More Often Than Not, We’re in Sync: Patient and Caregiver Well-being Over Time in Stem Cell Transplantation

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More often than not, we’re in sync:

Patient and caregiver well-being over time in stem cell transplantation

Running Title: Interdependence of well-being in transplant

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Abstract.

Background. Hematopoietic stem cell transplantation (HSCT) is an aggressive medical procedure which significantly impacts the shared emotional well-being of patients and family caregivers (FC). Prior work has highlighted the significant overlap in well-being among patients and FCs; however, how this interdependence may change over the course HSCT has received less attention.

Methods. We conducted secondary analyses of a supportive intervention delivered to 154 FCs of HSCT patients and examined relationships at baseline, 6 weeks, 3 and 6 months post-HSCT. Actor Partner Interdependence Modeling examined patient quality of life (QOL) and FC anxiety/depression.

Results. The data did not fit a multigroup approach limiting our ability to test intervention effects; however, bivariate analyses indicated FC depression significantly correlated to patient QOL at baseline ($r = -.32$), 6 weeks ($r = -.22$) and 6 months post-HSCT ($r = -.34$; $p's < .05$); whereas anxiety was only correlated at the first two timepoints ($p's < .05$). There was an unexpected, albeit small, partner effect such that worse patient QOL at 6-weeks significantly related to lower FC depression at 3-months ($B = .182; p = .026$) and changed direction with patient QOL at 3-months being related to more FC depression at 6-months ($B = -.192; p = .001$).

Conclusions. These findings highlight the significant, yet nuanced, interdependence of patient QOL and FC well-being during HSCT. Specifically, greater interdependence was observed between patient QOL and FC depression compared to FC anxiety, suggesting potential treatment targets for patients and their families.
Trial was registered at ClinicalTrials.gov Identifier: NCT02037568; first registered: January 16, 2014; https://clinicaltrials.gov/ct2/show/NCT02037568

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Background

Cancer impacts not only patients, but also their family members and informal caregivers. There are approximately 3.2 million unpaid family cancer caregivers in the United States today. (1) The number of caregivers needed to support cancer patients continues to rise. (2) As cancer treatment at large moves toward the outpatient setting, caregivers will be expected to provide increasing levels of unpaid care, (3) potentially contributing to the already known physical and psychological morbidity associated with caregiving. (4) Caregiving for cancer patients can increase risk for caregivers’ social isolation, sleep problems, (5) loneliness, (6) depression, and anxiety. (7)

The emotional toll of cancer caregiving can have detrimental effects on both caregivers and their patients. Indeed, a large body of evidence suggests that caregivers’ and their patients’ psychological functioning are inextricably linked (8, 9) such that when caregivers become more depressed, patients are likely to experience similar depressive symptoms, and vice versa. This reciprocity is often termed interdependence (10) or, in more stark terms, an emotional contagion. (11) While there is agreement that this interdependence occurs over the course of cancer treatment, we know much less about how and when interdependence within patient-caregiver dyads may change. (12)

Psychological interdependence among patient-caregiver dyads is particularly important during hematopoietic stem cell transplant (HSCT). HSCT is an aggressive medical procedure in which patients’ bone marrow is ablated with chemotherapy, with or without radiation, donor cells are carefully matched to the patients and then infused into the patient, and the medical team supports the patient while the immune system is reconstituted over the next year or more. (13) For patients, emotional distress typically
peaks leading into HSCT, and symptomatology continues to increase through the
course of transplant during hospitalization. Patients’ anxiety and depression begin to
decrease 3 and 6 months following HSCT. For caregivers, distress is also high
leading up to HSCT, with depression and anxiety increasing during the hospitalization
and course of transplant. Caregivers’ physical and emotion well-being can
deteriorate in the months following transplant.

Despite the interdependent nature of patients and caregivers’ well-being during
the HSCT process, relatively little work has examined this dynamic over time. For
the current study, we sought to address this gap by drawing from patients undergoing
HSCT in the context of a stress management intervention targeting the caregiver. The
intervention, called PEPRR (PsychoEducation, Paced Respiration, and Relaxation),
was effective at reducing caregiver distress, yet dyads’ interdependence over time
was not investigated. Thus, our goal was to examine the potential interdependence of
caregiver well-being and patient quality of life and, potentially, how the PEPPR
intervention impacted dyad’s shared well-being during HSCT. In line with other dyadic
research in HSCT populations as well as our work with this study’s baseline
data, we hypothesized that the emotional well-being of patients and caregivers
would demonstrate a stronger interdependence over time in the PEPRR group, as
caregivers may attend to their own emotional needs, thereby growing the emotional
bond within the dyad.
Methods.

These secondary data analyses drew from a 1:1 randomized clinical trial in which HSCT patients and their caregivers were randomly assigned to either PEPPR or enhanced treatment as usual (eTAU; intervention materials were provided without prompting or coaching).(18) Study timepoints were anchored to patients’ day zero of HSCT (baseline), then data were collected at 6 weeks, 3 months and 6 months post-transplant. The Colorado Multiple Institutional Review Board approved the study (www.ClinicalTrials.gov identifier: NCT02037568).

Participants. Participants were recruited between March 1st, 2014 and 4 November 4th, 2016 during routine transplant prescreening. Recruitment occurred at a community-based transplant program (n = 98) and a university-based cancer center (n=61). Eligibility criteria included 1) Allo-HSCT patient and their primary caregiver both agreed to participate, 2) spoke/read English, 3) telephone access, and 4) ≥ 18 years old. Exclusion criteria included 1) uncontrolled psychiatric disorder in past 18 months. Caregivers were defined as the individual in the patient’s life primarily responsible for care posttransplant, emotionally invested in the patient, and responsible for major care decisions.

Intervention. PEPRR originated from a stress management intervention for medically ill patients(21) that was modified for caregivers originating using a cognitive behavioral framework.(17) The PEPPR intervention was delivered by three master’s level social workers for eight, 60-minute sessions during the 100-day posttransplant period.
Additional details regarding the intervention are available elsewhere. The first PEPPR session began 17.4 days (95% CI: 10.3-24.5) after transplant. Weekly sessions typically occurred for the first four weeks and then every other week. For the eTAU control group, caregivers were emailed all sections from the PEPRR workbook.

Measures.

The parent study examined a combined distress composite, combining measures of depression, anxiety and perceived stress. In the current analyses, we examined these mood outcomes in caregivers and patients that are particularly salient in HSCT. Depression is observed to be a particularly meaningful outcome in its relationship to caregiver burden and sensitive to change during the course of HSCT. Depression and quality of life (QOL; compared to anxiety, fatigue or symptom burden) may also be most responsive to supportive interventions in patients and caregivers undergoing HSCT. Patient QOL was selected given its importance to long-term clinical outcomes in HSCT.

Anxiety. Symptoms of caregiver anxiety were measured using the Speilberger State-Trait inventory of Anxiety. This 40-item scale has internal consistency ranging from 0.89 to 0.92, test-retest correlations ranging from 0.73 to 0.86 and is validated in both healthy participants and with caregivers of patients with serious illness. Higher scores indicate greater anxiety.
**Depression.** To measure caregiver depressive symptoms, we used the Center for Disease Control-Depression scale (CESD). The 20-item scale has been validated in cancer populations and in caregivers specifically, with higher CESD scores reflecting greater depression, ranging from 0 to 60. Similar to studies in the general population,(31) internal reliability was high across all timepoints (α=.82).

**Patient Quality of Life.** To measure patient QOL, the Functional Assessment of Cancer Therapy Scale (FACT-BMT) was used. The FACT is a widely used instrument and is a comprehensive measure of QOL in HSCT.(32) Scores from 47 items combine into one continuous scale in which higher scores indicate better QOL. The questions are anchored to the past 7 days in which scores are normed and scored with possible ranges from 0 to 148. Internal reliability in the current sample was good (α=.87).

**Statistical approach.** First, we examined all descriptive statistics and bivariate correlations between study variables. Guided by the Actor Partner Interdependence Modeling framework (APIM),(33) we then tested dyadic interdependence over time with structural equation models (SEM). This approach allows for simultaneous estimate of an individuals’ QOL on their subsequent QOL ratings (“actor” effects) while controlling for other estimates in the model, in addition to testing how one member of the dyad’s QOL impacts the other member’s depression/anxiety (“partner” effects). As such, one can garner the unique contribution of each effect. Models were evaluated through consideration of model fit statistics and parameter estimates; specifically, CFI scores of >.90 and scores of <.05 indicating good model fit for RMSEA and SRMR.(34) Chi-
square difference tests compared constrained and unconstrained models to test
differences in parameter estimates between treatment groups. Missing data was
handled by full information maximum likelihood (FIML) with the commonly used missing
at random assumption.(35) SPSS(36) was used for descriptive and linear models and
Mplus(37) was used for all SEMs.

We examined two different models of patient and caregivers’ well-being over
time: 1) a model of patient QOL and caregiver anxiety, 2) a model of patient QOL and
caregiver depression. In both models, constructs were measured at the four study time
points of baseline, 6 weeks, 3-months and 6-months post-transplant admission. For our
primary research question of whether dyadic associations differed between the PEPPR
and eTAU groups, we tested multi-group models in which all parameters were freely
estimated in each group and then all parameters were constrained to be equal between
groups. The fit between models was compared using chi-square difference tests.

Results

Allo-HSCT patient/caregiver dyads (n = 407) were approached at both
participating hospitals and 331 dyads met eligibility criteria. One hundred and fifty-four
patient and caregivers participated in this study and provided baseline data for
analyses. As previously reported,(18) there were no differences of demographics
between PEPPR and eTAU. Greater caregiver age was also significantly related to
lower caregiver depression at baseline ($r = - .22; p = .006$) and younger patient age was
related to worse patient QOL ($r = .17; p = .031$). Accordingly, all models accounted for
baseline age.
APIM Multi-group Models.

Multi-group SEM’s were estimated at the dyad level between PEPPR \((N=76)\) and eTAU \((N=83)\). For the first model of caregiver anxiety and patient QOL, a model in which all paths were constrained to be equal between groups \((\chi^2(71)=93.69; p=0.37)\) was compared to a model in which all paths were freely estimated \((\chi^2(52)=68.34; p=.064)\). A chi-square test did not reach the critical value at alpha < .05; thus, the data fit a constrained, more parsimonious model not taking group (PEPPR vs. eTAU) into account. Next, the second model involving caregiver depression and patient QOL was considered. Similar to the first model of caregiver anxiety, a chi-square difference test between the two models suggested that the constrained model was a better fit \((\chi^2(71)=94.51; p=.13)\) than the unconstrained model \((\chi^2(52)=88.02, p=.0013)\) again indicating support for the constrained model. Although no differences emerged between the PEPPR and eTAU groups given that the constrained model provided a better fit to the data in both models, it was still of interest to examine dyadic effects over time from the full sample.¹

Patient quality of life and caregiver anxiety.

First, we examined bivariate correlations across all timepoints, which are displayed in Table 1. Higher patient QOL was significantly correlated with lower caregiver anxiety at baseline \((r=-.31; p=.00028)\) and at 6 weeks post-admission \((r =-.29; p=.007)\), but not at subsequent timepoints.

¹ Including group assignment as a covariate in each model did not alter any of the findings presented.
Next, within the SEM model of patient QOL and caregiver anxiety, all actor effects were significant (all $p$’s<.05). This means that prior patient QOL was a significant predictor of subsequent patient QOL at each of the three follow-up time points. Similarly, caregiver anxiety was a significant predictor of subsequent caregiver anxiety at each of the three follow-up time points (Figure 1).

**Partner Effects.** No significant partners effects were supported meaning that caregiver anxiety did not predict subsequent patient QOL when controlling for prior patient QOL. Similarly, patient QOL did not predict subsequent caregiver anxiety when controlling for prior caregiver anxiety. Importantly, as suggested in bivariate comparison, a significant correlation was shown between baseline caregiver anxiety and patient QOL. A significant relationship was not found for the final time point (Figure 1).

**Patient quality of life and caregiver depression.**

First, bivariate relationships demonstrated that higher patient QOL was significantly related to lower caregiver depression at all timepoints, except for at the 3-month timepoint ($r$=.048, $p$=.690). Specifically, across the course of stem cell transplant, the relationship between patient QOL and caregiver depression changed, such that the two variables were significantly related at baseline ($B$=-.32; $p$ = .000), 6 weeks ($B$=-.22; $p$=.044), and the 6-month timepoint ($B$=-.34; $p$=.009; Table 2).

Next, we estimated longitudinal SEM models as described above. Across all timepoints, significant actor effects emerged. This indicated that patients’ QOL predicted subsequent ratings of their own quality of life at latter time points (all $p$’s<.05). Similarly,
all caregiver ratings of their own depression were significantly related to subsequent ratings of their own depression at later time points (all p’s<.05).

**Partner Effects.** Two significant partner effects emerged in our analyses. First, worse patient QOL at 6 weeks was significantly related to lower caregiver depression at 3 months following transplant ($B=.182; p=.026$). Second, this relationship also changed over time, such that worse patient QOL at 3 months was significantly related to more caregiver depression at 6 months ($B=-.192; p=.001$; Figure 2).

**Exploratory analyses.** Because the first partner effect was in the unanticipated direction (worse patient QOL related to lower depression at the subsequent timepoints), we ran a series of follow-up regression models to isolate this effect and potentially explain this finding. We considered two patient variables as potential moderators: days of patient hospitalization and number of readmissions to the hospital. Although the number of readmissions was not related to change in caregiver depression between 6 weeks and 3 months, greater days in the hospital approached significance in its relation to greater caregiver depression at 3 months ($B=.19; p=.093$), after controlling for caregiver depression and patient QOL at 6 weeks. This suggests that length of the hospital stay may be related to the interdependence of patient QOL and caregiver depression at 3 months post-HSCT.

**Discussion**

Caregivers are critical to patients during the cancer journey, particularly in HSCT. There is emerging data highlighting that patient and caregiver well-being is often
interdependent,(20) but may change over time.(38, 39) The current study aimed to
examine the interdependence of patients’ QOL and caregivers’ anxiety and depression.
Overall, it is noteworthy that the data fit one parsimonious model as opposed to a
multigroup SEM for the PEPPR and eTAU groups as originally hypothesized suggesting
similar associations between dyads and across time in these two groups. In the full
sample, we observed significant actor effects over the course of HSCT (patients’ QOL
scores predicting their subsequent QOL and caregivers’ depression predicting their own
subsequent depression). Additionally, we detected somewhat surprising partner effects,
suggesting the interdependence changes over time; namely reverses direction such that
if a patient has worse QOL at 6 weeks, their caregiver will be doing better (lower
depression) at the 3-months. Finally, comparing the models examining caregivers’
anxiety and depression, we observed greater interdependence over time for caregiver
depression and patient QOL, than for caregiver anxiety and patient QOL across HSCT.
It is first worth commenting on the finding that the data did not fit a multigroup
model as originally hypothesized. There are several reasons why the constrained model
was retained over the multigroup model. We may have been underpowered to detect
group differences with multiple estimated parameters, a common concern in longitudinal
SEM’s.(40) Further, while the PEPPR intervention demonstrated a significant effect on
caregiver distress,(18) this effect may not be robust to extend to patient QOL, or dyads’
interdependence over time. As demonstrated in exploratory regression models, a
number of medical factors likely impact QOL (length of hospitalization) and may
overshadow any dyadic relationships of well-being. Future studies will benefit from
more repeated measures of patients and caregivers, potentially harnessing
technologies to track changes over more granular periods of time(41) and closely
monitoring how changes in patient status relate interdependence.

The dyadic changes that we detected over time, while small in effect, are
intriguing for several reasons. First, the significant relationship that we expected
between FC mood and patient QOL at baseline based on prior work(20) continued at 6
weeks, but was no longer significant at 3 months. This may relate to patient and
caregivers’ interrelatedness changing as care transitions to an outpatient setting in
which more care is provided by the medical team and, potentially, relieve the caregiver
or impose additional details of patient care that caregivers feel they need to observe.

Second, we detected an unanticipated change in the direction of the relationship
between patient QOL at 6 weeks and caregivers’ depression at 3-months in that
caregivers were less depressed at 3 months when their patient had poorer QOL at 6-
weeks post-HSCT. Changes in patients’ medical treatment - experienced by both
members of the dyad - may also explain changing interdependence over time. We
attempted to explore this hypothesis by looking at the impact of hospitalized days as
predictors of in the regressions suggesting that the greater number of days that patients
were in the hospital approached significance as a predictor of greater depression at 3-
months post-transplant. Future research can build on these initial findings by closely
monitoring changes in patients’ medical status.

Differences between the models examining caregivers’ anxiety and depression
also deserve further comment. Prior research suggests both depression and anxiety
worsen over the course of transplant(15) but caregiver distress may dissipate over
time(16) potentially explaining, in part, the change in interdependence for caregiver
anxiety and patient QOL. This finding mirrors other work in breast cancer suggesting that reductions in anxiety are more closely related to general reductions in distress (a commonly used screener) and depression(42) remain more stable.(43) Anxiety is often conceptualized as having an anticipatory component, so a natural decrease would make sense following diagnosis and treatment initiation as patients and caregivers prepare for, and recover from, the hospital. Indeed, , the primary analyses with the current data showed the intervention improved distress overall, with slightly greater effect sizes for anxiety than depression.(18) Taken together, depression may demonstrate greater interdependence than anxiety over the course of HSCT, which coincides with other research suggesting depression remains more stable over time and is a salient treatment target for supportive interventions.

The current findings should be qualified with several limitations. First, the patients and caregivers recruited were fairly homogenous, with the majority of caregivers being white females and patient-caregiver dyads being spousal. Future research should seek a more diverse demographic sampling to increase generalizability and examine whether similar patterns of interdependence are observed in other patient-caregiver relationships (e.g., parent-child dyads). Additionally, the current analyses represent secondary data analyses and the original study may not have been powered to detect dyadic relationships over time, as multigroup SEMs often require hundreds of participants.(40) Larger samples will allow for additional mediation or moderation models to further explore dyadic relationships,(44) or potentially, different mechanisms(45) of intervention effects.

Conclusions
This study highlights the interrelated, yet nuanced, patient and caregiver relationship during the course of stem cell transplantation. These results highlight the need for not only additional support for the patient, but also the caregiver and possibly the closely connected dyad. While future work may identify how these change in the context of the intervention, our findings imply some constructs (e.g., depression) may relate to greater interdependence over time than others (e.g., anxiety) and interventions that seek to improve patient-caregiver well-being should target these outcomes as clinically meaningful endpoints. Future research should explore these relationships and include longer-term follow-up to identify when, and how, to better support patients and their closely connected caregivers.
Table 2. Bivariate correlations among patient and caregiver well-being over time

|                          | Patient quality of life – Baseline (M = 97.94; SD = 18.25) | Patient quality of life – 6 weeks (M = 96.33; SD = 19.39) | Patient quality of life – 3 months (M = 101.43; SD = 19.09) | Patient quality of life – 6 months (M = 101.49; SD = 21.89) |
|--------------------------|------------------------------------------------------------|----------------------------------------------------------|-------------------------------------------------------------|-------------------------------------------------------------|
|                          | -.32** .12 .048 -.16                                      | -.042 -.22* .12 -.11                                      | .029 -.044 -.048 -.19                                       | -.23 -.14 -.26 -.34**                                      |
| Caregiver Depression     |                                                            |                                                          |                                                             |                                                             |
| – Baseline (M = 20.29;   |                                                            |                                                          |                                                             |                                                             |
| SD = 6.61)               |                                                            |                                                          |                                                             |                                                             |
| – 6 weeks (M = 19.26;    |                                                            |                                                          |                                                             |                                                             |
| SD = 5.58)               |                                                            |                                                          |                                                             |                                                             |
| – 3 months (M = 19.0;    |                                                            |                                                          |                                                             |                                                             |
| SD = 6.40)               |                                                            |                                                          |                                                             |                                                             |
| – 6 months (M = 20.06;   |                                                            |                                                          |                                                             |                                                             |
| SD = 7.20)               |                                                            |                                                          |                                                             |                                                             |
| Caregiver Anxiety – Baseline (M = 40.59; SD = 12.88) |                                                            |                                                          |                                                             |                                                             |
| – 6 weeks (M = 38.98; SD = 12.21) |                                                            |                                                          |                                                             |                                                             |
| – 3 months (M = 38.41; SD = 12.64) |                                                            |                                                          |                                                             |                                                             |
| – 6 months (M = 37.65; SD = 12.98) |                                                            |                                                          |                                                             |                                                             |

Note. N = 154; **p < .001; *p < .05
Declarations.

**Ethics approval and consent to participate**

The Colorado Multiple Institutional Review Board approved the study (www.ClinicalTrials.gov identifier: NCT02037568).

**Consent for publication**

Not applicable

**Availability of data and material**

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

**Competing interests**

Author MY consults for Bluenote Therapeutics; the authors report no other conflicts of interest.

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**Authors’ contributions**

TS: Was involved with the study design, analytic plan, intervention delivery and manuscript preparation.

KR: Was involved with the analytic plan, conducting all analyses and manuscript preparation.

MY: Was involved in the analytic plan and manuscript preparation.

BWB: Was involved with study design, intervention delivery and manuscript preparation.

JMJ: Was involved in the analytic plan and manuscript preparation.

SC: Was involved in the analytic plan and manuscript preparation.

GRU: Was involved in the analytic plan and manuscript preparation.

NAP, CN, and MLL: Were involved with the study design, analytic plan, intervention delivery and manuscript preparation.

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Figure Legends:

Figure 1. APIM model of caregiver anxiety and patient quality of life across the course of hematopoietic stem cell transplant

Figure 2. APIM model of caregiver depression and patient quality of life across the course of hematopoietic stem cell transplant

All estimates are unstandardized path coefficients; Significant estimates are presented in bold. N = 154; **p < .001; *p < .05
Figures

Figure 1

APIM model of caregiver anxiety and patient quality of life across the course of hematopoietic stem cell transplant. All estimates are unstandardized path coefficients; Significant estimates are presented in bold. N = 154; **p < .001; *p < .05

Figure 2

APIM model of caregiver depression and patient quality of life across the course of hematopoietic stem cell transplant. All estimates are unstandardized path coefficients; Significant estimates are presented in bold.
bold. N = 154; **p < .001; *p < .05

Supplementary Files

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- CopyofDyadCharacteristicTable16.20.21.xlsx