

Coping in caregivers of patients with hematologic malignancies undergoing hematopoietic stem cell transplantation

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Key Points

- Caregivers of patients with hematologic malignancies undergoing HSCT cope with high caregiver burden, psychological distress, and worse QOL.
- Approach-oriented coping strategies were associated with less psychological distress and better QOL.

Caregivers of patients with hematologic malignancies undergoing hematopoietic stem cell transplantation (HSCT) must cope with substantial caregiving burden, high rates of psychological distress, and diminished quality of life (QOL). However, data describing coping strategies before HSCT and the association between coping, QOL, and psychological outcomes in this population are lacking. We conducted a secondary analysis of data collected during a multisite randomized clinical trial of a supportive care intervention in HSCT recipients and their caregivers. Caregivers completed the Brief COPE, Hospital Anxiety and Depression Scale, and the Caregiver Oncology Quality of Life Questionnaire to measure coping strategies, psychological distress, and QOL, respectively. We grouped coping into 2 higher-order domains: approach-oriented (ie, emotional support and active coping) and avoidant (ie, self-blame and denial). We used the median split method to describe the distribution of coping and multivariate linear regression models to assess the relationship between coping and caregiver outcomes. We enrolled 170 caregivers, with a median (range) age of 53 (47-64) years. Most were White (87%), non-Hispanic (96%), and female (77%). Approach-oriented coping was associated with less anxiety ($\beta = -0.210$, $P = .003$), depression symptoms ($\beta = -0.160$, $P = .009$), and better QOL ($\beta = 0.526$, $P = .002$). In contrast, avoidant coping was associated with more anxiety ($\beta = 0.687$, $P < .001$), depression symptoms ($\beta = 0.579$, $P < .001$), and worse QOL ($\beta = -1.631$, $P < .001$). Our findings suggest that coping is related to distress and QOL among caregivers of HSCT recipients even before transplant. Hence, caregivers of patients with hematologic malignancies undergoing HSCT may benefit from resources that facilitate adaptive coping with the demands of caregiving.

Introduction

Caregivers (ie, friends and family) of patients with hematologic malignancies undergoing hematopoietic stem cell transplantation (HSCT) are essential in providing support and care throughout HSCT and recovery. Yet, this vulnerable caregiver population experiences enormous unmet psychosocial needs.¹

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Most HSCT centers require patients preparing for HSCT to designate a formal caregiver willing to support the patient in the first 100 days after transplantation, and the lack of a reliable primary caregiver may negatively affect a patient's transplant experience and clinical outcomes.²⁻⁴ Caregivers must cope with myriad responsibilities, which include managing complex medication regimens, monitoring potential indicators of transplant-related complications, preparing meals that follow posttransplant guidelines, and communicating with the patients' medical teams.^{5,6} Even before the coronavirus disease 2019 pandemic, caregivers had the added responsibility and stress of minimizing the risk of infection, which could have been detrimental to a patient recovering from a stem cell transplant because of their immunocompromised state.² Hence, a comprehensive understanding of unmet coping needs in this caregiver population is critical to developing resources to help caregivers cope with the demands of HSCT.^{7,8}

Approximately 20% to 50% of caregivers of patients with cancer suffer from significant mood disturbance throughout their loved ones' cancer diagnosis and treatment.⁹ Caregivers report prominent feelings of distress, uncertainty, loneliness, fatigue, sleep disturbance, financial worry, and poor quality of life (QOL).^{2,10} Many caregivers report feeling ill-prepared for their caregiver role and are overwhelmed by the uncertainty of their loved ones' diagnosis.^{2,5} These factors put caregivers at a greater risk of poor health outcomes and contribute to caregiver burden.^{5,6} For patients with hematologic malignancies and/or those undergoing HSCT, caregiver distress has been reported to be higher than that of the patients in their care and has been associated with worse clinical outcomes for both caregivers and patients.^{4,5,11,12} For example, caregiver fatigue is associated with poor patient outcomes such as longer time to neutrophil engraftment and poorer sleep efficiency.^{5,13,14} Although caregivers' symptoms of depression increase and QOL declines throughout HSCT recovery,¹⁵ caregivers experience higher levels of distress right before the HSCT hospitalization.¹⁶ Hence, characterizing factors that contribute to caregiver distress before HSCT is essential to bolstering supportive resources to identify and reduce the risk of distress in caregivers before transplantation.

Coping is associated with how caregivers manage distress and caregiver burden.⁹ However, this association has not been studied extensively among allogeneic or autologous HSCT recipient caregivers. Among caregivers of patients with acute myeloid leukemia, those who more often engaged in coping mechanisms such as avoidance, escape, and distancing experienced significantly higher caregiver burden.¹⁷ In contrast, caregivers who used active mechanisms such as positive appraisal reported a significantly lower caregiver burden.¹⁷ Active coping among caregivers can also enhance caregiver self-efficacy and health outcomes (eg, lower levels of fatigue, sustained physical activity, and healthier eating).³ Although coping contributes to clinical outcomes among caregivers of patients with hematologic malignancies undergoing HSCT, there is still a dearth of research that describes coping in this population. Hence, for this study, we describe coping strategies used among caregivers before HSCT and examine the relationship between coping styles and caregiver outcomes. We hypothesized that greater use of active coping mechanisms (eg, acceptance) would be associated with better QOL and less symptoms of distress.

Methods

Study procedure

We conducted cross-sectional analyses of data from 170 caregivers of patients who had been admitted and scheduled to undergo autologous or allogeneic HSCT. These patients were enrolled in a multisite randomized trial of an inpatient palliative care intervention (NCT03641378) at Massachusetts General Hospital, Boston, MA, Duke University Medical Center, Durham, NC, and the Fred Hutchinson Cancer Research Center from October 2018 to January 2022.¹⁸ The Institutional Review Boards at all participating sites approved this study. With permission from their oncologist, we approached the patient, who identified and provided permission to approach their caregiver within 72 hours of the patient's admission for HSCT. All caregivers who agreed to participate provided written informed consent.

Participants

Eligible participants were adult (≥ 18 years of age) caregivers of patients with hematologic malignancies hospitalized to undergo allogeneic or autologous HSCT. We chose to include both allogeneic and autologous HSCT recipients because prior studies have shown that caregiver burden during the acute recovery after transplant is similar across these 2 groups.^{19,20} We defined a caregiver as: (1) an individual identified by the patient as their primary caregiver, (2) a spouse, relative, or friend taking care of the patient undergoing HSCT, and (3) an individual living with the patient or having inperson contact with the patient twice weekly or more. Eligibility criteria also entailed the ability to read and respond to questions and complete questionnaires in English or Spanish with assistance from an interpreter. We excluded caregivers of patients undergoing HSCT for a benign hematologic condition, given the differences in the illness experience and stressors on both patients and caregivers.

Sociodemographic and clinical data

At enrollment, caregivers provided demographic information including age, gender, education, relationship to patient, race, ethnicity, marital status, religious beliefs, employment status, and income.

Caregiver-reported measures

Within 72 hours of the patient's admission for HSCT, caregivers completed baseline assessments. Caregivers' use of coping strategies was measured with the Brief COPE, a 28-item questionnaire that assesses the use of 14 coping methods with 2 items for each method.²¹ To reduce questionnaire burden for participants, we limited our assessment to the following 8 coping strategies previously used in other studies to assess coping in patients who have undergone HSCT^{8,22}: use of active coping, positive reframing, acceptance, emotional support, religious coping, self-blame, denial, and behavioral disengagement. Scores for each scale range from 2 to 8, and higher scores indicate greater use of that coping strategy. With an aggregate of individual domain scores, we grouped 7 coping strategies into 2 higher-order domains of coping informed by prior literature: avoidant coping (ie, self-blame, denial, and behavioral disengagement) or approach-oriented coping (ie, use of emotional support, active coping, positive reframing, and acceptance).^{8,16-18} We reported scores for religious coping separately

because it is not included in the 2 higher-order domains. The overall Cronbach's α for the Brief COPE is 0.70 showing good consistency among items.

We used the 14-item Hospital Anxiety and Depression Scale (HADS) to assess depression and anxiety symptoms.²¹ The HADS contains 2 7-item subscales that measure symptoms of depression (Cronbach's $\alpha = 0.86$) and anxiety (Cronbach's $\alpha = 0.78$) within the past week. Each subscale ranges from 0 to 21, and higher subscale scores indicate worse distress symptoms.

We assessed caregiver QOL with the 29-item Caregiver Oncology Quality of Life Questionnaire, which is a multidimensional measure that assesses 10 domains of caregiving.²³ All domains range from 0 to 100, with higher scores indicating a better caregiving experience. We calculated a composite QOL score using a weighted sum of all items in the questionnaire.²⁴ The internal consistency, that is, Cronbach's $\alpha = 0.72$ to 0.89.²⁴

Statistical analysis

We performed all statistical analyses using STATA 17.0 (Stata-Corp, College Station, TX). We summarized participants' baseline characteristics using descriptive statistics (eg, mean and median) for continuous variables and proportions for categorical variables.

As in previous studies,^{8,21,22,25} we used the median split method to describe the distribution of coping domains in our sample because there are no validated cut-offs for high vs low coping published in the literature for caregivers. We calculated the median scores for each of the 7 coping domains with the median split method, then described the proportion of caregivers with a score greater than the median as "high utilizers" for each coping strategy.²⁶⁻²⁸ Caregivers, whose score was the median, were included in the "low utilizers" group. We considered the median score (8) as the cut-off point for "high utilizers" for the acceptance coping strategy use because the median score was the same as the highest possible score (8). As in previous studies,^{7,21,22,29} we considered "use of multiple avoidant coping strategies" as the use of 2 or more coping strategies (with a score greater than the median) out of 3 in the avoidant coping domain. We considered the "use of multiple approach-oriented coping strategies" as the use of 3 or more coping strategies (with a score greater than the median) out of 4 in the approach-oriented coping domain.

We first used unadjusted linear regression models to assess relationships of approach-oriented and avoidant coping strategies with caregiver-reported outcomes (symptoms of anxiety and depression and QOL). We then used multivariate linear regression models to examine associations of coping with caregiver-reported outcomes. For all models, we adjusted for sociodemographic factors (ie, age, race, ethnicity, religious beliefs, sex, education, relationship to the patient, and education status) shown to be associated with coping in other cancer caregiver populations.¹⁹ Given the potential of collinearity for anxiety, depression, and QOL, we built separate models for each outcome. We used complete case analyses without accounting for missing data. With a low missingness rate of 0.17%, there were no observed differences in missing data by coping. Because this work was a hypothesis-generating secondary data analysis, we did not have an a priori specified power analysis. Nonetheless, based on our prior work that examined the association between coping and QOL in

Table 1. Participant characteristics

Patient characteristics	N = 170
Age, median (range)	53.4 (47-64)
Female sex, n (%)	130 (76.5%)
Race, n (%)	
White	147 (86.5%)
Black	7 (4.1%)
American Indian	2 (1.2%)
Asian	11 (6.5%)
Other	1 (0.60%)
Missing	2 (1.2%)
Non-Hispanic or Latino	163 (95.9%)
Caregiver Relationship to Patient, n (%)	
Married or living as if married	130 (76.5%)
Divorced/Separated	2 (1.2%)
Child (Daughter or Son)	13 (7.7%)
Parent (Mother or Father)	14 (8.2%)
Sibling (Brother or Sister)	5 (2.9%)
Friend	3 (1.8%)
Other Family	3 (1.8%)
Religion, n (%)	
Catholic	45 (26.5%)
Non-Catholic Christian	78 (45.9%)
None	26 (15.3%)
Jewish	4 (2.6%)
Atheist	8 (4.7%)
Other	9 (5.3%)
Education, n (%)	
High school	28 (16.5%)
College	98 (57.7%)
Postgraduate	44 (25.9%)
Caregiver Employment, n (%)	
Employed	94 (55.3%)
Caring for home/family	23 (13.5%)
Unemployed	2 (1.2%)
Unable to work/disability or illness	3 (1.8%)
Retired	40 (23.5%)
Other	8 (4.7%)

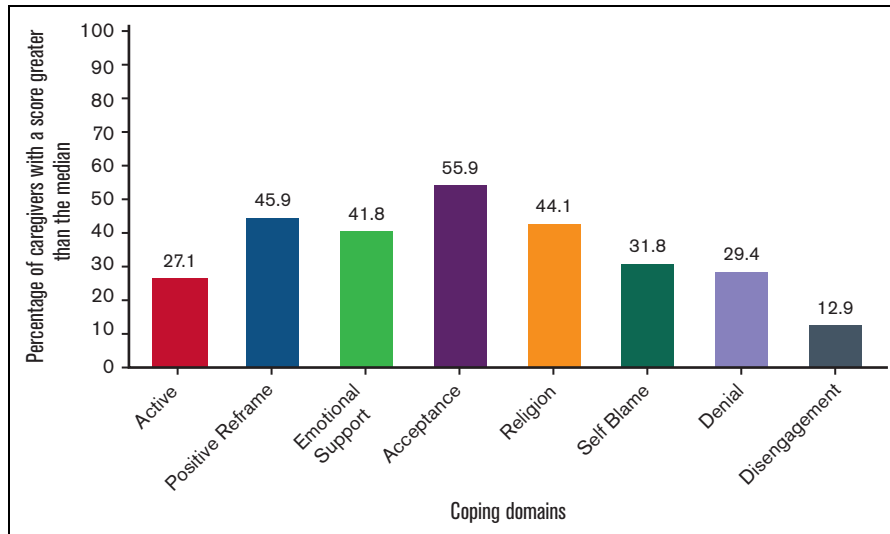
patients with blood cancers (ie, approach-oriented coping: $\beta = 1.491$, standard error [SE] = 0.501, $P = .003$) and our current sample size of 170, we would have >80% power to detect a significant association between caregiver approach-oriented coping and their QOL. We considered a 2-sided P -value <.05 as statistically significant.

Results

Demographics and participant characteristics

Of 201 eligible caregivers, 170 (84.6%) enrolled. Table 1 shows participants' characteristics. Participants were mostly females

Figure 1. Distribution of coping strategies. The proportion of caregivers with a score greater than the median for each coping strategy is shown. For the acceptance coping domain, the median was the maximum score for that domain. Median scores for each coping strategy were active, 7.0; positive reframing, 6.0; emotional support, 7.0; acceptance, 8.0; religious, 6.0; denial, 2.0; self-blame, 2.0; behavioral disengagement, 2.0.

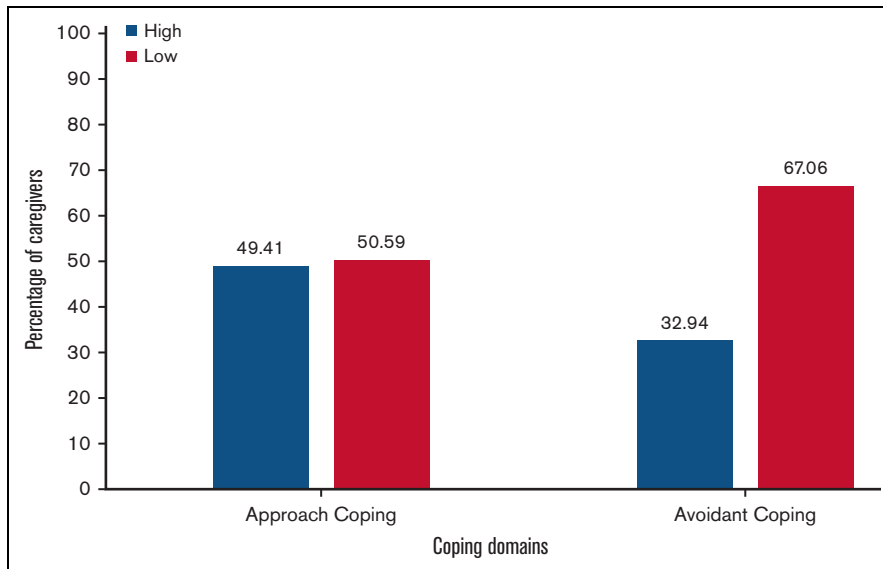


(n = 130; 76.5%), White (n = 147; 86.5%), and non-Hispanic (n = 163; 95.9%), with a median age of 53.4 years (range = 47-64 years). Of them, 77% (n = 130) were married, 55.3% (n = 94) were employed, 57.7% (n = 98) were college educated, and 45.9% (n = 78) were identified as non-Catholic Christian.

Distribution of coping strategies

Figure 1 displays the distribution of caregivers' coping strategies, characterized by the proportion of caregivers who scored above the median for a given coping domain. Caregivers scored above the median for use of acceptance (55.9%), positive reframing (45.9%), and religious (44.1%) coping. Conversely, a lower proportion of caregivers scored above the median for disengagement (12.9%), active (27.1%), and denial (29.4%) coping. Overall, more caregivers reported high use of approach-oriented coping strategies (49.4%)

Figure 2. Distribution of caregivers based on approach and avoidant coping strategies. The proportion of caregivers with approach and avoidant coping strategies based on the median split for each coping strategy is shown. Median scores for each coping strategy are as follows: approach, 26; avoidant, 7.



compared with the proportion of caregivers who reported high use of avoidant coping strategies (32.9%), see Figure 2.

The use of multiple coping strategies

Figures 3 and 4 show the distribution of caregivers who were “high utilizers” of multiple approach-oriented and avoidant coping strategies, respectively. High utilizers of multiple approach-oriented coping scored above the median for 3 or 4 approach-oriented coping domains. High utilizers of multiple avoidant coping strategies scored above the median for 2 or 3 avoidant coping domains. Overall, although 30.6% of caregivers scored above the median for 3 or 4 approach-oriented coping domains, only 4.1% of caregivers scored above the median for 2 or 3 avoidant coping domains. No caregiver-reported high use of both avoidant and approach-oriented coping strategies.

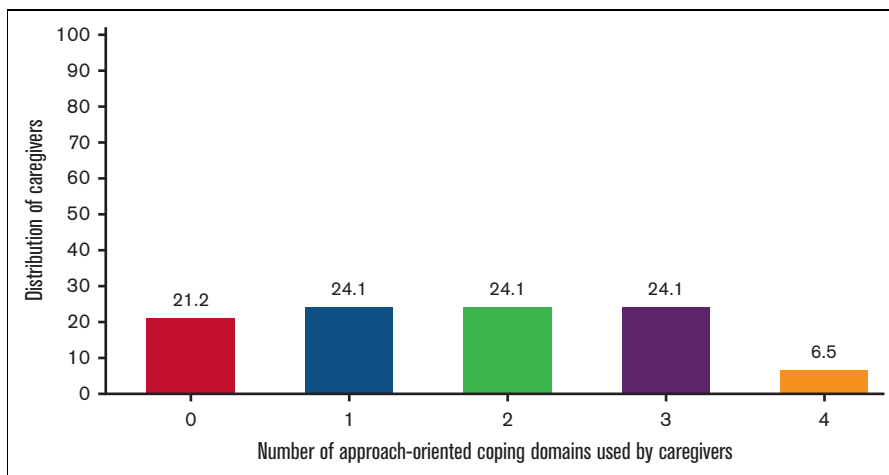


Figure 3. Distribution of caregivers who were 'high utilizers' of multiple approach-oriented coping domains: emotional support, reframe, active, and acceptance. The distribution of caregivers who were "high utilizers" of approach-oriented coping domains defined as caregivers who scored above the median on a coping domain is shown. For the acceptance coping domain, "high utilizers" were patients who scored the median (8) because the median was the maximum score for that domain. Although 21% of patients scored below the median or median (for acceptance) for all approach-oriented coping domains, 24%, 24%, 24%, and 6.5% were high approach-oriented copers based on 1, 2, 3, and 4 domains, respectively.

Associations of coping strategies with psychological distress and QOL

Multivariate regression models that adjusted for several socio-demographic factors showed that approach-oriented coping was associated with less anxiety ($\beta = -0.210$, $SE = 0.070$, $P = .003$) and depression symptoms ($\beta = -0.160$, $SE = 0.060$, $P = .009$). In contrast, avoidant coping was associated with more anxiety ($\beta = 0.687$, $SE = 0.174$, $P < .001$) and depression symptoms ($\beta = 0.579$, $SE = 0.147$, $P < .001$). Additionally, approach-oriented coping was associated with better QOL ($\beta = 0.526$, $SE = 0.165$, $P = .002$) whereas avoidant coping was associated with worse QOL ($\beta = -1.631$, $SE = 0.408$, $P < .001$), [Table 2](#).

Associations of multiple coping strategies with psychological distress and QOL

In [Table 3](#), we show the association between caregivers' use of multiple coping strategies, psychological distress, and QOL. Caregivers who used multiple approach-oriented coping strategies reported less anxiety ($\beta = -1.930$, $SE = 0.666$, $P = .004$), depression symptoms ($\beta = -1.632$, $SE = 0.563$, $P = .004$), and better QOL ($\beta = 4.041$, $SE = 1.568$, $P = .011$). In contrast, caregivers who used multiple avoidant coping strategies did not have statistically significant differences in anxiety ($\beta = 2.095$, $SE = 1.639$, $P = .203$), depression symptoms ($\beta = 1.058$, $SE = 1.389$, $P = .448$), and QOL ($\beta = -6.118$, $SE = 3.829$, $P = .112$).

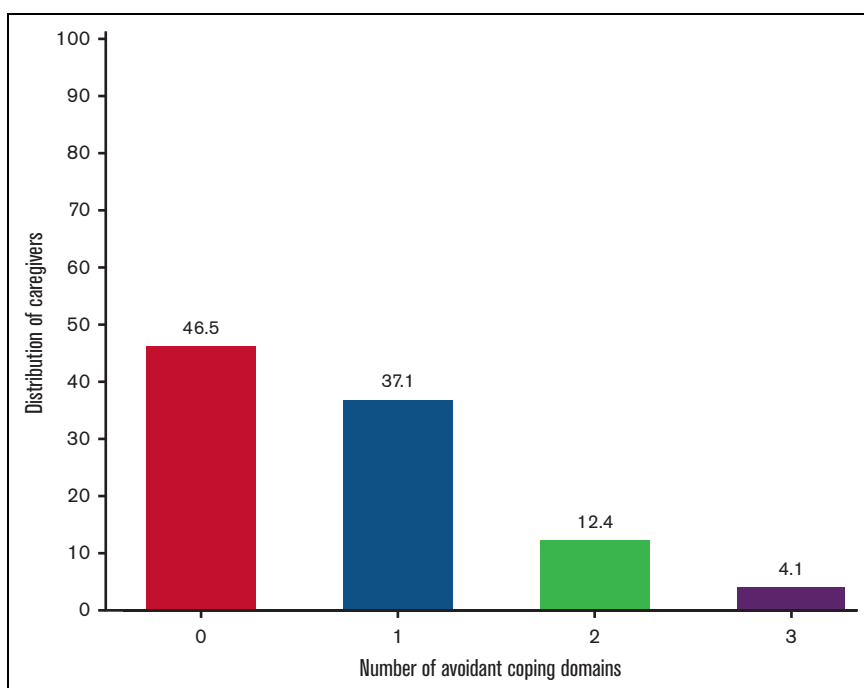


Figure 4. Distribution of caregivers who were 'high utilizers' for multiple avoidant coping domains: denial, self-blame, and disengagement. The distribution of caregivers who were "high utilizers" of avoidant coping domains defined as caregivers who scored above the median on a coping domain is shown. Although 47% of caregivers scored below the median for all 3 avoidant coping domains, 37%, 12%, and 4% were high avoidant copers based on 1, 2, and 3 domains, respectively.

Table 2. Association between avoidant and approach coping strategies, psychological distress, and QOL

Coping strategies	QOL			Depression			Anxiety		
	β	SE	P	β	SE	P	β	SE	P
Approach	0.526	0.165	.002	-0.160	0.060	.009	-0.210	0.070	.003
Avoidant	-1.631	0.408	<.001	0.579	0.147	<.001	0.687	0.174	<.001

Linear regression models adjusted for patients' age, sex, race, ethnicity, education, relationship to patient, religious beliefs, and employment.

Religious coping, psychological distress, and QOL

Although 44.1% of caregivers scored above the median for religious coping, it was not associated with either anxiety ($\beta = -0.193$, SE = 0.157, $P = .223$), depression symptoms ($\beta = -0.038$, SE = 0.134, $P = .777$), or QOL ($\beta = 0.144$, SE = 0.0370, $P = .699$).

Discussion

In this cross-sectional study of 170 caregivers of patients with hematologic malignancies hospitalized to undergo HSCT, a significant proportion of caregivers reported high use of acceptance (55.9%), positive reframing (45.9%), and religious coping (44.1%). Although 49.4% of caregivers reported high use of approach-oriented coping strategies, 32.94% of our cohort reported high use of avoidant coping strategies. The use of approach-oriented coping was associated with less symptoms of anxiety and depression, and better QOL. In contrast, the use of avoidant coping was associated with more symptoms of anxiety and depression, and worse QOL. Our findings underscore the essential role of coping on psychological well-being and QOL, which should be further explored with prospective studies in this caregiver population.

Although caregivers must both cope with various challenges that could accompany their loved one's disease, HSCT, and recovery, to our knowledge, this is the first study to characterize multiple dimensions of coping strategy use in caregivers of patients with hematologic malignancies and/or patients undergoing HSCT. Although caregivers in our cohort reported a variety of coping strategies in both the approach-oriented and avoidant coping domains, high use of acceptance, positive reframing, and religious coping were reported by most. This distribution of coping is different from those reported by patients with hematologic malignancies (ie, emotional support and active coping).^{21,22} Indeed, these observed differences in coping strategies between patients and caregivers underscores the necessity to tailor supportive resources to the unique needs of caregivers.

A substantial proportion of our caregivers reported seeking solace in religious or spiritual beliefs and practices. Robust evidence posits that religion and spirituality play a crucial role in how various

patients with cancer cope and manage their illness, treatment, and recovery^{28,30-34}; yet, data are limited about the impact of religious coping on caregivers of patients with hematologic malignancies or those undergoing HSCT. Although we did not find any association between religious coping and caregiver distress or QOL, in a recent study of caregivers of patients with stroke, positive religious coping was associated with less caregiver burden and more family harmony.³⁵ Because religious coping could be a potential source of resilience in this caregiver population with existential distress and tremendous unmet psychosocial and well-being needs,^{36,37} the impact of religion and spirituality merits further exploration. Future research with larger sample sizes should also examine the potential impact of integrating religious coping strategies into multimodal caregiver interventions.

We found that the use of approach-oriented coping was associated with less anxiety and depression symptoms whereas avoidant coping was associated with symptoms of more distress. One-third of our cohort reported high use of denial and other avoidant coping strategies, consistent with reports in other caregiver populations.³⁸ For example, a significant strong correlation between caregiver burden and avoidant coping strategies, such as escaping and distancing, has been documented in caregivers of patients with stroke.³⁸ Caregiver distress has also been observed to fluctuate over the course of illness, HSCT, and recovery, with caregiver distress rates often exceeding those of the patient.³⁹⁻⁴¹ Ongoing efforts seek to understand the vital mechanisms by which caregiver interventions confer benefit.²⁵ Although our findings highlight approach-oriented coping strategies as a likely contributor, future work should aim to establish and elucidate this mechanism, including how and when in the care cycle to integrate coping interventions to improve the psychological well-being of caregivers.

Consistent with prior work among patients with high-risk acute myeloid leukemia,²² we showed that approach-oriented coping was associated with better QOL, whereas avoidant coping was associated with worse QOL. It is well-known that caregiver QOL declines over time during the patient's initial HSCT hospitalization.^{41,42} Higher caregiver burden over the illness and treatment course has also been associated with lower caregiver QOL.⁴³⁻⁴⁵ Although prior work showed that improved coping skills mediated

Table 3. Association between the use of multiple avoidant or approach-oriented coping strategies, psychological distress, and QOL

Use of multiple coping strategies	QOL			Depression			Anxiety		
	β	SE	P	β	SE	P	β	SE	P
Use of multiple approach-oriented coping strategies	4.041	1.568	.011	-1.632	0.563	.004	-1.930	0.666	.004
Use of multiple avoidant coping strategies	-6.118	3.829	.112	1.058	1.389	.448	2.095	1.639	.203

Linear regression models adjusted for patients' age, sex, race, ethnicity, education, relationship to patient, religious beliefs, and employment.

the impact of a supportive intervention on QOL among caregivers of patients with hematologic malignancies hospitalized for HSCT,²⁵ no studies have described the association between different pre-HSCT coping strategies and QOL in this caregiver population. Hence, our findings suggest training in approach-oriented coping skills (eg, cognitive-behavioral skills-based strategies, which facilitate emotion-focused coping, active coping, cognitive reframing, and acceptance)¹⁵ incorporated in supportive interventions could boost caregiver QOL before transplantation.

Several limitations of our study deserve consideration. First, the cross-sectional focus of this analysis precludes our ability to comment on the directionality of the associations reported in the present study. Second, although we performed this study at 3 academic cancer centers, our sample lacked racial and ethnic diversity; thus, our findings may not be generalized to caregivers from underrepresented minority backgrounds who may use different coping strategies while managing the demands of HSCT. Third, because the majority of our caregivers were females, and sex variations in coping have been established,⁴⁶ our findings may not be generalized to male caregivers. Fourth, most of our sample were married or family caregivers. Although most research about cancer caregivers have focused on family caregivers, coping strategy used in families may not translate to nonfamilial caregivers. Future research should seek to investigate these relationships in diverse caregiver populations. Finally, distress and coping evolve over the course of any illness and treatment, even among caregivers.^{41,42} Because we measured caregiver distress and coping 72 hours after the patient's admission for HSCT, caregiver distress and coping at this timepoint might not accurately reflect distress and coping before or beyond the transplant hospitalization. Hence, longitudinal studies of coping in caregivers of patients with hematologic malignancies and/or HSCT recipients and its association with clinical outcomes (eg, distress) are critically needed to elucidate the role of coping over the illness, treatment, and recovery course.

In summary, our findings suggest coping is likely related to distress and QOL among caregivers of patients with hematologic malignancies and/or those undergoing HSCT before the transplantation and even before the high caregiving burden that could accompany the acute recovery after HSCT. Thus, this vulnerable caregiver

population would likely benefit from evidence-based (ie, via randomized trials), supportive resources that could facilitate adaptive coping with the countless psychological and physical demands which may accompany caregiving for patients undergoing stem cell transplantation.

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Authorship

Contributions: All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data, were involved in drafting the article or revising it critically for important intellectual content, provided final approval of the manuscript, and agreed to be accountable for all aspects of the work.

Conflict-of-interest disclosure: T.W.L. reports personal fees for consulting or advisory boards from AbbVie, Agios/Servier, Astellas, BlueNote, CareVive, Bristol Myers Squibb/Celgene, Flatiron, Genentech, GlaxoSmithKline, Novartis, and Pfizer; royalties from UpToDate; speakers bureau fees from Agios, AbbVie, and Bristol Myers Squibb/Celgene; and grants and/or research contracts from the American Cancer Society, AstraZeneca, Bristol Myers Squibb, Jazz Pharmaceuticals, and the National Institute of Nursing Research/National Institutes of Health, and Seattle Genetics. P.C.J. consults for AstraZeneca. The remaining authors declare no competing financial interests.

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