



REVIEW

Health-Related and Economic Burden Among Family Caregivers of Patients with Acute Myeloid Leukemia or Hematological Malignancies

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ABSTRACT

Introduction: Acute myeloid leukemia (AML) is associated with lower survival and greater unmet need compared with some other hematologic malignancies (HMs). Despite differences in acuteness between AML and other HMs, the burden of family caregivers (FCs) of patients with these malignancies offer similar patient experiences. A targeted literature review was conducted to explore FC burden of patients with AML and HM with and without hematopoietic stem cell transplant (HSCT). Instruments to measure and interventions to address FC burden were identified.

Methods: Studies on economic burden and compromised health-related quality of life (HRQoL) associated with FC burden, family

affairs, and childcare from 1 January 2010 to 30 June 2019 were identified through database and hand searches. Published English articles on randomized controlled trials or standardized qualitative or quantitative observational studies were included. FCs were those in close familial proximity to the patient (i.e., spouse, parents, children, relatives, other family members, significant others).

Results: Seventy-one publications were identified (AML, $n = 3$; HM, $n = 29$; HSCT, $n = 39$). Predominant burden categories included humanistic ($n = 33$), economic ($n = 17$), and interventions ($n = 22$); one study was classified as humanistic and economic. FCs lack sufficient resources to manage stressors and experience negative psychological, behavioral, and physiological effects. FCs of patients with HMs reported post-traumatic stress disorder, significant sleep problems, moderate-to-poor HRQoL, and negative impacts on family relationships. Instruments designed to measure caregiver burden were generic and symptom-specific. Educational, expressional, and self-adjustment interventions were used to improve FC burden. **Conclusion:** Findings indicate a need for additional research, public health approaches to support FCs, and effective interventions to address FC burden. Minimizing FC burden and improving quality of life may reduce the overall healthcare service use and allow FCs to more effectively fulfill caregiver tasks. Support systems to alleviate caregiver burden may create

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reinforced integrators, thus positively affecting quality of life and possibly the outcomes of patients.

Keywords: Acute myeloid leukemia; Caregiver burden; Stem cell therapy

Key Summary Points

Acuteness between acute myeloid leukemia and other hematologic malignancies differ, yet the burden on family caregivers of patients with these malignancies offer similar patient experiences.

Studies in acute myeloid leukemia focused on caregivers are sparse despite the low survival rate associated with this disease, and prospective studies in adults and pediatric patients are needed to provide a more comprehensive understanding of the burden on caregivers.

Systematic interventions are needed to support family caregivers of patients with acute myeloid leukemia, hematologic malignancies, and other hematologic malignancies due to hematopoietic stem cell transplant.

Minimizing family caregiver burden and improving caregiver quality of life may reduce the use of overall healthcare services and allow caregivers to more effectively fulfill their roles.

in the USA [1]. Complete remission of AML is achieved with intensive therapy in 60–80% of younger patients and in 40–60% of patients aged 60 years or older. Only 20–30% of patients can achieve durable remissions after reinduction in the relapsed/refractory setting, and the rate of survival after relapse is poor [3]. In addition to poor outcomes that create an unmet need in patients with AML, patients with AML report poor health-related quality of life (HRQoL) and psychological distress [4–6].

Compared to other forms of leukemia, AML is associated with lower 5-year survival and significant unmet need related to treatments and patient quality of life [7, 8]. AML shares similarities with other hematologic malignancies (HMs) in terms of adverse patient outcomes such as economic and humanistic detriments, some of which are shared across both AML and other HMs due to hematopoietic stem cell transplant (HSCT). As such, family caregivers (FCs) such as significant others, caregivers, and family members experience distress when caring for these patients [9, 10]. FCs find themselves under excess levels of stress [11, 12] and may experience burden associated with the shift in responsibility during transition from inpatient to outpatient care [13]. Therefore, FCs may benefit from specifically structured and systematic interventions [14] and appropriate “fit-for-purpose” instruments to assess FC burden. Despite differences in acuteness between AML and other HMs, the literature on FC burden of patients with them offer similar patient experiences. Therefore, we conducted a targeted literature review (TLR) to explore the FC burden of patients with AML and HMs, including any form of leukemia.

INTRODUCTION

Acute myeloid leukemia (AML) is a common form of acute leukemia in the USA [1]. In 2019, there were an estimated 21,450 new cases of acute AML in the USA and 10,920 estimated deaths [2]. The incidence of AML increases with age and patients over 65 years old are diagnosed with AML more frequently than younger patients. The median age at diagnosis is 68 years

METHODS

The primary objectives of this TLR were to explore FC burden of patients with AML, patients with HM (including any form of leukemia) who did not receive HSCT (referred to as HM below), and patients with HM receiving HSCT (referred to as HSCT below). The exploratory objectives were to identify

instruments used to measure FC burden and interventions used to address FC burden.

Literature Search Strategy

The data sources used to identify the relevant studies were published in Pubmed, Embase, MEDLINE® (via Ovid), and Ovid. The database search strings identified all relevant studies (full papers or abstracts from any conferences) indexed in Embase and were modified for MEDLINE and the Cochrane Library, to account for differences in syntax and thesaurus headings. Searches included terms for free text and Medical Subject Heading (MeSH) terms. Search terms included the following: acute myeloid leukemia with multiple spelling variations; hemopoietic stem cell transplantation, stem cell transplantation, or HSCT; caregiver burden, caregiver support, caregiver stress, caregiver strain, family burden, or titles of multiple caregiver indexes and inventories; financial problem, financial toxicity, productivity loss, absenteeism, presenteeism, wage loss, low or low income (Supplementary Table S1).

Eligibility Screening

FC was defined as those in close familial proximity to the patient by family ties, such as spouse, parents, children, relatives, other family members, or significant others. This TLR did not include the burden experienced by healthcare professionals or providers (e.g., nurse practitioners, physicians). The title and abstract of citations identified in the electronic database searches were screened to assess eligibility based on the eligibility criteria. Full publications of studies deemed to be potentially relevant were then obtained and studies assessed on the basis of the full texts. The reasons for exclusion of non-relevant citations were documented descriptively and using a prospectively designed code system. English articles on randomized controlled trials or qualitative or quantitative observational studies published from 2010 to 2019 that fit the following PICOS (P: population, I: intervention, C: comparator, O: outcomes, and S: study design) criteria were

included. The study population included FCs (including spouses, parents, children, relatives, other family members, or significant others) of patients with AML, HM and oncologic diseases who also received HSCT, and patients with HMs including “leukemia” in general. Patients receiving HSCT for reasons other than HM or AML were excluded, as were all other populations that did not meet the eligibility criteria. Papers were not restricted on the basis of intervention or comparisons. Interventions for FC burden management and instruments for FC burden measurement are separately reported.

Studies were included if they reported the following key study outcomes: humanistic burden (i.e., HRQoL, such as distress, post-traumatic stress, anxiety, depression, physical function, social function, role function, emotional function, cognitive function, and mental/psychological burden), economic burden (i.e., productivity challenges, loss of employment, financial burden), or instruments to measure caregiver burden.

Study Selection

Any study was included that reported on economic burden, including studies with indirect costs, and compromised quality of life associated with FC burden while trying to keep work and life balance faced with work, family affairs, childcare (for adults, at least one of whom diagnosed with AML and with children that need care), including HRQoL. Additionally, hand searches were performed on references from select seminal articles and checked for duplication.

Two reviewers independently selected studies for inclusion using pre-specified PICOS eligibility criteria in two phases: (1) title/abstract screening, (2) full-text screening. Discrepancies between the two reviewers were settled by a third reviewer.

Data Extraction

Relevant data from included studies were extracted into a data extraction table in Microsoft® Excel, which collected data on general

information (i.e., title, type of publication, year, authors, country), study characteristics (i.e., study objective, study design, study period, follow-up period, details of interventions/comparators, data analysis methods), participant demographics (i.e., patient and target population characteristics; inclusion criteria, exclusion criteria, number of target population, age, gender, marital status, education level, income level, relationship with patients, if they have children or not), instrument used to measure caregiver burden or quality of life, reported outcomes, author conclusions, and limitations. Data extraction was conducted by a single analyst, and randomly selected 20% of included studies were quality checked by another analyst. Quality assessments were performed of the final articles included in the TLR.

Ethics Compliance

This article is based on previously conducted studies and does not contain any new studies with human participants or animals by any of the authors.

RESULTS

The electronic database search identified 670 citations, of which 147 were identified as duplicates and excluded. The remaining 523 citations were screened on the basis of title and abstract, and 350 were then excluded, leaving 173 citations to be screened on the basis of the full publications. During full-text screening, 127 publications were subsequently excluded, resulting in 44 publications from the electronic database searches to be included in the TLR. Also, 27 additional full-text articles were identified by hand through reference search, resulting in 71 full-text publications included in the TLR (Fig. 1).

The publications were categorized according to the target population of the study: AML ($n = 3$), HM ($n = 29$), and HSCT ($n = 39$). The AML category included papers on AML only. For the HM and HSCT categories, AML may have been included as a HM if other leukemias were also reported. The HM category included papers

that reported FC burden with patients with HM including “leukemia” in general. These studies may have included multiple cancer types as long as they also included “leukemia”, “acute leukemia”, “hematologic cancer”, “hematologic oncologic disease”, or “blood cancer” among the reported cancer types. The HSCT category included publications that reported FC burden of patients with HM receiving HSCT; studies were excluded if patients were receiving HSCT for diseases other than HM (e.g., sickle cell disease, severe infections). The papers were then further categorized into burden categories based on predominant burden described: humanistic ($n = 33$), economic ($n = 17$), and interventions ($n = 22$) (Fig. 2); one study [15] was included in both humanistic and economic categories.

Demographic Characteristics of Patients and FCs

Overall, 65 articles reported demographics characteristics of patients and/or FCs. The most frequently reported demographic characteristics of caregivers included age, gender, marital status, relationship between caregivers and patients, employment status, and income level. With respect to age of patients and caregivers, the mean age of sample adult patients ranged from 40.7 to 64.7 years, and the mean age of sample pediatric patients ranged between 5.6 and 13.4 years. As for the age of caregivers, the mean age of the sample caregivers of adult patients was between 33.1 and 61.6 years, while the mean age of caregivers of pediatric patients ranged from 34.6 to 44.7 years. Among 54 articles that included FC gender, 40 articles reported that at least 60% were female. Among the 46 articles that included marital status, 37 reported that at least 60% of FCs were married. Among papers that reported the relationship between the patient and FC, many (41.7–100%) FCs were spouses of adult patients. Additionally, almost 100% of FCs of pediatric patients were their parents and 48–100% were mothers. Among the 28 papers that reported work status, caregivers were either employed (i.e., active, full-time, part-time, independent worker, other) or not employed (i.e., retired, on leave, homemaker, or

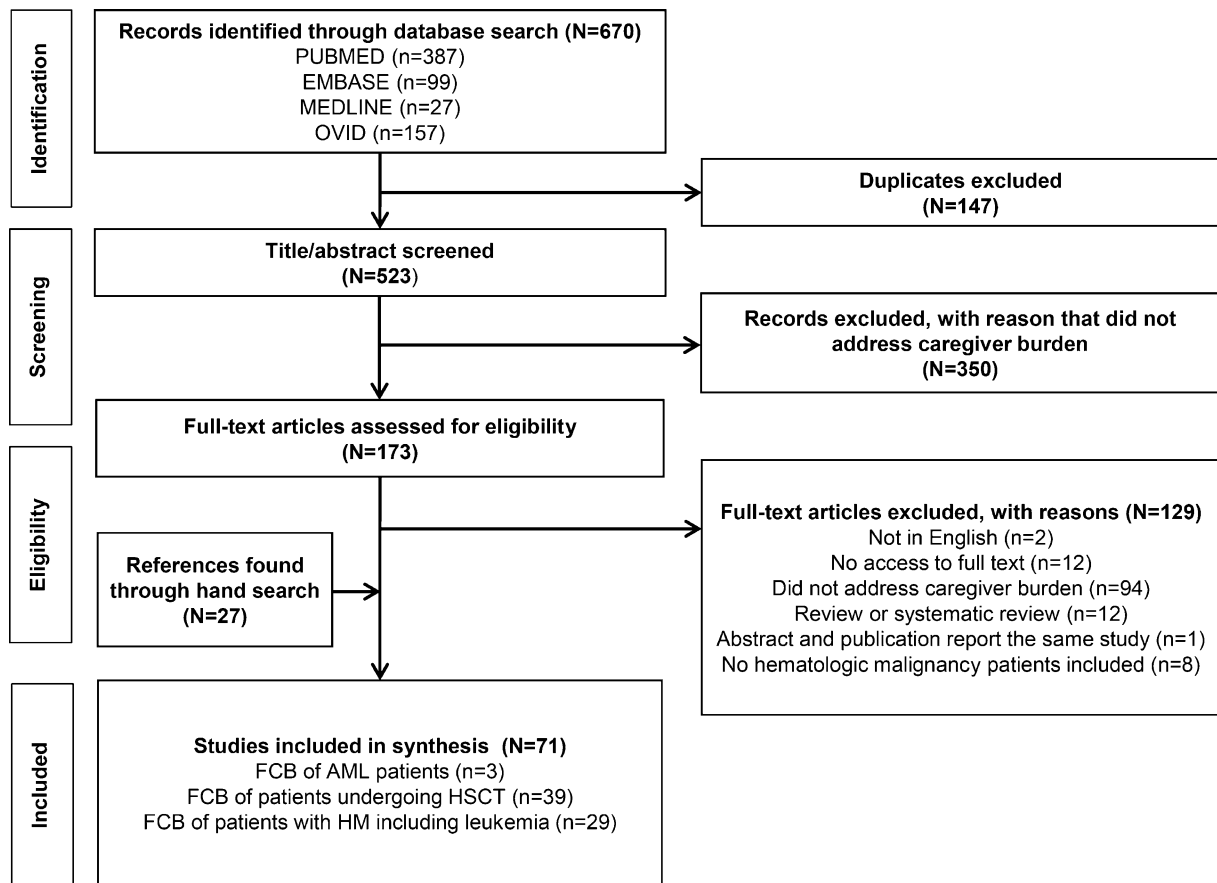


Fig. 1 PRISMA flow diagram. *AML* Acute myeloid leukemia, *FCB* family caregiver burden, *HM* hematologic malignancy, *HSCT* hematopoietic stem cell transplantation

nonactive). For adult and pediatric patients, 15.4–93.8% and 35.3–60.0% of FCs, respectively, were employed full-time.

Humanistic FC Burden

A total of 33 studies examined FC humanistic burden (Table 1). The most common types of psychosocial burden were anxiety, depression, and distress.

Caregivers of Patients with AML

Two articles were identified that reported humanistic FC burden of patients with AML [16, 17]. It was found that negative psychological, behavioral, and physiological impact of FC burden could drive extreme notions [16] in caregivers of patients with AML. As the

intensity of FC burden of patients with AML increased, positive caregiving experience was significantly diminished [17]. Furthermore, positive aspects of caregiving were negatively associated with high levels of burden, with FCs of patients with AML reporting high levels of inconvenience and low levels of care satisfaction [17].

Caregivers of Patients with HM Undergoing HSCT

Twenty-one studies reported humanistic FC burden in patients with HM undergoing HSCT. Sleep and psychosocial burden are often-reported FC burdens associated with HSCT [36, 37]. FCs have significant sleep problems, including sleep disturbance, wake after sleep onset, and insomnia [30, 36, 37]. FCs without proper psychosocial support suffered from

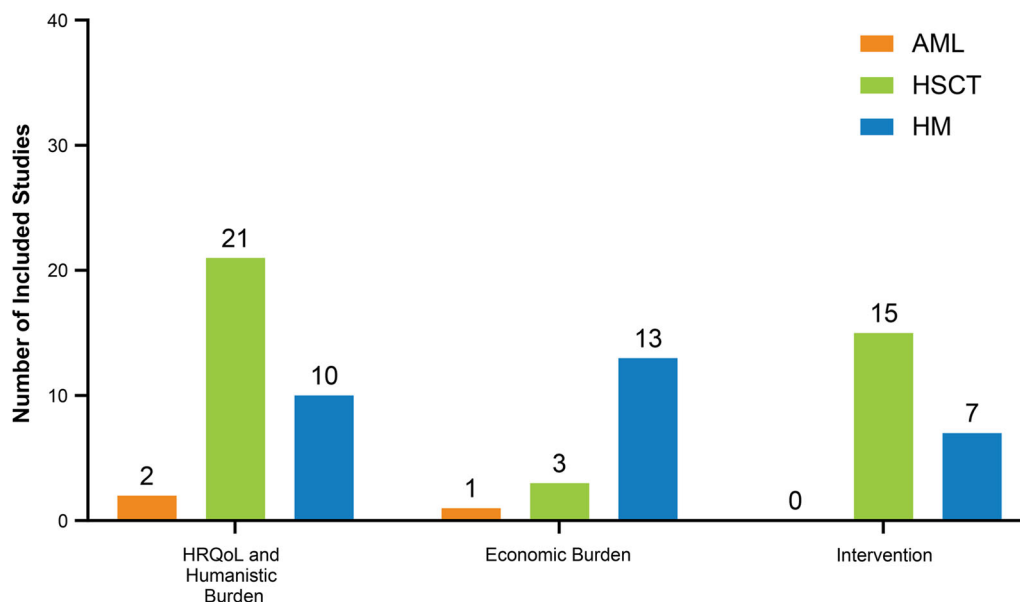


Fig. 2 Summary of included publications by FC type. *AML* Acute myeloid leukemia, *FC* family caregiver, *HM* hematologic malignancy (non-AML), *HRQoL* health-related quality of life, *HSCT* hematopoietic stem cell transplant

significant role strain. Quality of life was moderate to poor for caregivers. The more prepared that caregivers felt in their role, the better they felt about the care they were providing [21]. In terms of psychosocial burden, anxiety, depression, stress, and distress were among often-reported psychological burdens experienced by FCs [26, 31]. One study of patients scheduled to undergo HSCT revealed that their caregivers reported higher levels of anxiety and depression than the patients ($P < 0.01$); additionally, 30% of caregivers versus 17% of patients were clinically anxious [31]. More seriously, high levels of anxiety and distress were shown to lead to post-traumatic stress disorder (PTSD) and adverse outcomes for both the patient undergoing allogeneic HSCT and the FC. A study assessing the rates and risk factors for PTSD among patients undergoing HSCT and their FCs revealed that rates of PTSD were significantly higher among FC than patients (6.6% vs 3.3%; $P = 0.02$) [26]. Moreover, FCs also reported fatigue, and negative experience in sexual and family relationships [30].

Caregivers of Patients with HMs Including Leukemia

Ten studies reporting humanistic caregiver burden of adult and pediatric patients with one of multiple forms of cancer that included HM/leukemia were also identified. Over 75% of adult patients with HMs received informal care. Being male (OR = 0.26), having a partner (OR = 0.14), and being employed (OR = 0.11) were associated with lower likelihood of receiving informal care (95% CI not reported; significance level ≤ 0.10) [45]. Patients diagnosed with acute leukemia were 6.4 times (95% CI not reported; significance level ≤ 0.05) more likely to receive family care (informal care) during the pre-transplant period relative to patients with lymphoma, and 42.2 times (95% CI not reported; significance level ≤ 0.01) more likely to receive it during the second and third year of post-transplantation [45].

The burden experienced by children who were caregivers of their parents differs from that of parent caregivers. Adult children-caregivers of their ill parents with high parent-patient dependency (vs lower dependency) reported higher PTSD, higher caregiver burden, and higher dissatisfaction with social support, which played a significant mediator role

Table 1 Summary of articles by burden or intervention

	Study country ^a	Design (intervention type; if applicable)	Specific instruments to measure burden ^b	Number of caregivers	Population age group
Health-related quality of life and humanistic burden					
AML					
Bevans and Sternberg [16]	USA	Case report	Instrument not specified	1	Adult
Grover [17]	India	Cross-sectional study	SPACE, FBI, CSI	30	Adult or pediatric
HSCT					
Bergkvist [18]	Sweden	Case series	Non-specific instrument (semi-structured interviews)	14	Adult
Bevans [19]	USA	Prospective cohort study	BSI-18, Distress Thermometer	91	Adult
Coleman [20]	USA	Cross-sectional study	General Sleep Disturbance Scale	17	Pediatric
Cooke [21]	USA	Cross-sectional study	SIP (Sleep and Rest, Emotional Behavior, Home Management, Ambulation, Recreation & Pastimes scales); Scales to measure caregiver concepts of mutuality, preparedness, predictability, and rewards of caregiving; City of Hope QOL Scale Family	56	Adult
Deniz and Inci [22]	Turkey	Cross-sectional study	Burden Interview; CQOL-C	123	Adult
Jim [23]	USA [24]	Cross-sectional study	Non-specific instrument (focus group interview questionnaire)	16	Adult
Larsen [25]	Denmark	Cross-sectional study	Non-specific instrument (semi-structured in-depth interviews)	16	Pediatric
Liang [26]	USA	Retrospective cohort study	PCL, Cancer and Treatment Distress scale	333	Adult
Norberg and Forinder [27]	Sweden	Cross-sectional study	PCL, HADS-Anxiety and HADS-Depression, SMBQ	284	Pediatric
Norberg [28]	Sweden	Cross-sectional study	SMBQ	285	Pediatric

Table 1 continued

	Study country ^a	Design (intervention type; if applicable)	Specific instruments to measure burden ^b	Number of caregivers	Population age group
Pai [29]	USA	Multicenter prospective study	PAT-HCT	140 (Part 1) and 12 (Part 2)	Pediatric
Polomeni [30]	France	Cross-sectional study	FACT-BMT, WHO-QOL-Bref, DAS	48	Adult
Posluszny [31]	USA	Cross-sectional study	SF-36, HADS, Cancer and Treatment Distress Scale Acute version (caregiver version), General Self-Efficacy Scale; instruments measuring perceived threat and relationship quality	110	Adult
Riva [32]	Sweden	Cross-sectional study	HADS, SMBQ, PCL (civilian version), and the post-traumatic growth inventory	260	Pediatric
Rodday [33]	USA	Prospective cohort study	PREMO screener, Structured Clinical Interview for DSM-IV Axis I Disorders	117	Pediatric
Sands [34]	USA	Cross-sectional study	BAI, BDI, IES-revised, Mental Health Inventory positive well-being scale	108	Pediatric
Sannes [35]	USA	Cross-sectional study	PSQI, PSS, CESD, POMS, STAI, IES, SF-36–Mental Health component	140	Unspecified
Sannes [36]	USA	Cross-sectional study, secondary exploratory analysis	PSQI, PSS, CESD, POMS-TMD, STAI, IES	124	Adult
Simoneau [37]	USA	Cross-sectional study	POMS, CESD, STAI, IES, CRA; SF-36; PSQI	109	Adult
Vrijmoet-Wiersma [38]	Netherlands	Cross-sectional study	General Health Questionnaire, PIP-SF, Child Vulnerability Scale	73	Pediatric

Table 1 continued

	Study country^a	Design (intervention type; if applicable)	Specific instruments to measure burden^b	Number of caregivers	Population age group
Ward [39]	USA	Cross-sectional study	BAI, BDI, PSS, Parent Stress Scale, SF-36, Physical Symptom Inventory	61	Pediatric
HM/leukemia					
Aung [15]	Singapore	Cross-sectional study	Impact-On-Family Scale	79	Pediatric
Fladeboe [40]	USA	Prospective cohort study	Sibling Relationship Questionnaire, Negative Life Events Scale for Children (adapted), Treatment-Related Events Questionnaire, Economics In My Family Questionnaire, Assessment of Life Threat and Treatment Intensity Questionnaire	103	Pediatric
He [41]	China	Cross-sectional study	Parental Perception of Uncertainty Scale (Chinese version), Coping Health Inventory for Parents (Chinese version), Coping Health Inventory for Parents (revised), Growth Through Uncertainty Scale	95	Pediatric
Iwai [42]	Japan	Cross-sectional study	Non-specific instrument (questionnaire survey)	27	Pediatric
Nam [43]	USA	Cross-sectional study	IES, IES intrusion and avoidance subscales	357	Pediatric
Olgunju [44]	Nigeria	Cross-sectional study	CESD-revised	72	Pediatric
Ortega-Ortega [45]	Spain	Cross-sectional study	Non-specific instrument (questionnaire)	139	Adult or pediatric
Patel [46]	USA	Cross-sectional study	Parenting Stress Index-Short Form	44	Pediatric
Sulkers [47]	Netherlands	Prospective cohort study	PIP-D, CESD, STAI-Short Form, SF-20	95	Pediatric

Table 1 continued

	Study country ^a	Design (intervention type; if applicable)	Specific instruments to measure burden ^b	Number of caregivers	Population age group
Teixeira and Pereira [48]	Portugal	Cross-sectional study	DASS-21, IES-revised, Satisfaction with Social Support Scale, Burden Assessment Scale	214	Adult
Economic burden					
AML					
Hong [49]	China	Cross-sectional study	Non-specific instrument (survey)	474	Pediatric
HSCT					
Denzen [50]	USA	Cross-sectional study	Socioeconomic Wellbeing Scale	16	Adult
Farnia [51]	USA	Case report	Non-specific instrument (cost comparison)	2	Adult
Majhail [52]	USA	Cross-sectional study	Non-specific instrument (baseline survey, bi-weekly diary, structured interview)	25 patients/caregivers	Adult or pediatric
HM/leukemia					
Aung [15]	Singapore	Cross-sectional study	Impact-On-Family Scale	79	Pediatric
Bona [53]	USA	Cross-sectional study	Survey about Caring for Children with Cancer questionnaire	71	Pediatric
Dussel [54]	USA and Australia	Cross-sectional study	Non-specific instrument (semi-structured parental survey)	141 (US) and 89 (Australia)	Pediatric
Fluchel [55]	USA	Cross-sectional study	Non-specific instrument (primary caretaker survey)	354	Pediatric
Ghatak [56]	India	Cross-sectional study	Non-specific instrument (cost diary)	50	Pediatric
Hollenbeak [57]	USA	Retrospective cohort study	Non-specific instrument (cancer survivor survey)	827	Adult
Kale and Carroll [58]	USA	Cross-sectional study	Cancer Self-Administered Questionnaire	1380 ^c	Adult or pediatric

Table 1 continued

	Study country^a	Design (intervention type; if applicable)	Specific instruments to measure burden^b	Number of caregivers	Population age group	
	Ortega-Ortega and Del Pozo-Rubio [59]	Spain	Longitudinal study	Non-specific instrument (questionnaire)	139 ^c	Adult
	Ortega-Ortega and Montero-Granados [60]	Spain	Retrospective cohort study	Non-specific instrument (questionnaire)	123 ^c	Adult
	Rativa Velandia and Carreno Moreno [61]	Colombia	Cross-sectional study	Non-specific instrument (questionnaire and family survey)	50	Pediatric
	Santos [62]	Portugal	Cross-sectional study	Impact on Family Scale-financial subscale, Family Ritual Questionnaire, HADS	244	Pediatric
	Sneha [63]	India	Cross-sectional study	Non-specific instrument (structured questionnaire)	70	Pediatric
	Warner [64]	USA	Cross-sectional study	Non-specific instrument (survey)	254 ^c	Pediatric
Interventions						
HSCCT						
	Badia [65]	USA	Cross-sectional study (self-adjustment)	Not applicable ^c	NA	Adult or pediatric
	Bevans [66]	USA	Prospective cohort study (Educational)	BSI-18, SPSI-R, FACES IV, SDS	8	Adult
	Bevans [67]	USA	Prospective cohort study (Educational)	BSI-18, CASE-t, Family Caregiving Inventory Mutuality Scale, MFSI-SF, PSQI	53	Adult or pediatric
	Devine [68]	USA	Cross-sectional study (Educational)	Awareness and Barriers to Counseling-Revised	312 (218 enrollees and 94 decliners in sub study)	Pediatric

Table 1 continued

	Study country ^a	Design (intervention type; if applicable)	Specific instruments to measure burden ^b	Number of caregivers	Population age group
Fauer [69]	USA	Prospective cohort study (Health technology)	Perceived Usefulness, PAM-C, CQOL-C, STAI, POM-2 [®] , POMS-2 [®] -depression, vigor, and fatigue subscales	39	Adult or pediatric
Kim [70]	USA	Cross-sectional study (Expressional)	POMS	6	Adult
Kroemeke [71]	Poland	Prospective cohort study (Expressional)	Berlin Social Support Scales (adapted), PANAS-Expanded Form	200	Adult
Langer [72]	USA	RCT study (Educational)	DAS, POMS-SF	121	Adult
Langer [73]	USA	RCT (Expressional)	PANAS-positive affect and negative affect subscales	58	Adult
Langer [74]	USA	Prospective cohort study (Expressional)	Non-specific instrument used (in-session ratings of communication)	40	Adult
Laudenslager [14]	USA	RCT (Educational)	PSS, CESD, STAI, CRA, POMS-TMD, PSQI, SF-36 summary scales, IES	148	Adult
Laudenslager [75]	USA	RCT (Educational)	PSS, CESD, STAI	24	Adult
Manne [76]	USA	Cross-sectional analysis from an RCT (Educational)	BAI, BDI, IES, Mental Health Inventory-positive well-being scale	218	Pediatric
Ouseph [77]	USA	RCT (Educational)	Non-specific instrument (survey questionnaire)	74	Adult or pediatric
Vinci [78]	USA	Cross-sectional study (Self-adjustment)	Non-specific instrument (in-depth interview)	18	Adult
HM/leukemia					
Barrera [79]	Canada	RCT (Educational)	Revised PAT, STAI	67	Pediatric

Table 1 continued

	Study country^a	Design (intervention type; if applicable)	Specific instruments to measure burden^b	Number of caregivers	Population age group
Creedle [80]	USA	Cross-sectional study (Educational)	Oberst Caregiving Burden Scale, Bakas Caregiving Outcomes Scale	38	Adult
Kubo [81]	USA	Cross-sectional study (Health technology, self-adjustment)	NCCN Distress Thermometer, HADS, PSQI, PROMIS Global Health Scale, Brief Fatigue Inventory	14	Adult
Kubo [82]	USA	RCT (Health technology, self-adjustment)	NCCN Distress Thermometer, HADS, PROMIS Pain Intensity scales, PROMIS Sleep Disturbance scale, FACT-G, CQOL-C, Brief Fatigue Inventory, Posttraumatic Growth Inventory, FFMQ-SF	31	Adult
Oh [83]	USA	Cross-sectional study (Educational)	PHQ-4	1397	Adult
Pailler [84]	USA	Prospective cohort study (Educational, expressional)	BSI-18, CQL-C	69	Adult or pediatric

Table 1 continued

	Study country ^a	Design (intervention type; if applicable)	Specific instruments to measure burden ^b	Number of caregivers	Population age group
	Rosenberg-Yunger [85]	Canada Cross-sectional study (Other ^d)	Non-specific instrument (structured interview)	29	Pediatric

AML acute myeloid leukemia, *BAI* Beck Anxiety Inventory, *BDI* Beck Depression Inventory, *BSI-18* Brief Symptom Inventory-18, *CASE-t* Cancer Self-Efficacy Scale–transplant, *CESD* Center for Epidemiological Studies Depression Scale, *CQOL-C* Caregiver quality of life scale-cancer, *CRA* Caregiver Reaction Assessment, *CSI* Caregiver Strain Index, *DAS* Dyadic Adjustment Scale, *DASS-21* Depression Anxiety Stress Scales, *DSM* Diagnostic and Statistical Manual of Mental Disorders, *FACES IV* Family Adaptability and Cohesion Evaluation Scale, *FACT-BMT* Functional Assessment of Cancer Therapy–Bone Marrow Transplant, *FACT-G* Functional Assessment of Cancer Therapy–General Scale, *FBI* Family Burden Interview, *FFMQ-SF* Five Facet Mindfulness Questionnaire–Short Form, *HADS* Hospital Anxiety and Depression Scale, *HCT* hematopoietic cell transplantation, *HM* hematologic malignancy, *HSCT* hematopoietic stem cell transplantation, *IES* Impact of Events Scale, *MFSI-SF* Multidimensional Fatigue Symptom Inventory–Short Form, *NCCN* National Comprehensive Cancer Network, *PANAS* Positive and Negative Affect Schedule, *PAM-C* Patient Activation Measure, *PAT* Psychosocial Assessment Tool, *PCL* post-traumatic stress disorder checklist, *PHQ-4* Patient Health Questionnaire-4 item tool, *PIP-D* Pediatric Inventory for Parents–difficult scale, *PIP-SF* Pediatric Inventory for Parents-short form, *POM* Profile of Mood States, *POMS-SF* Profile of Mood States short form, *POMS-TMD* Profile of Mood States total mood disturbance, *PREMO* performance of the parent emotional functioning, *PROMIS* Patient-Reported Outcomes Measurement Information System, *PSQI* Pittsburgh Sleep Quality Index, *PSS* Perceived Stress Scale, *QOL* quality of life, *RCT* randomized controlled trial, *SF-20* Health Perception Scale of the MOS Short-Form General Health Survey, *SF-36* Short Form Health Survey Version 2, *SDS* Symptom Distress Scale, *SIP* Sickness Impact Profile, *SMBQ* Shirom–Melamed Burnout Questionnaire, *SPACE* Scale for Positive Aspects of Caregiving Experience, *SPSI-R* Social Problem-Solving Inventory, *STAI* State-Trait Anxiety Inventory, *WHO-QOL-Bref* World Health Organization-Quality of Life-abbreviated 26-item version

^a Study country based on author affiliations if not explicitly stated

^b Only includes specific instruments; other methods for measuring caregiver burden included semi-structured patient interviews, focus group interview questionnaires, in-depth interviews, primary caretaker or parental surveys, diaries, and other instruments

^c Study reported financial burden for patients with cancer/their families

^d Other includes plan-do-study-act and social-emotional support, practical support, financial/public aid programs

^e The study did not use a patient or caregiver reported outcome assessment

between psychological morbidity and caregiver burden [48]. Parent caregivers of children with other cancers including leukemia experience depression, anxiety, and stress due to their child’s symptom burden, and also uncertainty during survivorship. In a study of parent caregivers and their children with cancer, more than two thirds of caregivers screened positive for depression and a positive correlation was noted between the child’s symptom burden and depressive symptoms among caregivers [44].

Child cancer survivors and their family members continue to live in fear even after treatment has concluded. One study reported that child cancer survivors indicated that both parents and children generally had similar levels of anxiety and stress during survivorship, and that survivors had significantly less knowledge of latent effects of cancer treatment in advance of receiving treatment than their parents [42]. The stress of a child with cancer affects sibling relationships as well. In a study of families with an adult parent caregiver, a child

with cancer, and another child at least 5 years younger than the child with cancer, higher average levels of general life stressors, cancer-related stressors, and economic stress were more strongly associated with higher sibling conflict at the end of the first year of treatment [40]. Furthermore, although caregiver stress was found to decrease over time, it could be negatively impacted by being a single parent and by the pediatric patient being the only child [47]. In a study of children who survived cancer involving central nervous system-directed treatments, parents of survivors with neurocognitive late effects, particularly executive functioning difficulties, experience high caregiver stress [46].

Caregivers of younger patients with a diagnosis of AML had higher intrusion scores (caregiver cancer-specific distress as measured on the Impact of Event Scale questionnaire) than caregivers of patients with acute lymphoblastic leukemia, solid tumors, or brain tumors. Additionally, caregivers had higher Impact of Event Scale scores and intrusion scores if their child was still under treatment, compared to those off-therapy. Additionally, income status affected the FCs psychological burden. Caregivers with household incomes below US \$40,000 reported higher distress scores than those with incomes of at least US \$40,000 [43].

Economic FC Burden

A total of 17 studies examined FC economic burden (Table 1). Few reports on the economic FC burden of patients with AML have been published. The only AML economic burden study reported that in China, 55.7% of FCs abandoned a child with AML because of loss of hope for a cure, extreme financial hardship due to no healthcare coverage, and inability to pay for treatment [49]. However, policies may have improved since the report was published as data was collected from 2002 to 2012.

Both short-term and long-term financial burden experienced by caregivers were studied. Financial burden prior to HSCT and up to 2 years after HSCT was reported in reports of

these studies. A case report estimated that the annual pharmaceutical out-of-pocket costs of two patients receiving HSCT were US \$12,400 and US \$16,000 in 2017, respectively [51]. In another study, on the basis of survey data results from 25 patients/caregivers from 2009 to 2010, the median (range) reduction in household income from diagnosis to HSCT was US \$15,690 (US \$3500–70,000). In the first 3 months after HSCT, the median (range) out-of-pocket patient cost was US \$2440 (US \$199–13,769), and patients and caregivers who had to travel had higher total median expenses (US \$5247) compared to those who did not (US \$716) [52]. FCs of patients undergoing HSCT also led to substantial work loss. Two years after HSCT, 54% of patients had not returned to work, with 80% of patient-caregiver dyads reporting a significant detrimental effect on household income [50].

Parent FCs of children with HM/leukemia face significantly heavier economic burden 1–5 years from diagnosis than parents with healthy children as a result of unexpected hospitalizations (approximately 20% of families reported at least five hospitalizations) and work disruption [64]. In another report, 94% of FCs of pediatric patients reported some sort of work disruption and 50% of the poorest families reported losing more than 40% of their annual household income [53]. A study of patients with HMs reported that in 85.4%, 80.5%, and 33.3% of households, more than 40% of monthly income would have to be devoted to formal care in the short, medium, and long term, respectively, because of inability to find sustainable informal care [59]. One study found that wives of patients with cancer were less likely to be employed 2–6 years after diagnosis; however, wives or husbands of survivors that were working at follow-up were more than twice as likely to be working full-time and worked more hours per week than other working spouses [57].

Interventions and Instruments to Measure Burden

In the TLR, 22 studies investigated different approaches to help relieve or cope with

caregiver burden (Table 1). Of them, four articles targeted caregivers of pediatric patients only and five included both adult and pediatric patients.

The interventions were classified into four primary types. Interventions that used education informed caregivers about how to solve the problems they are facing. Some interventions stressed the importance of expression and communication. Others focused on self-adjustment, which included engaging in relaxation techniques. In recent years, studies focused on using digital/mobile health interventions to help FCs relieve burdens.

Educational intervention programs resulted in improvements in self-efficacy and distress, better health outcomes (e.g., fatigue) [67], reduced mental health service use [77], and lower levels of stress, depression, and anxiety [14, 77]. Expressional interventions were also shown to be effective in decreasing anxiety and depression [70]. Additionally, FCs and patients who participated in couples-based communication intervention reported feeling supported and closer to their partner [74]. FCs who participated in self-adjustment interventions, such as “caregiver’s week” and mindfulness-based stress management programs, reported positive feedback and thought the programs would be helpful [78]. A tablet-based health information technology application was shown to decrease depression, distress, fatigue, and anxiety for FCs of patients undergoing HSCT [69].

Among the included articles, instruments designed specifically to measure caregiver burden were captured and included those designed for parents of pediatric patients. In addition, both generic instruments and symptom-specific instruments were captured in the TLR (Table 1). The instruments/scales in the latter category were designed to assess specific diseases or symptoms (e.g., sleep, distress, mood, depression, anxiety, etc.). Of the instruments specifically designed for caregiver burden, the Caregiver Reaction Assessment (CRA) questionnaire and the Caregiver Quality of Life Index Cancer (CQOLC) scale [86] were used most frequently. The CRA questionnaire consists of five subscales (24 items), including disrupted schedule, financial problems, lack of family

support, health problems, and self-esteem. It can be used for measuring both positive and negative caregiver reactions. The CRA has been proven to be a reliable and valid instrument for assessing burden of FCs of patients with cancer, with the standardized Cronbach’s alpha varying between 0.62 and 0.83. The CQOLC is a 35-item instrument that assesses quality of life for FCs of patients with cancer, including the physical, social, emotional, and financial aspects of well-being [87]. The reliability and validity of different language versions (i.e., English, Korean, Turkish, French, Chinese) have been demonstrated [87–91].

DISCUSSION

The main purpose of this review was to explore the caregiver burden of patients with AML primarily; the review was expanded to include other HMs including “leukemia” because of lack of evidence on FC burden of patients with AML only. Most of the 71 articles included in the TLR emphasized patients undergoing HSCT. Only three studies focused specifically on the caregivers of patients with AML (i.e., patients with leukemia types other than AML were not included). This paucity of findings in the literature demonstrates a significant unmet need in determining caregiver burden of patients with AML and illustrates the need for a greater focus on this important aspect of AML management. Because the adverse patient outcomes associated with AML can have similar connotations to those observed with HM and HSCT, the scope of the TLR was expanded to explore the FC burdens of patients with AML, HM (including leukemias), and HSCT; however, the need for a greater understanding of caregiver burden of patients with AML should not be overlooked.

AML accounts for 1.1% of all cancers [92] and is more frequently seen in patients over 65 years of age [1]. By 2030, it is estimated that 73 million people in the USA will be at least 65 years of age [93], many of whom may require care. Therefore, the FC burden associated with AML, HMs, and HSCT will have important social, humanistic, and economic implications.

The FC burden may not be limited to or unique to patients with AML. Working FCs who have to provide consistent and demanding care may face significant impediments due to economic burden and compromised quality of life [21, 51, 59]. Common FC burden experiences reported among HMs were economic burden such as work disruptions and high out-of-pocket costs [59].

Many FCs currently do not have access to sufficient resources to be able to manage and control their stressors and, therefore, experience negative psychological, behavioral, and physiological effects [26, 31]. Overall, studies evaluating FC burden in pediatric caregivers focused on psychological burden, rather than physical or financial burden. This may, in part, be due to the likelihood that pediatric caregivers are parents of the patients, most of whom are employed middle-aged adults, and, therefore, financial implications and their own healthcare issues are less important to them than the psychological stresses they are facing. Caregivers of children undergoing HSCT are likely to have a higher employment rate and household income than those of caregivers of adult/elderly patients. Likewise, the reported mean age of FCs of pediatric patients was 35 to 45 years old. Therefore, they are less likely to suffer health problems. Thus, these factors may explain why relevant research for this group emphasized psychological burden.

Federal policies in the USA increasingly incentivize community-based as opposed to institutional care, presuming that family members or friends are available and able to provide these services, or to at least coordinate care services [94]. The US Centers for Disease Control and Prevention (CDC) has stated that caregiving and the resultant stress on caregivers is an important public health issue that affects the quality of life of millions of individuals [95]. The survey results in the CDC report indicated some major findings: (1) nearly one in four adults over the age of 45 years provided care or assistance to a family member or friend with a health problem or disability in the last 30 days; (2) almost one in three caregivers provided 20 or more hours per week of care; (3) over half had given care or assistance for 24 months or more;

(4) the demands of caregiving are emotionally and physically challenging, with nearly one in seven caregivers reporting 14 or more mentally unhealthy days in the past month, and nearly one in six reported 14 or more physically unhealthy days in the past month; (5) four in ten caregivers reported having two or more chronic diseases, showing that caregivers may often neglect their own personal health needs.

FCs spend an estimated US \$190 billion per year on their care recipients for out-of-pocket, care-related expenses [96]. In 2011–2012, informal caregiving in the USA was estimated to account for about 30 billion hours and a loss of approximately US \$522 billion in forgone wages [97]. Therefore, the financial strain associated with the caregiving experience can be considerable; systemic buffers of stress, such as workplace or social policies, can help mitigate some of the effects from the financial aspects of caregiving [94].

A limitation of the included articles is the small sample size of each study, and thus the results and conclusions may not be generalizable to a broader population. We included studies from a number of countries; differences in underlying healthcare systems and in the social and economic systems of countries mean that the studies are not directly comparable and may further limit the generalizability of the observations. The studies also included a homogenous sample and were typically single-center studies, again limiting the generalizability of the observations. Most studies were not longitudinal, and the TLR included almost entirely observational studies, with very few randomized controlled trials reported, making it difficult to draw definitive conclusions on the nature and degree of FC burden. Furthermore, selection and publication biases are potential limitations of this TLR, limiting the ability to establish causality. Some articles were included because the sample population of these studies included leukemia among other cancer diagnoses. A broad inclusion of patients with cancer may cause confounding results. For example, Teixeira and Pereira [48] conducted a study in which it was not possible to distinguish results of patients with AML, acute lymphocytic leukemia (ALL), and solid tumors. The AML/ALL

patient population in this study accounted for less than 12% of the total population. Nevertheless, this study was included because the study population included patients with leukemia. Although grouping leukemic and non-leukemic FC burdens may create bias or confounding in results, excluding publications that included patients with leukemia could have resulted in missing relevant information. Papers that did not mention leukemia among the enrolled cancer populations were excluded, even where the population included patients who had received stem cell therapy [98]; this may have led to the exclusion of potentially insightful information. Finally, the TLR was conducted for papers published from 2010 onwards, thus omitting any earlier publications on FC burden.

This TLR demonstrated more studies are warranted that target FC burden of patients with AML because only three such studies were found. In particular, prospective studies assessing FC burden in pediatric and adult patients would be useful. Caregivers of patients with AML may experience severe consequences of burden from early in their caregiving role. Although there could be some similarities with FC burden of other patients with HM and patients receiving HSCT, more attention is needed to separate the FC burden of unique HM diseases for more effective intervention design because each case of leukemia has a unique trajectory of impact on FC burden. Similarly, it is likely that the FC burden for caregivers of pediatric patients differs from that facing caregivers of adult patients; in particular, FC burden for parents of pediatric patients may differ from FC burden for other family members. We suggest that prospective studies are undertaken to assess the HRQoL and humanistic burden and the economic burden for FCs of adult and pediatric patients with AML. To provide a more comprehensive understanding of the burden on FCs, we suggest a more granular approach would be to identify FC burden with patient–burden dyads, an approach which has the potential to highlight a pathway towards meaningful interventions that can be structured systematically to answer the needs of patients with AML and their FCs. Once humanistic and

economic burdens have been more comprehensively identified and quantified, further study on the effect of systematic interventions to reduce FC burden should be undertaken.

CONCLUSION

A need exists for systematic interventions to support FCs of patients with AML, HM, and HSCT. Examples of effective interventions could include work support, locally available specialized health support, and financial support for caregivers of working age. Reducing FC burden and improving FC quality of life may reduce the use of overall healthcare resource utilization. Caregivers can thus become more effective in fulfilling their roles. Systematic support systems designed to alleviate or relieve caregiver burden may create reinforced integrators, thus having a positive and lasting effect on the quality of life and outcomes of patients with AML and other cancer types.

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