematic review and meta-analysis support previous systematic reviews (64-66) and individual studies (7, 9) showing that adult patients with newly diagnosed cancer experience significant objective financial toxicity and impaired HRQoL. It is important to note that the deteriorating HRQoL occurred in several domains, including physical well-being, social well-being, emotional well-being and functional well-being. As demonstrated by a study from HIC, financial toxicity directly impact the complete well-being of gastrointestinal cancer patients with higher earners reporting less challenges with accessing community resources, pain, fatigue, anxiety and depression (67).

The results of this study show that cancer patients in LMICs often need to finance their medical and non-medical costs by using personal savings, selling assets, skipping bill payments, borrowing or incurring bank debt. Waiving medical bills and implementing social policies that assist with necessities, such as food, accommodation and transport for treatment are critical coping strategies to reduce the financial impact on cancer patients and their families. However, previous studies (68, 69) have reported that most African countries have limited or no social protection systems to provide safety nets for patients, thereby forcing unsustainable coping strategies that increase the risk of bankruptcy.

Strengths and limitations

Strengths of this study include the comprehensive search strategies, rigorous selection criteria and a thorough review process. This is the first systematic review and meta-analysis to identify the extent of cancer-related financial toxicity and how it has been measured in LMICs. There are limitations in this study. First, substantial heterogeneity in the included studies was detected. Hence, we applied random-effects model, which allows for the true effect to vary between studies. We also used sub-group analysis to help with the interpretation of results. Second, it was challenging to explicitly model

cost variables and determinants in the meta-analysis due to several reasons, including: incomplete reporting; and the limited number of included studies.

Conclusion

This systematic review and meta-analysis indicates that cancer diagnosis, treatment and care impose high financial toxicity on cancer patients in LMICs. More high-quality research on cancer-related financial toxicity is needed, particularly from Africa. Future research needs to create and validate an instrument that will be available to LMICs to measure financial toxicity in cancer patients.

Declarations

Funding

N/A

Conflicts of interest/Competing interests

The authors declare that they have no conflict(s) of interest.

Ethics approval

This article is based on a secondary analysis of the existing literature and does not contain any studies with human participants or animals performed by any of the authors. The PRISMA guideline for reporting systematic and meta-analysis was followed

Consent to participate

N/A

Consent for publication

N/A

Availability of data and material

All data generated or analysed during this study are included in this published article.

Code availability

N/A

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Authors' contributions

Study protocol and design were developed by AD, VDA-A, FY, ET, DK-M and EKA. All authors contributed to the development of the manuscript. The article search and management were performed by AD. Article screening was completed by ET, EKA and AD. Data extraction was completed by DK-M, FY and AD. Quality assessment and study description were performed by AD and FY. The data analysis was done by AD and consensus discussions and finalising with VDA-A, ET, FY, EKA, DK-M, VV, JY, KAK, SA-S, JK and OK. Table design was completed by AD, DK-M and FY. All authors read and approved the final manuscript.

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