

# Psychosocial considerations in hematopoietic stem cell transplantation: implications for patient quality of life and post-transplant survival

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Many patients undergoing hematopoietic stem cell transplantation (HSCT) report distress over their treatment. This article reviews the literature on the psychosocial sequelae of HSCT, the evidence of a prospective relationship between psychosocial factors and post-transplant survival, the clinical implications of these findings, and considerations for future research.

**H**ematopoietic stem cell transplantation (HSCT) is indicated in the treatment of several malignant (eg, leukemia) and non-malignant (eg, sickle cell anemia) diseases. In the case of malignancy, HSCT can offer the possibility of remission or even a cure when other treatments prove insufficient; however, the procedure itself is invasive and is associated with relatively high rates of morbidity and mortality.<sup>1</sup> The elevated rates of morbidity include not just physical complications such as opportunistic infection and graft-versus-host disease (GVHD), but also psychosocial sequelae that can include clinically significant elevations in depression, anxiety, and family discord.<sup>2</sup> Like the physical complications, the psychosocial sequelae of HSCT are important with respect to patient quality of life and deserve consideration in their own right. In addition, and of particular interest to the medical community, a recent comprehensive review of the literature<sup>3</sup> provides evidence of an independent and clinically significant relationship between psychosocial factors and survival after HSCT.

## Psychosocial sequelae of HSCT

To summarize a series of studies,<sup>4</sup> the seven most common causes of distress among individuals undergoing treatment for cancer include uncertainty regarding treatment outcome, recurrence, and mortality; the impact of treatment on their family; changes in appearance and sexuality; the long-term burden of treatment such as reduced functional

status; interaction with the medical system, communication with medical personnel, and obtaining information; financial considerations such as insurance, the cost of treatment, and supporting self/family; and acute symptoms such as nausea/vomiting, mouth sores, and pain. Collectively, significant worry or concern about these issues is referred to as cancer treatment distress, an outcome that can be

### KEY POINTS

Approximately 80% of individuals undergoing hematopoietic stem cell transplantation (HSCT) report distress over their treatment; approximately one-third of patients report symptoms consistent with a diagnosis of clinical depression.

There is now preliminary evidence to suggest that psychosocial factors (eg, social support) independently predict survival following transplant, even when adjusting for relevant biomedical covariates. Two studies found that poor social support predicted a three-time higher risk of mortality in these patients.

Thus far, the evidence warrants the inclusion of psychosocial services on transplant units and additional research.

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accurately and reliably assessed with a brief, self-report measure.

In a 5-year longitudinal study of 335 individuals undergoing HSCT for leukemia or lymphoma,<sup>2</sup> cancer treatment distress peaked prior to transplant and remained elevated through 90 days post transplant before declining steadily for the duration of follow-up assessments. However, even at 1-year follow-up, 79% of patients reported a clinically significant level of cancer treatment distress. At the 3- and 5-year assessments, this number fell to 42% and 13%, respectively. It is noteworthy that by the 1-year assessment, the majority of survivors showed a near-complete recovery from the physical limitations associated with transplant but continued to report high levels of other elements of cancer treatment distress.

In a substantial minority of cases, the distress associated with HSCT may be significant enough to contribute to a mental disorder. The threshold of mental disorder is met when (a) an individual demonstrates psychological symptoms in excess of what is typical or expected and (b) these symptoms cause clinically significant distress or impairment in at least one major area of functioning (eg, social).<sup>5</sup>

Major depressive disorder, sometimes simply referred to as clinical depression, is among the most common mental disorders observed in both the general population and individuals affected by cancer. Its symptoms include a sustained reduction in mood; a marked decreased interest in activities (ie, anhedonia); and disturbances in appetite, sleep, psychomotor functioning, and cognitive functioning. Depression can also be accompanied by suicidal ideation; however, this is not a requirement for diagnosis. With respect to HSCT, it has been found that depression is most frequently observed during the pretransplant and acute recovery phases, with approximately 33% of patients endor-

ing clinically significant symptoms during these times.<sup>2</sup> Five years post transplant, 19% of patients continued to exhibit clinically significant symptoms of depression.

The psychosocial sequelae associated with HSCT are not limited to the patient but can also extend to the patient's caregiver, typically the patient's partner/spouse or close family member. One study<sup>6</sup> found that for at least as long as 1 year post transplant, caregivers continued to report significantly higher levels of depression, anxiety, and marital dissatisfaction than did their partners (ie, the patients). During the transplant and recovery periods, caregivers tended to prioritize the needs and concerns of the patients over their own, an understandable and adaptive coping strategy. However, over the long term, subjugating one's own concerns can take a toll.

In summary, these data demonstrate that cancer treatment distress is commonplace among HSCT patients and their partners; that approximately one-third of HSCT patients experience symptoms consistent with a diagnosis of clinical depression at some point during their treatment; and that the psychosocial recovery from HSCT is a long-term process, one that typically takes longer than physical recovery. Moving beyond these descriptive statements, we are now in a position to begin to predict which individuals will experience cancer treatment distress and depression during treatment and recovery.

From a medical standpoint, chronic GVHD and a treatment history are predictive of depression.<sup>2</sup> Psychosocially, inadequate social support represents a risk factor for both cancer treatment distress and clinical depression.<sup>2</sup>

Social support is a well-researched construct that refers to one's perception that others (ie, spouse/partner, family, friends, and other social network members) are available and willing to provide some form of help during

times of need.<sup>7</sup> For many individuals going through treatment for cancer, members of their social network rally to their side and provide both tangible assistance (eg, assuming household chores) and emotional support (eg, offering encouragement). Unfortunately, this is not always the case, as many cancer patients report that they perceive insufficient support or even problematic support—that is, when the support provided does not match their needs. As will be reviewed in the next section, inadequate social support also appears to be a risk factor for poor medical outcomes after HSCT.

### The relationship between psychosocial factors and survival after HSCT

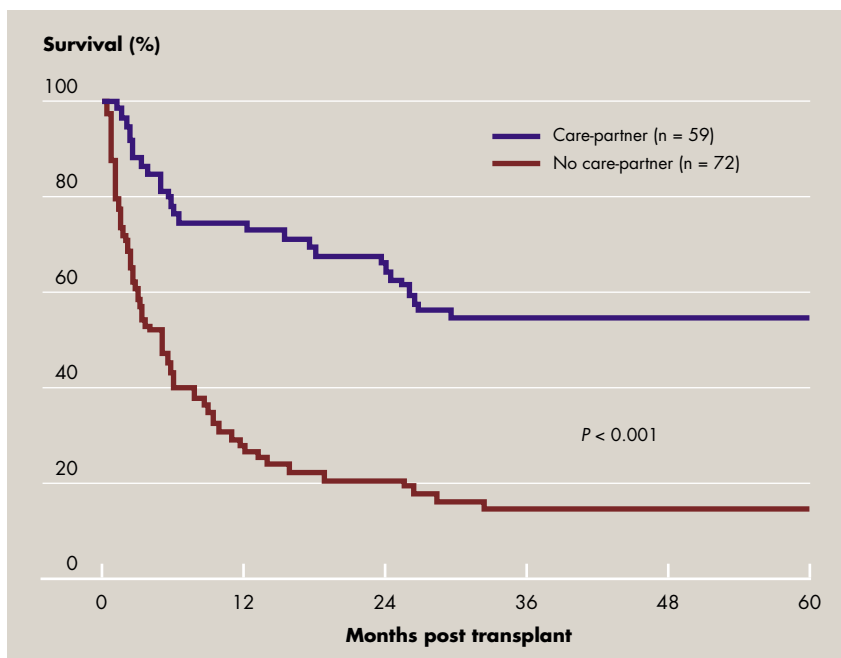
Unfortunately, the potentially life-threatening complications associated with HSCT are common and many. To improve overall survival rates, there has been great interest in better understanding which factors contribute to poor outcomes. The more notable factors include the age and general health of the patient, the specific cancer diagnosis, the disease status, the relationship of the donor to the patient, and the type of transplant.<sup>1</sup> A review of the unique advantages and risks associated with each type of transplant is beyond the scope of this article, but interested readers are directed to Appelbaum.<sup>1</sup>

Recently, investigators have begun to consider whether psychosocial factors also contribute to post-transplant survival rates. Psychosocial factors do predict physical health outcomes, including mortality, in a range of other chronic illnesses, such as heart disease, human immunodeficiency virus/acquired immunodeficiency syndrome, and autoimmunity.<sup>8</sup> Any discussion of a relationship between psychosocial factors and survival in cancer, however, has proven to be much more controversial. After almost 20 years of research on the topic, the results are mixed and appear to depend large-

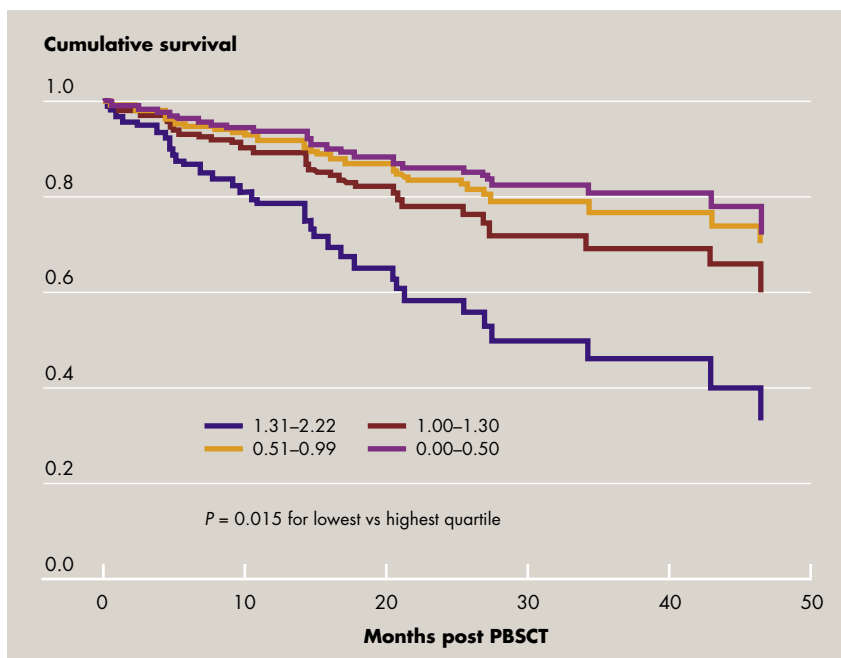
ly on the specific cancer site and the stage of disease. In the case of survival after HSCT, data from methodologically sophisticated studies do in fact support a link between psychosocial factors and survival.<sup>3</sup>

Perhaps the most eloquent study on the topic, conducted by Foster and colleagues,<sup>9</sup> assessed whether social support during allogeneic transplant predicted survival over a 5-year follow-up in a sample of 131 adult patients. The study's investigators operationalized social support simply by recording whether an "in-hospital lay care-partner" was consistently present during the patient's hospital admission, with a consistent presence defined as being at the bedside for at least 7 hours a day, at least 5 days a week. Just under half (45%) of the patients had a consistent in-hospital lay care-partner, the majority of whom (61%) were the patient's spouse, followed by the patient's parent (34%). After adjusting for disease status (active vs remission), diagnosis, relationship of the donor to the patient, and GVHD, the authors reported that the risk of mortality was more than three times higher among patients who did not have an in-hospital lay care-partner consistently present than among patients who did (hazard ratio = 3.06;  $P < 0.001$ ; Figure 1). Within 1 month of the transplant, 19% of patients without a care-partner had died, compared with 0% of patients with a care-partner; 1 year post transplant, 74% of patients without a care-partner had died, compared with only 25% of patients with a care-partner. In both groups, the most common causes of death were GVHD, relapse, and infection.

Although the Foster et al study produced compelling data, it did not consider the quality of the relationship between the patient and the care-partner. Support can be present but problematic, as in the case of a care-partner criticizing the patient, presenting an overly pessimistic out-



**FIGURE 1** After adjusting for disease status (active vs remission), diagnosis, relationship of donor to the patient, and graft-versus-host-disease, the risk of mortality was more than three times higher among patients who did not have an in-hospital lay care-partner consistently present than among patients who did (hazard ratio = 3.06;  $P < 0.001$ ). Adapted, with permission, from Foster et al.<sup>9</sup> © The Haworth Press.



**FIGURE 2** Patients scoring in the lowest quartile (0.00–0.50) of "problematic social support," a measure of criticism, pessimism, and other forms of unhelpful support, had the highest rates of survival, adjusting for Karnofsky Performance Status, interferon treatments, and depression. PBSCT = peripheral blood stem cell transplantation. Adapted, with permission, from Frick et al.<sup>10</sup> © John Wiley & Sons Ltd.

look, placing demands on the patient, or minimizing the patient's concerns. Frick and colleagues<sup>10</sup> investigated the prospective relationship between problematic support, assessed by patient self-report before the transplant, and survival over a 4-year period in a sample of 99 patients undergoing autologous transplant. The authors reported that after controlling for Karnofsky Performance Status, interferon treatments, and depression, patients with high scores on problematic support (ie, experienced more criticism, pessimism, etc.) had more than three times the risk of mortality as did patients with low scores (relative risk = 3.649;  $P = 0.015$ ; Figure 2).

These reports represent but two studies in a relatively small but growing area of research. Not all studies uniformly support the hypothesis that social support predicts survival in post-transplant patients. In addition to the two studies reviewed here, there have been at least five earlier studies that tested this hypothesis, three of which supported the hypothesis and two did not. Nevertheless, the two studies reviewed here are more sophisticated methodologically than the five earlier studies, with larger sample sizes, statistically sound methods of data analysis, adjustment for medical and demographic factors, and valid and reliable measures of social support. Beyond social support, there is also preliminary evidence to suggest that other psychosocial factors (eg, hopefulness, fighting spirit, depression) are also associated with post-transplant survival. With further research, we can be more definitive and specific in our conclusions.<sup>3</sup>

Evidence of an association between psychosocial factors and survival begs the question by what mechanism? In other words, how does something as intangible as social support "get into the body" and affect medical outcomes? This is a wide-open question that requires further study; however, some initial hypotheses can be gen-

erated. From a behavioral standpoint, social support has been associated with improved overall coping, including better adherence to a healthy diet, adequate exercise, and prescription medications and other medical recommendations.<sup>7</sup> Given the importance of preventative care and adherence to medical recommendations after transplant, behavioral factors alone may be sufficient to explain the relationship between psychosocial factors and survival.

There is also evidence of a more physiologic mechanism at work. To begin, we know from histologic evidence<sup>11</sup> that there is noradrenergic, cholinergic, and neuropeptidergic innervation of the bone marrow, providing the "infrastructure" for communication between the nervous and immune systems. We also know from well-controlled studies that stress and poor social support increase the risk of infection (eg, rhinovirus) in otherwise healthy individuals, a finding that is not fully explained by health practices.<sup>7</sup> Thus, from a theoretical standpoint, one could argue that psychosocial factors may affect survival in HSCT patients via an immunologic mechanism.

Indeed, in a sample of 71 autologous HSCT patients, McGregor and colleagues<sup>12</sup> found that, adjusting for medical risk, pretransplant levels of self-reported depression predicted rates of white blood cell (WBC) reconstitution in the days after transplant. To provide a clinical context for their finding, patients with a high score in reported depression symptoms took approximately 16 days post transplant to reach a WBC count of 1,000/mm<sup>3</sup>, nearly a week longer than patients with a low score in reported depression symptoms.

To summarize the literature to date, the evidence on balance suggests there is a clinically significant relationship between psychosocial factors and survival, one that warrants further investigation. Before we address the topic of future research, the next

section considers the clinical implications of the evidence thus far.

### Clinical implications

The evidence reviewed here points to the need to include psychosocial services on transplant units. Hoodin and colleagues wrote, "Considering all the available data, it seems imperative that transplant teams should include psychological evaluations in the pretransplant workup."<sup>3</sup> Anticipating, undergoing, and recovering from HSCT are stressful experiences for patients and their families. Psychosocial services can be instrumental in alleviating the distress with which patients and families are confronted. Although the research has yet to bear this out, psychosocial services may even contribute to improved medical outcomes for transplant patients.

To be maximally effective, psychosocial screenings and interventions should be offered early in the treatment process, given the research on the relationship between factors such as pretransplant social support and post-transplant survival. Consistent with this model of care, the staff at the Helen F. Graham Cancer Center at Christiana Care Health System in Newark, Delaware, includes clinical psychologists, social workers, and care coordination nurses who are available to meet with patients and families to address their psychosocial needs and concerns in preparation for transplant.

### Future directions

Although the documented use of HSCT as a cancer treatment was first reported in 1956, its widespread application can be traced to the 1980s.<sup>13</sup> Even more recently, the first scientific reports on the relationship between psychosocial factors and survival did not appear until the 1990s, with the more methodologically sophisticated studies published only in the past few years. In other words, the psycho-oncology of HSCT is in its infancy, and yet the field has produced compelling

findings that at least warrant additional study.

First, it will be important to replicate the existing findings on the relationship between psychosocial factors and survival, preferably with studies that employ a prospective design, recruit participants from multiple sites, and assess psychosocial factors with valid and reliable measures. Second, more attention should be paid to the mechanisms that mediate these relationships. Finally, new research is needed to investigate which psychosocial interventions are most effective at addressing cancer treatment distress, mental disorders, and family discord among transplant patients. The results of these kinds of studies can lead to improved psychosocial screening and intervention techniques, which may enhance both the quality and length of life for the survivors of HSCT.

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