

**SEMMELWEIS EGYETEM
DOKTORI ISKOLA**

Ph.D. értekezések

3238.

JANICSÁK HENRIETTA

Pszichiátria

című program

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Correlation of psychosocial status and health-related quality of life in hematopoietic stem cell transplanted patients

PhD thesis

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Budapest
2025

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LIST OF ABBREVIATIONS

aGVHD	Acute graft versus host disease
allo-HSCT	Allogeneic hematopoietic stem cell transplantation
auto-HSCT	Autologous hematopoietic stem cell transplantation
BDI	Beck Depression Inventory
BMT	Bone Marrow Transplantation
CGI	Clinical Global Impression
cGVHD	Chronic graft versus host disease
DLI	Donor lymphocyte infusion
EORTC-QLQ-C30	30 item Quality of Life of Cancer Patients European Organization for Research and Treatment of Cancer
FACT-BMT	Functional Assessment of Cancer Therapy–Bone Marrow Transplant
FACT-G	Functional Assessment of Cancer Therapy-General
GVHD	Graft versus host disease
HSCT	Hematopoietic stem cell transplantation
HRQOL	Health-related quality of life
MT	myeloablative
NIH	National Institute of Health
NRM	Non-relapse mortality

PACT	Psychosocial Assessment of Candidates for Transplantation
PBSC	Pheripheral blood stem cell
PTSD	Post-traumatic stress disease
RIC	Reduced intensity conditioning
RTW	Return to work
SES	Socioeconomic status
SF-36	36-Item Short Form Survey
SIPAT	Stanford Integrated Psychosocial Assessment for Transplantation
SSTAI	Spielberger State-Trait Anxiety Inventory
TERS	Transplant Evaluation Rating Scale
TRM	Transplant-related mortality
WHO	World Health Organization

1. INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) has become a routine and potentially curative treatment for different malignant and non-malignant hematological illnesses, and the number of survivors is quickly increasing globally. (1, 2) . Transplant-related serious medical consequences, such as graft-versus-host disease (GVHD) and mortality, continue to be a significant and well-documented concern despite recent advancements in this field (3-6). As more advanced techniques have been developed and mortality rates have dropped over recent decades, attention has focused to the psychosocial issues associated with transplantation. The psychosocial challenges associating transplantation are discussed in the field of both health-related quality of life (HRQOL) and psychopathological research. Findings from the extensive research on psychological symptoms, predictors' relationship, post-transplant physical and mental recovery, long-term psychosocial functioning, and HSCT-related HRQOL have been controversia (7-12). More recently, research has focused on the unique features of special populations (eg.: old patients, chronic GVHD (cGVHD) patients) and different conditioning and treatment regimens in terms of psychosocial difficulties and HRQOL. The most researched psychiatric comorbidities of HSCT are anxiety, depression, sleep and sexual disorders, delirium and post-traumatic stress disorder (PTSD) (2, 13). Creating guidelines for the treatment of psychiatric symptoms and psychosocial interventions in HSCT patients and close family is also essential to consultation–liaison psychiatrists and transplant teams (10, 12-20). Research examining the determinants of positive outcomes after HSCT may encourage interventions with preventive focus (7, 9, 21, 22). The major disadvantage of research are the methodological barriers and diversity of studies that prevent to draw precise conclusions.

The issues addressed in literature review include the assessment instruments and methodological concerns of HRQOL in HSCT; evaluation of the research on psychosocial functioning and HRQOL in the course of HSCT; differences in HRQOL between patients treated with various treatment regimens - allogeneic (allo-HSCT), autologous HSCT (auto-HSCT), standard-dose chemotherapy - healthy matched controls, and population norms. In addition, the effects of GVHD, reduced-intensity conditioning

(RIC) and psychosocial determinants of HRQOL and psychosocial functioning are discussed, emphasizing the impact of comorbid mental disorders.

1.1. Diagnostic tools for screening psychosocial difficulties and health-related quality of life in hematopoietic stem cell patients

Historically, psychosocial assessments were applied to select appropriate candidates for solid organ transplantation because of the limited availability of donor organs (23, 24). Additional aim was to supply information for customized treatment planning (25, 26). However, since positive correlations between pre-transplant psychosocial problems and post-transplant medical and psychosocial problems have been reported (27-29), the focus on pre-transplant psychosocial assessment has changed to identifying patients at increased risk (i.e., patients with significant psychopathology, substance abuse or poor treatment adherence) (30, 31). The goals of pre-transplant psychosocial assessment are presented in Table 1 (24).

Table 1. Goals of psychosocial pre-transplant evaluation

Equal access to care
Efficient resource utilization
Maximizing benefits and minimizing risks by identifying risk factors (substance abuse, compliance issues, psychopathology) to optimize post-transplantation compliance
Providing information for individualized treatment planning for patients at high risk
Implementing appropriate treatments

Pre-transplant psychosocial assessment instruments used for solid organ transplantation were adapted for hematopoietic stem cell transplantation (HSCT). The Psychosocial Assessment of Candidates for Transplantation scale (PACT) and the Transplant Evaluation Rating Scale (TERS) are the most frequently used evaluating scales (32). Furthermore, the Stanford Integrated Psychosocial Assessment for Transplantation (SIPAT) have been developed as a standardized and comprehensive measurement of psychosocial vulnerability before transplantation (24, 33). Numerous

research confirmed the reliability and validity of these psychosocial evaluation tools in HSCT (34-39).

Evidence supports the utility of psychosocial assessment instruments in predicting psychosocial difficulties and medical outcomes during and after transplantation (30, 32, 40, 41). Research in this field recommend uniformed and comprehensive pre-transplant psychosocial screening yet standardized screening process is still missing (39, 40). Implement of standardized assessment tools in selection procedure requires standard minimal criteria of selecting candidates for HSCT that is also missing (42). Decision-making process for selecting suitable candidates for HSCT – particularly allogeneic HSCT – would contain numerous patient, disease and transplant-related factors, including the assessment of psychosocial risk factors (24).

With advances in treatment outcomes and longer survival times, patients' HRQOL is becoming more significant reflected in the development of diagnostic instruments used to assess the HRQOL of different patient populations. Historically general measures of psychological and functional status were applied for assessing patients' well-being during and after cancer therapies. General HRQOL measures are suitable for comparison of various patient populations with general population, but less sensitive to treatment side effects. Most frequently used general HRQOL measurement in HSCT population is the 36-Item Short Form Survey (SF-36). Cancer-specific instruments were developed specifically for cancer population. Currently used HRQOL assessment instruments comprise both symptom- and treatment-specific scales for different cancer populations and treatment regimens (43, 44). Two integrated and well documented HRQOL instrument - FACT-BMT and the 30 item Quality of Life measurement of European Organization for Research and Treatment of Cancer (EORTC-QLQ-C30) became available for HSCT population with acceptable psychometric qualities (45-49). Both were constructed on similar, modular concept with a generic core questionnaire in combination with disease or treatment-specific modules. Nonetheless comparative studies indicate essential differences between the content of subscales and direct comparison of results might lead to misleading conclusions (43, 44, 50). Consensus is lacking regarding which type of measure would be methodologically more appropriate. Evidence supports essential benefits of cancer and treatment specific instrument compared to broad instruments. FACT-BMT has better differentiated between the effect of acute and chronic

GVHD on HRQOL than SF-36 in HSCT population (51). The characteristics of commonly used diagnostic tools are summarized in Table 2 (33, 51-56).

Table 2. Characteristics of diagnostic instruments used for screening psychosocial risks and quality of life in hematopoietic stem cell transplantation patients

Diagnostic instrument	Factors	Aim	No. of items	Score range	Ref.
Psychosocial Assessment of Candidates for Transplantation	4: Social support, psychological health, lifestyle factors, and understanding of transplant and follow-up	To stratify psychosocial risk in solid organ transplant recipients	8	8-40	Olbrisch et al, 1989 [51]
Transplant Evaluation Rating Scale	Not divided into factors	To assess the reliability and validity of the selection of transplant candidates	10	26.5- 79.5	Twillman et al, 1993 [52]
Stanford Integrated Psychosocial Assessment for Transplantation	4: Patients' level of readiness and illness management; level of readiness of patients' social support system; psychological stability and psychopathology; and lifestyle and substance use	To assess the psychosocial variables and behaviors that frequently have negative effects on all types of transplant candidates	18	0-115	Maldonado et al, 2015 [31]

Functional Assessment of Cancer Therapy (FACT)-version 4	4: Physical well-being, social/family wellbeing, emotional well-being, and functional well-being	To measure dimensions of healthrelated quality of life in cancer patients	27	0-108	Cella et al, 1993 [53]
Functional Assessment of Cancer Therapy–Bone Marrow Transplant (FACT-BMT)–version 4	5: Physical, functional, emotional and social well-being, and BMT-specific complaints	To evaluate multidimensional aspects of quality of life in BMT patients	50: 27 (FACT) +23 (BMT specific)	0-200	McQuellon et al, 1997 [54]
EORTC-QLQ-C30	8: multitem scales (functional and symptoms scales) 6: singe items (dyspnea, apetite loss,sleep disturbance, constipation, diarrhea, financial problems) 1: global health scale 1: global quality of life scale	To measure quality of life in all cancer patients	30	0-126	Aaronson et al, 1993 [55]

1.2. Health-related quality of life and psychosocial adjustment following hematopoietic stem cell transplantation

1.2.1. Methodological considerations

Psychosocial adjustment and HRQOL are broad concepts to define with numerous difficulties in assessment methodology. Studies investigating HRQOL and psychosocial adjustment associated with HSCT are heterogeneous in their study designs, patient populations, comparison groups, assessment tools and assessment time frames (57). Psychosocial adjustment comprising wide range of psychological reactions and assessed as psychological distress or depression and anxiety in research, that may vary from common feelings of sadness and fear to manifestation of a psychiatric disease. Studies revealed only moderate agreement in patients' and health-care professionals' evaluations of psychological distress and reflect different degree of anxiety and depression in perceptions of distress. Health-care staff probably perceives more anxiety in psychological distress rather than depression (58).

Longitudinal studies have more appropriate design to investigate HRQOL and psychosocial variables, although attrition, mortality and study withdrawal might be significant challenges to manage. Study attrition due to morbidity and mortality ranges from 29%-65% in the first year after HSCT (59-61). Generally, research has confirmed the conclusion that patients with better HRQOL and less psychopathology are more likely to complete study data (9, 62, 63). Attrition has not been statistically assessed in most research leading to potentially overestimated HRQOL outcomes. Research controlling for attrition supports a stable biased overestimation of quality of life in the first six month following transplant (63). In addition, the presentation of HRQOL evaluations in form of means and standard deviations hide variability in the trajectory of quality of life over time. However significant individual variations have been examined in both physical and mental HRQOL (63). These findings on variability in the trajectory of recovery following HSCT are partly influenced by the assessment instruments. General assessment tools are less sensitive to changes in HRQOL than treatment specific instruments (63).

Detecting changes in HRQOL after HSCT is essential in providing appropriate care for patients. High attrition rates highlight the difficulties in collecting HRQOL data from patients. The usefulness of proxy evaluations also has been investigated in HRQOL research in several chronic diseases. General finding in research that health care providers and caregivers underestimate patients' HRQOL compared to patients' evaluations, and patient-proxy agreement is better for concrete, observable aspect (daily activities, physical complaints) than subjective domains (psychosocial functioning) (64). These inconsistent ratings may reflect differences in the personal phenomenology of HRQOL appraisal and have the function of coping with life threatening illness and treatment. These phenomenological factors related to intra individual changes in internal standards, values and meaning of HRQOL mentioned as response shift in research. Underlying cognitive appraisal mechanisms are inherent in all HRQOL assessment and affect measurement outcomes (64). Recent research additionally reported that agreement in patients' and physicians' HRQOL ratings in allogeneic patients have been affected by the severity of cGVHD. Discrepancy in patient-physician ratings increased with decreased cGVHD severity (65).

1.2.2. Psychosocial adjustment to hematopoietic stem cell transplantation and health-related quality of life

HSCT recipients commonly experience multiple treatment failures or relapses, and experience physical and psychological distress even before HSCT, which is usually the last potentially curative therapy. Underestimating the morbidity and mortality associated with HSCT and overestimating benefits are frequent psychological responses. (12). The anticipation of successful transplantation and the elimination of disease often result in unrealistic expectations about restoring pre-illness functioning and lifestyle. Discrepancy between pre-HSCT expectations and post-HSCT functioning was associated with greater psychological distress in previous study (66). Potential benefit of HSCT is influenced primarily by disease type, disease stage and cytogenetics. Controlling (seeking or avoiding risks) transplant-related information to manage anxiety is frequent psychological reaction (16). Therefore, patients' education regarding the potential risks and benefits of transplant should be evolved to allow the selection of relevant information.

Examination of patients' prognostic comprehension showed that their perceptions were more positive than their physicians'. Patients with more realistic prognostic views reported noticeably higher levels of depression prior to HSCT (67). Consequently, interventions for enhancing patients' prognostic comprehension should be implemented rather during decision making process than before inpatient period. Following that, psychological treatments are more appropriate to concentrate on improving coping skills and sustaining an optimistic perspective regarding outcomes.

The intense treatment and recovering from HSCT begin with a lengthy hospitalization period with painful side effects, secondary infections and social isolation. The trajectory of recovery after HSCT involves a particularly vulnerable period characterized by a high risk of fatal complications, with length of approximately 100 days after emission. HSCT patients receive thorough routine follow-up care comprising regular medical screenings, active medication management, adherence to strict self-care recommendations and management of common complications in this period. Most patients experience acute medical post-transplant complications (68); for instance, in a recent study, only 13% of patients had no comorbidities while most of them suffered from numerous comorbidities (69). Another significant stage in recovery occurs at the end of the first post-transplantation year, when the rigorous treatment standards begin to ease. Generally, functionality gradually improves following a notable drop in the early post-transplant period (70, 71). Successful recovery from HSCT typically takes three to five years, beginning with physical stabilization, followed by emotional stabilization and finally rearrangement of social functioning (62, 70, 72, 73). Patients are exposed to various psychological challenges at different phases of the transplantation process. Psychological reactions constitute a broad spectrum ranging from normal functioning to psychiatric disorders. Psychiatric evaluations are required to be capable of differentiate psychiatric symptoms from normal reactions to a life threatening illness, a new or recurrent psychiatric disorder and treatment manifestation or side effect (13). Psychosocial evaluations rather would focus on vulnerability factors for developing psychiatric comorbidities. Normal adjustment to HSCT is a difficult concept to define regarding the variability of psychological reactions and underlying mechanism such as patients' coping style. Coping mechanism are evidenced based determining factors in managing stressful life events or illness. Evidence suggests that avoidant coping style increase the probability

of affective symptoms (13). Evidence supports relevant psychosocial and medical vulnerability and protective factors that affect psychosocial functioning before, during and after HSCT (13).

A significant minority of research emphasize the positive components of psychological adaptation to HSCT including optimism, gratitude, hope and perseverance (21). However, HSCT survivors frequently experience that their disease and transplantation have enhanced appreciation for life, reordered life priorities, increased empathy and self-esteem, or facilitated spirituality (7). Theoretically, associations between HSCT and positive or negative outcomes frequently have been interpreted within the framework of trauma or stress and coping paradigm representing a cognitive perspective (1). Positive psychological reactions frequently have been investigated within the framework of trauma conception as post-traumatic growth. Several studies have documented a potentially beneficial effect of HSCT on psychosocial functioning and emphasized patients' interpersonal or spiritual post-traumatic growth. Patients are frequently able to reframe and convert the adversity of HSCT into a meaningful life narrative, despite their HRQOL deficits (7, 9). A number of research findings have found improved mental health after allogeneic HSCT supporting the theory of post-traumatic growth (9, 22). The psychological mechanism referred as „response shift” or “cognitive reframing” might explain this result (22, 74). After significant impairments in HRQOL, patients might be vulnerable to consider HRQOL acceptable or even good.

A high prevalence of post-HSCT psychological distress, with symptoms of depression, anxiety, sleep disturbances and sexual problems, has been detected (13). Most studies have found mild to severe depressive (5-40%) and anxiety (10-30%) symptoms in a high number of HSCT patients that may not necessary fit the criteria of mental disorders and have specific themes at various phases of HSCT. (1, 11-13). Anxiety level is the highest before transplantation and decreases afterwards (61, 75, 76). Depressive symptoms is less prevalent before HSCT then increases during hospitalization and remains elevated or gradually decreases during the years following HSCT (1, 8, 75, 77). Even individuals with mild pre-transplant levels of depressive symptoms may experience post-HSCT depression symptoms, which can persist for a lengthy period (8, 77). Depressive symptoms impair patients' evaluations of their HRQOL following transplantation and interfere with treatment compliance and survival. (8). In allogeneic transplant patients,

female sex, younger age, chronic pain, and the severity of chronic GVHD are frequently determined to be predictive of depressive symptoms; in autologous transplant patients, only younger age and chronic pain are predictive (63). There is moderate to strong evidence that female sex and a lack of social support predict the prevalence of depressive symptoms, and that pre-transplant psychological distress and GVHD predict post-transplant psychological distress. (8, 70, 78). Overall, studies examining post-HSCT depressive and anxiety symptoms have revealed inconsistent findings.

Most frequent psychiatric diagnoses associated with HSCT are adjustment disorders (22.7%), mood disorders (14.1%) and anxiety disorders (8.2%) with the highest prevalence rates during the procedure (13, 29). Results might be misleading due to the higher probability of attrition of patients with affective symptoms, overlap between physical symptoms of mood disorders and disease or treatment side effects, and lack of structured diagnostic interviews in the assessment of affective symptoms. Furthermore, several patients with severe psychiatric disorders are possibly excluded because of ineligibility to HSCT (74).

Life-threatening medical diseases and associated treatments have been recognized as stressors that stimulate the development of PTSD, particularly in cancer populations; but, as previously noted, these can also facilitate post-traumatic psychological growth (7, 79). Overall, the literature reports a low to moderate prevalence of PTSD (3%-28%) in HSCT populations (1, 2, 80-82). Cancer related intrusive thoughts have been most frequent before HSCT with significant decrease during the first year. Similar decline have been observed in avoidance symptoms in this period (1). Medical issues, pain, low HRQOL, and depression during hospitalization prevent social interaction and support, and avoidance-based coping predicts PTSD after HSCT (1, 2, 80, 82).

During hospitalization, delirium is a frequently observed psychiatric symptom in HSCT patients, with prevalence rates ranging from 35% to 73%, mostly during the engraftment phase (2, 13). The frequent underlying medical conditions include medications, infection, metabolic dysfunction, neutropenia, pancytopenia and long hospitalization (13). Delirium during hospitalization has impact on post-HSCT HRQOL (2).

In HSCT survivors, neurocognitive dysfunction has been estimated between 10% to 40% when neuropsychological tests have been applied and affects attention, memory,

mental processing, coordination and executive functioning (2, 13). Self-reported neurocognitive deficits are more frequent (40-60%) (83). Cognitive symptoms are frequently associated with emotional disturbances and deficits in physical functioning and management of HSCT-related symptoms, leading to restricted HRQOL and treatment adherence (2, 84, 85).

Sexual dysfunctions, including decreased libido, infertility, erectile and ejaculatory dysfunction, premature menopause and dyspareunia, are prevalent and persistent long-term consequences of HSCT (85-88). Changes in body image, depression and anxiety symptoms, and chronic GVHD induce long-term sexual dysfunction and negatively impact intimacy in partnership and HRQOL (1, 88). Evidence support gender differences in sexuality following HSCT referring to more sexual problems in women. Sexual difficulties are among the most prevalent and persistent long-term consequences of HSCT.

Several medication frequently applied in HSCT have psychiatric complications ranging from psychological symptoms to psychiatric diseases (antibiotics, antifungal agents, antiviral agents, immunosuppressive agents, gastrointestinal symptoms management, opioids, chemotherapy, seizure prophylaxis) (Table 3) (2).

Table 3. Commonly used medications in HSCT	
Medication	Psychiatric complications
Antibiotics	
Fluoroquinolones	delirium, psychosis
SMX/TMP (Bactrim)	anxiety, insomnia, delirium, depression, psychosis
Antifungal agents	
Fluconazole	
Posaconazole	1-17%: insomnia
Voriconazole	2-12%: psychosis
Antiviral agents	
Valacyclovir	7%: depression
Valganciclovir	6-20%: insomnia ≥ 5%: anxiety, depression

	< 5%: agitation, delirium, psychosis
Immunosuppressive agents	
Alemtuzumab	16%: insomnia 7%: anxiety
ATG	12-20%: insomnia 7%: anxiety
Corticosteroids	insomnia, depression, mania, emotional lability, personality changes
Cyclosporine	
Mycophenolate mofetil	41-52%: insomnia 28%: anxiety 3-20%: agitation, delirium, depression, psychosis
Tacrolimus	> 10%: anxiety, agitation, insomnia, delirium, depression, psychosis
Gastrointestinal symptoms management	
D2 Antagonists (e.g Prochlorperazine,	
Lorazepam	≤ 16%: sedation Anxiety, agitation, irritability, insomnia, mania, suicidal ideation, delirium, memory impairment, psychosis
Promethazine Ondansetron	6%: anxiety, agitation
Opioids	Serotonin syndrome
Chemotherapy	
Busulfan	84%: insomnia 72%: anxiety 23%: depression agitation, delirium, psychosis
Carmustine	delirium
Cyclophosphamide	< 1%: delirium

Cytarabine	delirium, leukoencephalopathy
Etoposide	delirium
Fludarabine	≤1%: depression < 1%: agitation, delirium
Methotrexate	delirium, memory impairment
Thiotepa	< 1%: delirium, depression, psychosis
Seizure prophylaxis	
Levetiracetam	7-13%: anxiety, agitation, irritability, emotional lability, depersonalization 3-5%: depression 2-3%: delirium

Patients' psychosocial functioning during and after HSCT is often assessed in the concept of HRQOL. HRQOL is a dynamic and multidimensional construct comprising physical, emotional, and role functioning, and most often assessed via self-report. It refers rather to patients functioning than symptoms. However, functioning is affected by symptoms therefore symptoms are frequently examined as part of HRQOL assessment. The World Health Organization (WHO) defines HRQOL as „individuals' perceptions of their position in life in the context of the culture and value system in which they live and in relation of their goals, expectations, standards and concerns" (10). Investigations on HRQOL have revealed significant deficits even before and during HSCT. HRQOL has regularly been observed to return to a comfortable level for most patients over the post-transplantation year, however some areas of functioning remain affected (9, 61, 69, 73, 75, 89-91). Even if HSCT patients estimate their HRQOL as satisfactory or good, it remains considerably poor when compared with healthy controls and population norms (9, 75, 89, 92, 93). Conflicting results and methodological diversities may cover different trajectories of physical and (94)psychosocial functioning (63). Late post-transplant medical complications, including chronic GVHD, secondary malignancies, infections, organ damage, endocrine dysfunction and various physical symptoms (persistent pain, fatigue, loss of appetite, physical weakness, sleep disturbances and drowsiness), can have major impacts on patients' psychosocial functioning and HRQOL (45, 50, 71, 86, 94-96). Non-medical complications comprising unemployment and financial hardship influence

patients' emotional and social functioning (93). Overall, despite inconsistent results, there is preliminary information suggesting that patients continue to improve during the years following HSCT (9, 10, 45, 63).

1.2.3. Factors influencing health-related quality of life and psychosocial adaptation following hematopoietic stem cell transplantation

Studies on the predictors of HRQOL and psychosocial adjustment have also yielded conflicting results regarding the impacts of clinical and psychosocial variables. The HRQOL literature discusses a variety of medical parameters that influence HRQOL following HSCT. The primary emphasis of current research is the relationship between HRQOL, transplantation type, and GVHD. GVHD, particularly chronic GVHD, has a consistently negative impact on HRQOL and psychopathology (5, 10, 12, 60, 78, 97-99). There is a scarcity of research investigating the effects of non-myeloablative conditioning, such as RIC regimes, on HRQOL (60, 78, 100, 101), although allo-HSCT is increasingly conducted with RIC conditioning, particularly in older individuals or patients with significant functioning deficits or comorbidities (102). Overall, the few research on RIC regimes imply that they offer advantages in terms of HRQOL when compared with myeloablative conditioning (103, 104). The effects of T-cell depletion or immunosuppressive treatments on HRQOL also have been investigated in several studies (59, 105).

Non-medical determinants, such as sociodemographic characteristics, have also received insufficient scientific attention. Demographic variables such as younger age and female gender are related with poorer HRQOL, and family relationships (social support) appear to be major predictors of physical and emotional recovery (73, 78, 98, 106, 107).

Recently, the impact of patients' socio-economic status (SES) and financial difficulties on the outcomes of HSCT has received greater attention (108, 109). Low SES - generally evaluated by income, education, and employment, tends to elevate both transplant-related mortality (TRM) and non-relapse mortality (NRM), and has a remarkable correlation with higher symptom burden, HRQOL, and physical and mental functioning (108, 110-112). Additionally, income independently predicted HRQOL (112), likely because patients with a higher SES had more financial resources, causing better access to recommended

medical treatments and supportive care, leading to less symptoms. In a recent study of allogeneic transplant survivors, employment was significantly correlated to HRQOL, however this relationship was mitigated by age and GVHD status (113). Overall, decreased income and unemployment have been associated with lower psychosocial functioning and poor HRQOL in multiple domains following HSCT and contributes to patients' financial stress (11, 114-116). Research revealed that 40% of HSCT patients were not capable return to work at 1 year after HSCT and 30% at 2 years after HSCT (115). Research data are inconsistent regarding the predictors of unemployment and the entire economic impact of HSCT remained understudied (107, 117). However economic influence is multifactorial, comprising medical costs, financial consequences of specific nutritional and hygienic conditions and follow-up care, and frequently referred as financial toxicity in recent research. Treatment and follow-up care is usually managed in centralized transplant centers and patients must relocate or manage transportation for frequent clinic visits. Multiple studies have demonstrated HSCT patients' financial hardship with prevalence rates of 20-70% (118). The costs of HSCT and cancer care represent significant burden even for insured patients and prevent access to high quality care and may affect treatment adherence (110, 116, 119). However, a recent study regarding the relationship between financial hardship and survival has not revealed any association (120). Allo-HSCT patients may be at greater risk regarding financial toxicity because of frequent, even late post-HSCT complications, return to work (RTW) difficulties and decreased income. Research outcome evaluating financial issues separately in this population indicate that patients experience even greater subjective financial burden than their objective financial status (121). Younger patients and patients with poor physical and mental functioning are also at greater risk for financial difficulties (112, 121). Physical and psychosocial problems associated with medical complications adversely affect employment and patients' financial burden and vice versa. Chronic GVHD is a major factor influencing allo-HSCT patients' return to work (RTW) and financial situation because of the prolonged trajectory of recovery (118). Study results suggest that chronic GVHD patients with low SES measured by income and inability to RTW experience higher symptom burden. In recent study 67% of the insured chronic GVHD patients reported financial difficulties, 33% health-insurance difficulties and 25% RTW difficulties. Increased anxiety and depression have been observed in patients

experiencing financial burden in this study (115). Research on treatment burden is a rather comprehensive approach assessing the association between disease management burden, medication burden, healthcare access burden, financial burden, time and travel burden with treatment adherence, HRQOL and morbidity (122). Besides patients, economic consequences of treatment frequently affect family caregivers because of travel expenses, time away from work, accommodation expenses. Patients and families with stable economic situation are more capable to apply recommended treatments, and follow-up care. Availability of financial resources and support in family are possibly decrease HSCT-related financial burden.

The relationship between pre-transplant psychological variables and HRQOL is a rather well-studied issue. Most authors conclude that psychological distress prior to transplantation - primarily anxiety and depression - predicts post-transplant HRQOL (76, 78). Interest in the association between clinically relevant depressive and anxiety symptoms and HRQOL is increasing (67). The most researched psychiatric disorders are major depressive disorder, generalized anxiety disorder, obsessive-compulsive disorder, and post-traumatic stress disorder (35, 36, 123). Affective symptoms interfere with treatment adherence, negatively influence survival, and decrease patients' estimates of HRQOL (9, 53). Research on HRQOL revealed that pre-transplant HRQOL, post-transplant psychological morbidity, and its association with HRQOL, is also a major predictor of post-transplant HRQOL (124). Different factors influence HRQOL at different time points during recovery after HSCT (73).

1.2.4. GVHD related psychosocial complaints

GVHD is a chief complication in 40%-60% of patients after HSCT and affect multiple organs, including the oral cavity, gut, liver, lung, skin, and eyes (125). Despite preventative regimes, a considerable proportion of recipients acquire the acute or chronic form of GVHD following HSCT: aGVHD affects 30% to 70% of recipients, whereas cGVHD occurs in 20% to 70% of recipients (126, 127). AGVHD and cGVHD is related to worse functional status, occupational outcomes, mental health and HRQOL (2, 9, 51). However acute and chronic GVHD are highly correlated, aGVHD has independent

contribution to HRQOL due to different organ manifestation affecting different trajectories in patients experiencing both forms (51).

The incidence of cGVHD is likely to increase due to the frequent use of HSCT in older patients, unrelated or mismatch related donor transplants, peripheral blood stem cell (PBSC) grafts and donor lymphocyte infusions (DLI), which are the consistently reported risk factors for cGVHD (128-130). Chronic GVHD is a common cause of long-term morbidity and non-relapse mortality, and affected individuals have a considerably decreased HRQOL relative to population standards and patients without GVHD symptoms (22, 51, 131). Physical functioning of HSCT patients is similar to patients with immune mediated disorders such as systemic sclerosis or systemic lupus erythematosus and multiple sclerosis (132). Treatment efficacy is often limited with significant toxicities further contributing to the morbidity and HRQOL impairment of this vulnerable population.

Results indicate reduced but stable long-term HRQOL in cGVHD patients compared to healthy population (133). Even mild cGVHD symptoms can decrease HRQOL to below population norms or HRQOL of patients without cGVHD (65, 134). The severity of cGVHD has an independent negative correlation with HRQOL (65, 99, 131, 132, 135). Fluctuations in the intensity of cGVHD symptoms reported by patients were also significantly related to changes in their HRQOL ratings (132, 134). An interesting outcome revealed significant association between cGVHD severity and change in HRQOL only in the case of patient-assessed cGVHD severity. Neither the National Institute of Health (NIH) criteria-assessed cGVHD severity nor physician-rated severity correlated (132). Such result demonstrates the utility of patient-reported outcomes in research and clinical assessment. Consistent with previous findings (128, 133), a recent large-scale investigation found that only currently active cGVHD reduced HRQOL, while resolved cGVHD had no effect on HRQOL after allo-HSCT (134, 135). This result encourages future improvements in therapeutic strategies in the treatment of cGVHD.

The results concerning the associations of age and sex with HRQOL in cGVHD patients are conflicting (67, 136). Recent comparison of different age groups of patients with cGVHD not revealed significant difference in clinical outcomes and symptoms burden between age groups. Despite significantly more physical and functional limitations, older patients reported preserved HRQOL even in subgroup of cGVHD

patients (136, 137). These finding highlights the utility and applicability of HSCT in older patients and also the risk of more HRQOL deficits in middle-aged patients compared to other age groups. Study concludes that discrepancy between functional limitations and expectations regarding HRQOL is essential in perceived HRQOL. Middle age patients probably experience more discrepancy because of less functional limitations in the younger and lower expectations in the older patients. Older patients with prior resolved cGVHD experience larger, however not significant HRQOL impairment than younger patients with resolved cGVHD compared to patients without cGVHD suggesting enduring HRQOL deficits due to prior cGVHD in older patients compared to younger counterparts (135). It is likely; however, that cGVHD has a major impact on the physical and functional domains of QOL (65, 132).

Studies examining the associations between psychosocial factors and HRQOL in cGVHD patients found various incidence rates of depression (20-40%) and anxiety (14-18%) (137). Recent cross-sectional evidence indicates significant physical and functional limitations and HRQOL impairments in cGVHD patients with depressive or anxiety symptoms (137, 138). Depressive symptoms in cGVHD patients have been associated with lower survival due to treatment adherence difficulties, suicide rate differences and psychobiological processes (137). Such results may be interpreted with limitations. Psychopathological symptoms and HRQOL deficits may be explained as consequences of physical and functional limitations, or patients with increased depression or anxiety perceive physical functioning and HRQOL negatively. A recent prospective study that evaluated the correlations between psychosocial factors and HRQOL in cGVHD patients identified clinically significant depression and anxiety symptoms in around one-third of patients at different time points following HSCT (51). The HSCT symptom burden predicted depressive symptoms, poorer functional status predicted anxiety symptoms, and both were correlated with HRQOL. Coping was a mediator component in this association: patients with predominantly negative emotion-oriented coping and less task-oriented and social diversion-oriented coping, who had also higher symptom burden and weaker physical functioning rated poorer HRQOL (51). Consequently, interventions designed to enhancing patients' coping mechanisms may raise HRQOL and decrease psychological suffering. Overall, patients with cGVHD, having high levels of depression and anxiety

represent a particularly vulnerable group for poor functioning, reduced HRQOL, and HCST-related mortality (137).

1.2.5. Impact of transplantation type on health-related quality of life and psychosocial functioning

Numerous investigations have compared the psychosocial adaptation and HRQOL in recipients receiving allogeneic and autologous transplants, but the methodological diversity of these studies has also resulted in inconsistent conclusions (9, 62, 70, 71, 105, 106, 139). Furthermore, confounding variables such as differences in age and pre-transplant comorbidities, higher rates of relapse in autologous transplant patients, and the existence of GVHD symptoms in allogeneic transplant patients prevent to draw conclusions from the literature. Recovery is not a unidirectional process of improvement. Patients' physical and mental rehabilitation shows great variability. While most patients experience stable physical and mental functioning after HSCT, a significant minority continue to decline in terms of physical and psychological health and are at risk for developing psychopathological symptoms (63). Post-transplant psychological morbidities, such as anxiety and depression symptoms, were discovered to be important indicators of HRQOL (140). Majority of studies have reported mild to severe depressive and anxiety symptoms in numerous HSCT recipients (12, 13). A recent study assessing comorbidities in long-term survivors of allogeneic HSCT identified depression and anxiety among the most frequent comorbidities (141). However, differences have not been detected between allo-HSCT and auto-HSCT patients' affective symptoms (75).

Research comparing allogeneic HSCT patients to autologous HSCT recipients revealed comparable or higher HRQOL deficits in allogeneic HSCT patients, and distinct recovery trajectories were observed between groups (9, 62, 71, 106, 139). The greatest impairments in overall HRQOL have been explored short-term (within 30 d) after HSCT in both patient population, but allo-HSCT patients experienced more decline in association with relatively better pre-HSCT functioning, and auto-HSCT patients (2-4 m) reach baseline functioning sooner than allo-HSCT patients (4-8 months) [9-10, 93]. However, these groups have different clinical manifestations, morbidity and mortality risks.

Research indicates significant impairments in physical functioning before transplant in both allogeneic and autologous patients potentially due to previous chemotherapy and residual symptoms of disease. Physical functioning further declines immediately after HSCT with various nadir time-points in studies between 30-100 days in allogeneic and 10-14 days to 4-6 weeks in autologous patients. Several studies suggest returning or exceeding baseline level of functioning 3, 6, or 12 months after autologous transplant (10, 142, 143). Long-term deficits have been perceived in great proportion of patients possibly due to age and relapse in this group [10]. Gradual improvement or improvement after a plateau in the first year have been evaluated in allogeneic patients over 4 years following HSCT with frequent deficits in physical functioning. Even 5 years after HSCT significant minority of patients reported major limitations (18%) and impairments (25%) in physical functioning (10, 72). 5-10 years after HSCT allogeneic transplant survivors still experience small to moderate deficits in physical functioning compared to healthy controls (7, 10, 93, 144). Despite these deficits many patients indicate physical condition similar to pre-transplantation level or those of normal population. Research have revealed impaired emotional well-being before and during the acute period of HSCT in both patients groups with small improvements in the allogeneic patients by day 100 and progressive development in autologous patients. Auto-HSCT patients reach or even surpass pre-transplant emotional functioning 3-6 month after HSCT, while depressive symptoms are frequent during the first year after allo-HSCT (92). Unfortunately, long-term data are missing regarding emotional functioning in auto-HSCT patients (142, 143). Research findings are conflicting regarding the long-term emotional functioning of allo-HSCT survivors. Some studies indicating stable findings, others report significant deficits compared to healthy controls even 5-10 years following allo-HSCT (6, 7, 93). Impaired social functioning has been observed before and immediately following HSCT with gradual improvements thereafter. Most allo-HSCT patients report similar or better social functioning at 1 year post-HSCT than before the procedure, some aspects still remain impaired in long-term follow-up compared to healthy controls or population norms (10). GVHD has been observed as important predictor of social functioning in allogeneic patients (99, 145). Literature supports a gradual recovery of social functioning in auto-HSCT patients reaching or exceeding pre-transplant level by 3-6 months following HSCT. Long-term data regarding social well-being are also missing (10). Role

functioning of patients decreased prior to HSCT due to the effects of previous treatment. Further, transient deficits in role functioning return to baseline 1 year post-transplant. However, some evidence suggests significant impairments even years after HSCT compared to healthy individuals, while others support similar level of role functioning (10). Female gender and extensive chronic GVHD was associated with reduced role functioning. Significant deficits have been observed even in pre-transplant role functioning in auto-HSCT patients, compared to population norms. After improvement in the years following HSCT long-term role functioning especially in younger patients appear to decline again.

A recent review discussed the possible risk factors for poor HRQOL separately for allogeneic and autologous transplant patients. More precisely, the review found strong evidence for GVHD and weak evidence for depressive symptoms as risk factors for poor overall HRQOL in the allogeneic group. The autologous group had not presented such association (78). Additionally, there is convincing evidence that persistent GVHD symptoms predict poor HRQOL, primarily in terms of physical well-being, while pre-transplant psychological distress predisposes to develop post-transplant psychological symptoms (78). Discrepancy in physical and psychological well-being between allogeneic and autologous transplant recipients is likely mediated by the effects of chronic GVHD (62). Insufficient research has been conducted on the negative effects of clinically meaningful anxiety and depressed symptoms on mortality and HRQOL after HSCT (29, 146). Nevertheless, such research reports the consistent adverse impacts of major depressive disorder, generalized anxiety disorder, obsessive-compulsive disorder and PTSD.

1.2.6. Psychosocial interventions and support for HSCT patients

The extensive literature on psychosocial factors, especially depression and anxiety, in the course of HSCT also highlights the relevance of psychological interventions. The optimal approach comprises the detailed assessment of the patient's pre-HSCT psychosocial functioning and economic situation, together with a brief screening of psychological symptoms and HRQOL, in order to establish the baseline for targeted interventions and psychosocial support (12, 114-116).

Psychological interventions during HSCT, include several treatment modalities such as relaxation and mindfulness training, communication techniques, psychoeducation and cognitive-behavioral therapy to enhance insight and strengthen coping skills (2, 10, 12, 88, 147). Most evidence supports the usefulness of cognitive-behavioral interventions to reduce anxiety and depressive symptoms (148). Emotion-focused interventions as relaxation and mindfulness therapy have significantly reduced patients' anxiety and only moderately affected depression (148). For clinically significant anxiety and depressive symptoms, benzodiazepines and antidepressants are also recommended. Patients' access to psychosocial treatments is limited because centralized transplant centers. Telemedicine interventions have applied to reduce severe anxiety symptoms as PTSD (149). Additionally, positive psychological interventions have recommended to enhance patients' HRQOL through strengthening optimism, gratitude and satisfaction (150, 151). Education on HSCT is suggested for all recipients to develop their knowledge of medication side effects, risks and complications (15). Educational interventions broaden patients' knowledge about HSCT, reduce anxiety and depression, improve HRQOL and facilitate treatment adherence (15). Patients express a desire for education about late complications, medications, nutrition, activity, and sexuality (16, 152). Physical exercises are effective in reducing physical limitations and enhancing activity after HSCT (16, 57, 153).

2. OBJECTIVES

The aim of this PhD research is to evaluate the HRQOL of a sample of the Hungarian hematopoietic transplant population and associations with medical and psychosocial factors.

Detailed objectives of the current dissertation-based research:

2.1. In the first study - Quality of life and its socio-demographic and psychological determinants after bone marrow transplantation

Our goals were:

- [1.] to investigate the HRQOL and psychological symptoms of a sample of the Hungarian HSCT patients
- [2.] to explore the psychosocial determinants of HRQOL in HSCT patients
- [3.] to examine the association between medical variables and HRQOL with particular emphasis on the relationship between severe medical complications such as a/cGVHD symptoms and related poor health status

2.2. In the second study - Impact of the type of hematopoietic stem-cell transplant on quality of life and psychopathology

We aimed:

- [1.] to investigate the impact of transplantation type on HRQOL, anxiety and affective symptoms, and test whether allogeneic transplant patients have lower quality of life and more depressive or anxiety symptoms than autologous patients
- [2.] to compare allogeneic transplant patients with GVHD symptoms in terms of HRQOL, anxiety and affective symptoms with allogeneic transplant patients without GVHD symptoms, and their autologous counterparts

3. METHODS

3.1. Subjects

Participants in the study included adults over the age of 18 with a range of hematological conditions (acute lymphoid leukemia, acute myeloid leukemia, chronic lymphoid leukemia, chronic myeloid leukemia, prolymphocytic leukemia, Hodgkin's lymphoma, non-Hodgkin's lymphoma, T-cell lymphoma, myeloma multiplex, myelofibrosis, severe aplastic anemia, myelodysplastic syndrome, chronic granulomatous disease) who underwent HSCT at the Bone Marrow Transplantation Unit of Szent Laszlo Hospital in Budapest, Hungary, between January 1, 1994, and December 31, 2008, and who were monitored at the unit's outpatient service. The time frame for this cross-sectional study was March 2009–May 2010. Participation in the study was open to any outpatients who visited Szent Laszlo Hospital's BMT Unit. While waiting for doctors, patients were directly approached by research professionals and requested to complete surveys. The study protocol was approved by the Institutional Review Board of Szent Laszlo Hospital (N.: 31/EB/2009). All participants signed an informed consent form before entering the study.

3.2. Assessment instruments

The sociodemographic data of the participants were obtained using a self-reported questionnaire prepared for the study, which comprised the following items: age, marital status, education, employment, place of residence, type of housing, monthly income, car ownership, debt. Medical variables were collected from the participants' medical records and assessed by the subject's hematologist when needed. These variables included the type and date of diagnoses and those of BMT, the type and severity of current GVHD, the severity of the disease at the time of the evaluation, which was rated on a 3-point scale, and the treatment and clinical global impression (CGI), which was rated on a 7-point scale. In the statistical analysis, the comorbid variables were diagnoses of medical or psychiatric problems prior to HSCT. HRQOL was assessed using the Hungarian

version of the Functional Assessment of Cancer Therapy–Bone Marrow Transplant (FACT-BMT) scale. The 50-item self-reported FACT-BMT questionnaire is divided into five domains: complaints unique to BMT, physical, functional, emotional, and social well-being. A 5-point Likert scale is used to rate the items. HRQOL values were computed by adding the item scores. In every domain, higher scores indicated higher HRQOL. Overall, the FACT-BMT has high psychometric qualities (Cronbach's $\alpha = 0.89\text{--}0.94$) for the entire test (47, 49, 55, 154). Depressive and anxiety symptoms were assessed using the Beck Depression Inventory (BDI) and Spielberger's State and Trait Anxiety Inventory (SSTAI), respectively (155, 156). The BDI is a self-report survey with 21 items. Higher total scores indicate more severe depressive symptoms and syndrome (mild depression: 10–18; moderate depression: 19–25; severe depression: above 25). Each BDI item includes four possible statements that signify increasing symptom intensity. Additionally, SSTAI is a self-rated questionnaire with 20 items for "state" and "trait" anxiety. While the "trait" scale determines a person's "anxiety proneness," the "state" scale assesses the present level of anxiety. A 4-point Likert scale is used to grade each question, and the highest possible score on each scale is 80.

3.3. Statistical analysis

The demographic factors, as well as the FACT-BMT, BDI, and SSTAI scores, are presented here with means and standard deviations or percentages, as applicable. When both variables displayed a normal distribution, Pearson's test was used to assess correlations between the FACT-BMT and sociodemographic and medical variables and the BDI and SSTAI. When that requirement was not met, Spearman's rank test was used. Skewness and kurtosis measurements, along with the Kolmogorov-Smirnov test, were used to assess normality. Using the FACT-BMT total score as the dependent variable, stepwise multiple linear regression analyses were performed to determine the components that independently contributed to HRQOL. Linear variables (BDI and STAI total scores) that exhibited a significant ($p < 0.05$) correlation with FACT-BMT total scores were among the independent variables. The two-sample t-test, the Mann-Whitney U test for binomial variables, and the Kruskal-Wallis test for comparisons involving more than two

groups were used to assess the effect of discrete variables on FACT-BMT results. Some statistical tests had decreased sample sizes due to missing variables.

A t-test with linear variables (BDI, SSTAI, and FACT-BMT total scores) was used when variables were normally distributed, and a Mann-Whitney U test otherwise. Pearson's chi-square test was used to compare groups with nominal variables when the predicted cell count was at least five, and Fisher's exact test or Cramer's V otherwise. The normal distribution was checked using the Kolmogorov-Smirnov test.

4. RESULTS

4.1. Health related quality of life and its socio-demographic and psychological determinants after HSCT

4.1.1. Descriptive statistics in the sample of HSCT patients

121 patients participated in the study, constituting 32% of the entire patient population receiving HSCT (378 patients) and 47% of all HSCT patients attending the outpatient service for follow-up during the study period (258 patients). 55% (208 patients) of the entire BMT population was approached; 23% (87 patients) refused participation. Reasons of non-participation included poor physical condition, problems with visual acuity, lack of time, and negative attitude toward psychological testing (Figure 1).

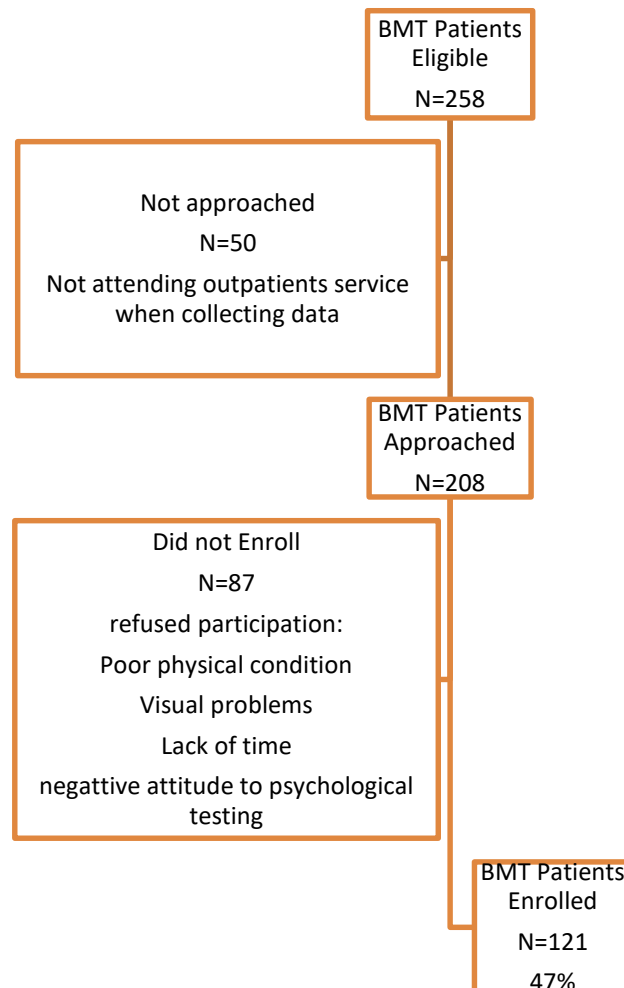


Figure 1. Flow chart of study enrollment and participation

The socio-demographic and disease-specific data of the whole sample are summarized in Tables 4 and 5.

The mean FACT-BMT score of the total sample was 142 ± 27 , with domain-specific values for physical well-being of 21 ± 5.6 , functional well-being of 21 ± 5.6 , emotional well-being of 19 ± 4.3 , social well-being of 17 ± 6.5 , and BMT-specific complaints of 64 ± 13.5 . The subscale domain scores distribution of the sample are demonstrated in Figure 2.

The mean BDI and SSTAI scores of the total sample were 10 ± 7.12 [normal range: 0–9; mild depression: 10–18; moderate depression: 19–25; severe depression: above 25] and 81 ± 19.7 . The mean scores of the SSTAI-Trait and State subscales were 39 ± 11.5 and 42 ± 9.7 , respectively.

Table 4. Socio-demographic characteristics of the subjects undergoing HSCT
(Janicsák H, 2013 p.3)

		Subjects
Age		44.8±13.4 years
Gender	Male	49.6% (60 patients)
	Female	50.4% (61 patients)
Marital status	Married	66.7% (80 patients)
	Partnership	4.2% (5 patients)
	Divorced	7.5% (9 patients)
	Widow	5% (6 patients)
	Single	16.7% (20 patients)
Education	Primary	11.7% (14 patients)
	Vocational	19.2% (23 patients)
	Secondary	37.5% (45 patients)
	Tertiary	31.7% (38 patients)
Employment	Employed	39.8% (47 patients)
	Unemployed	60.2% (71 patients)
Housing	Rented apartment	9.2% (11 patients)
	Own apartment	38.3% (46 patients)

	Own house	41.7% (50 patients)
	Council rental	0.8% (1 patients)
	With relatives	10% (12 patients)
Monthly income (per person in the family/household)¹	Below 100 000 HUF (US\$ 450)	64.4% (76 patients)
	100 001-150 000 HUF (US\$ 450-670)	23.7% (28 patients)
	150 001-200 000 HUF (US\$ 670-900)	5.9% (7 patients)
	Above 200 000 HUF (US\$ 900)	5.9% (7 patients)
Car ownership	Yes	79.3% (96 patients)
	No	20.7% (25 patients)
Debts	No	38% (38 patients)
	House	24% (24 patients)
	Car	18% (18 patients)
	Commercial credit	7% (7 patients)
	More than one type	13% (13 patients)

¹ date of currency exchange is 2012

Table 5. Medical variables related to the underlying hematological disease and its treatment (Janicsák H, 2013 p.3)

Diagnoses	Acute lymphoid leukemia (ALL)	5% (6 patients)
	Acute myeloid leukemia (AML)	28% (33 patients)
	Chronic lymphoid leukemia (CLL)	2% (3 patients)
	Chronic myeloid leukemia (CML)	7% (8 patients)
	Hodgkin disease (HD)	11% (13 patients)

	Non-Hodgkin lymphoma (NHL)	13% (16 patients)
	Myeloma multiplex (MM)	24% (29 patients)
	Other	10% (12 patients)
BMT type	Autologous	49% (58 patients)
	Allogeneic related	32% (37 patients)
	Allogeneic unrelated	19% (22 patients)
Time elapsed since transplant (months)		26±37 (1-136)
Duration of illness (months)		51±48 (4-228)
Graft-versus-host disease (GVHD)	Acute	13% (9 patients)
	Chronic	40% (22 patients)
Phase of recovery	Complete remission (CR)	60% (70 patients)
	Recovered	28% (33 patients)
	Active disease	12% (14 patients)
Active treatment		26% (30 patients)
Somatic comorbidity		32% (35 patients)
Psychiatric comorbidity		3% (3 patients)

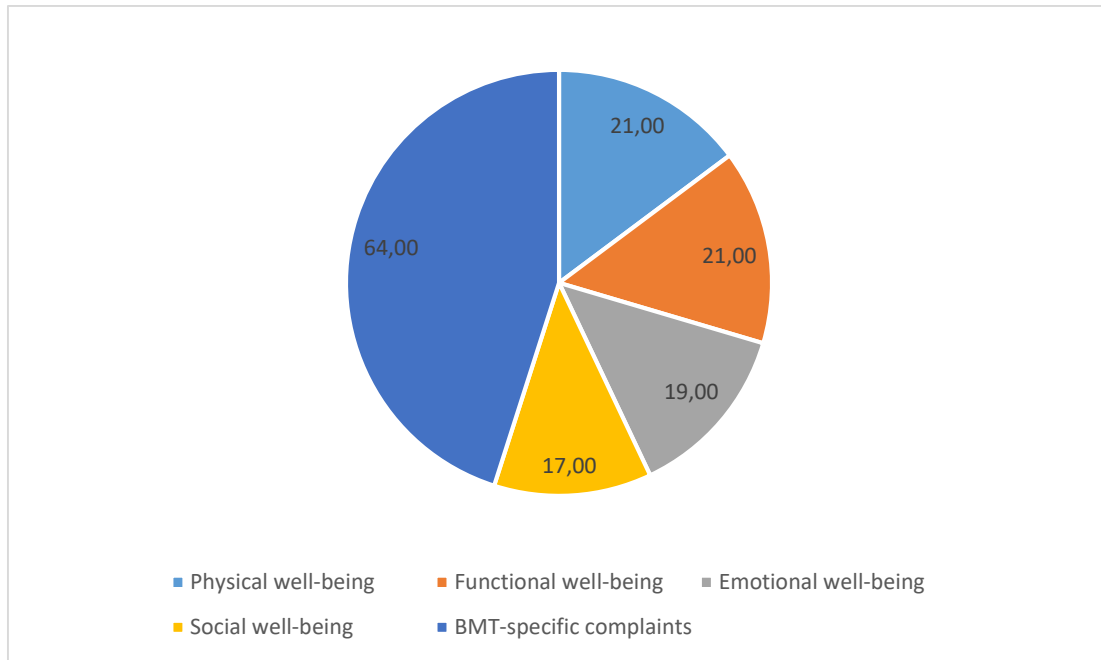


Figure 2. FACT-BMT subscales scores' distribution of the sample

4.1.2. Psychosocial determinants of FACT-BMT scores in HSCT patients

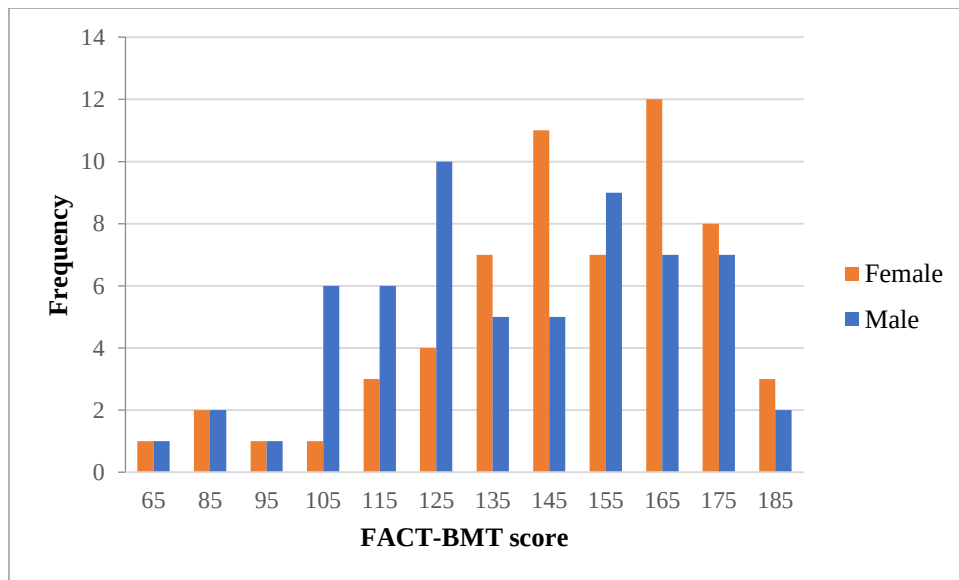
Correlations between the FACT-BMT scores and the psychosocial variables are presented in Table 6. Significant correlations were found between female gender (-0.18; $p = 0.05$), unemployment (-0.21; $p = 0.02$), psychiatric comorbidity (0.26; $p < 0.01$), depression (BDI score; -0.78; $p < 0.01$), anxiety (STAI score; -0.75; $p < 0.01$), and HRQOL scores.

Comparison of FACT-BMT values between groups formed by discrete variables revealed significant impact on HRQOL for gender ($p=0.05$), unemployment ($p=0.02$) and psychiatric comorbidity ($p=0.02$) (Figure 4-6).

The results of the stepwise multiple linear regression analysis used to explore the contributors to HRQOL are presented in Table 7. Poor HRQOL was independently associated with employment, psychiatric comorbidity, depression and anxiety. From FACT-BMT domains, depression and anxiety influenced significantly only the BMT-specific items, but not the more general cancer-specific issues in FACT-G scores. Gender affected only BMT-specific items.

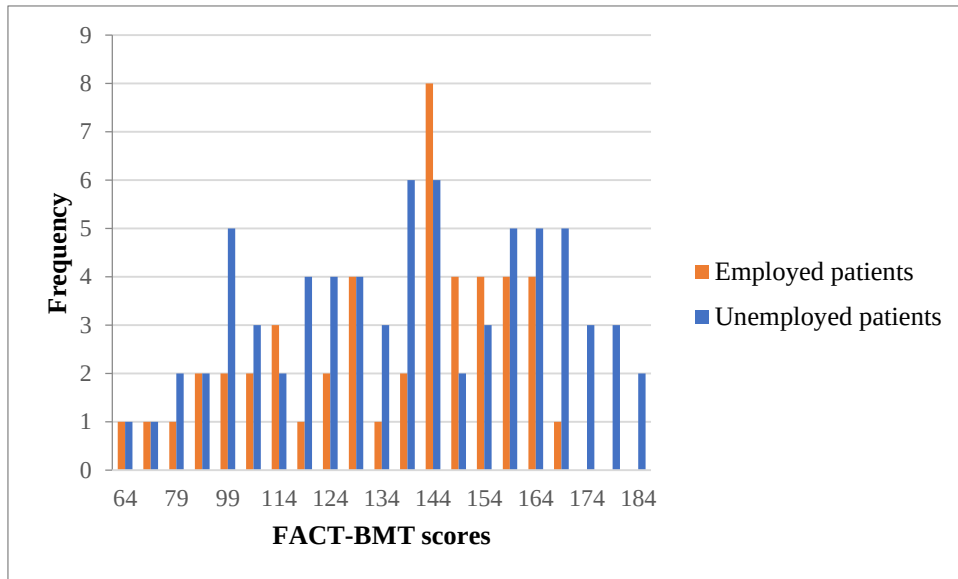
Table 6. Correlations between HRQOL and psychosocial variables	
	FACT-BMT-total
Gender	-0.18; p=0.05
Age	n.s.
Marital status	n.s.
Employment	-0.21; p=0.02
Housing	n.s.
Monthly income (per person in the family/household)	n.s.
Car possession	n.s.
Loan	n.s.
Time to travel to BMT center	n.s.
Psychiatric comorbidity	0.26; p<0.01
BDI	-0.78; p<0.01
SSTAI	-0.75; p<0.01

BDI: Beck Depression Inventory; CGI: Clinical Global Impression; SSTAI: Spielberger's State and Trait Anxiety Scale; FACT-BMT: Functional Assessment of Cancer Therapy - Bone Marrow Transplant Scale



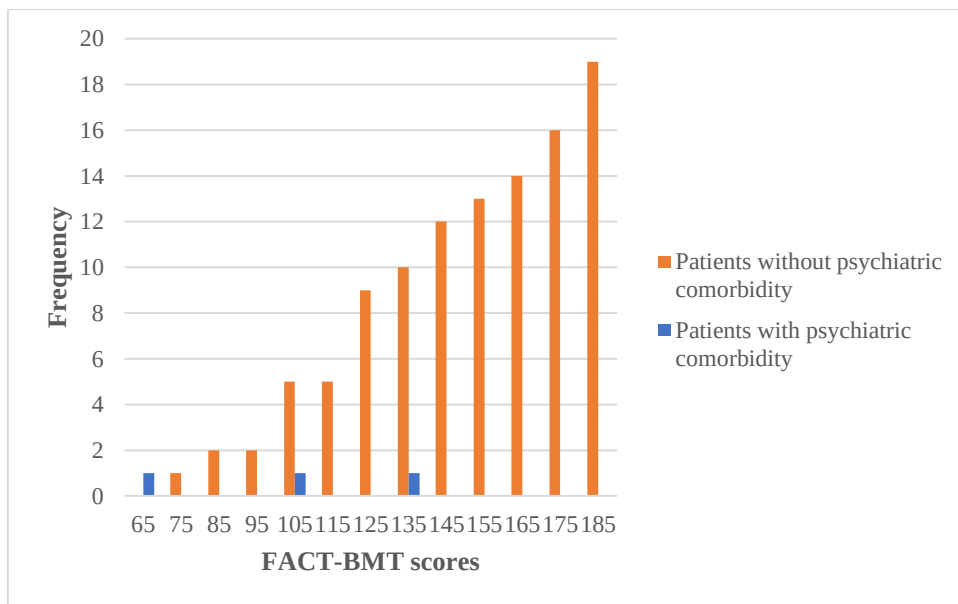
FACT-BMT: Functional Assessment of Cancer Therapy - Bone Marrow Transplant Scale

Figure 4. Gender differences in FACT-BMT total scores



FACT-BMT: Functional Assessment of Cancer Therapy - Bone Marrow Transplant Scale

Figure 5. Employment differences in FACT-BMT total scores



FACT-BMT: Functional Assessment of Cancer Therapy - Bone Marrow Transplant Scale

Figure 6. Differences in FACT-BMT total scores between patients with psychiatric comorbidity and without psychiatric comorbidity

Table 7. Socio-demographic, somatic and psychopathological variables independently associated with HRQOL (multiple regression analysis, stepwise method) []

	FACT-BMT		FACT-G		BMT	
	beta	t (p)	beta	t (p)	beta	t (p)
BDI	-0.700	-5.396 (p<0.001)	-0.614	-4.208 (p<0.001)	-0.600	-4.080 (p<0.001)
SSTAI	-0.390	-3.438 (p=0.001)	-0.508	-4.160 (p<0.001)	-0.374	-2.987 (p=0.005)
Psychiatric comorbidity	-0.334	-3.491 (p=0.001)	-0.390	-3.700 (p=0.001)	-0.252	-2.349 (p=0.023)
Employment	-0.152	-2.100 (p=0.042)				
Gender					-0.246	-3.061 (p=0.004)

FACT-BMT: Functional Assessment of Cancer Therapy-Bone Marrow Transplant Scale; FACT-G: Functional Assessment of Cancer Therapy; BMT: Bone Marrow Transplantation Subscale; BDI: Beck Depression Inventory; SSTAI: Spielberger's State and Trait Anxiety Scale

4.1.3. Medical determinants of FACT-BMT scores

Neighter analysis revealed significant associations between somatic and medical variables and HRQOL. AGVHD (-1.22 p=0.22) and cGVHD symptoms (-1.88 p=0.06), active treatments (-0.89 p=0.37), relapse (0.17 p=0.9) and CGI (-0.16 p=0.08) scores made no significant association with FACT-BMT scores. Though significant relationship was identified between aGVHD (2.17 p<0.05), cGVHD (2.30 p<0.05) immunosuppressive treatments (5.47 p<0.01) and CGI scores.

4.2. Impact of the type of HSCT on HRQOL and psychopathology

4.2.1. Descriptive statistics in the sample of autologous and allogeneic HSCT patients

The sociodemographic and disease-specific characteristics of the allogeneic and autologous patient population are summarized in Tables 8 and 9. Autologous patients were significantly older than allogeneic individuals. More patients in the allogeneic group reported to be recovered or in remission, and the period since HSCT was significantly longer in this group. Allogeneic HSCT patients also received more active treatment related to acute and chronic GVHD symptoms compared to patients who underwent autologous HSCT.

The FACT-BMT scores in the autologous and allogeneic cohort are presented in Table 10.

The mean BDI scores in the autologous and allogeneic cohorts were 8.96 ± 5.50 and 11.05 ± 8.22 , and the mean SSTAI scores were 80.72 ± 18.25 and 81.96 ± 21.24 , respectively. The SSTAI Trait and State subscales' mean scores were 41.11 ± 8.55 and 39.79 ± 11.24 , respectively, for the autologous cohort and 42.76 ± 10.78 and 39.54 ± 12.00 , respectively, for the allogeneic cohort. The BDI scores did not indicate depression in the autologous cohort and indicated only mild depression in the allogeneic cohort. Additionally, the SSTAI scores corresponded to the anxiety level found in general population in both groups.

Table 8. Sociodemographic characteristics of allogeneic and autologous participants undergoing HSCT (Janicsák H, 2023 p.4)				
		Autologous HSCT (n=58)	Allogeneic HSCT (n=63)	Comparison of autologous and allogeneic HSCT
Age		50.1±13.6 years	39.95±11.2 years	U=1040 p<0.01
Gender	Men	29 patients (50%)	31 patients (41%)	$\chi^2=0.00$ p=0.93
Marital status	Married	39 patients (68.4%)	41 patients (65.1%)	$P_{\text{fish}}=7.21$ p=0.12
	Partnership	4 patients (7%)	1 patient (1.6%)	
	Divorced	5 patients (8.8%)	4 patients (6.3%)	
	Widowed	4 patients (7%)	2 patients (3.2%)	
	Single	5 patients (8.8%)	15 patients (23.8%)	
Education	Primary	5 patients (8.8%)	9 patients (14.3%)	$\chi^2=14.47$ p<0.01
	Vocational	4 patients (7%)	19 patients (30.2%)	
	Secondary	23 patients (40.4%)	22 patients (34.9%)	
	Tertiary	25 patients (43.9%)	13 patients (20.6%)	
Employment	Employed	26 patients (47.3%)	21 patients (33.3%)	$\chi^2=2.38$ p=0.12
	Unemployed	29 patients (52.7%)	42 patients (66.7%)	
Housing	Rented apartment	7 patients (12.3%)	4 patients (6.3%)	$\chi^2=9.87$ p=0.04 V=0.28 p=0.04
	Own apartment	23 patients (40.4%)	23 patients (36.5%)	

	Own house	25 patients (43.9%)	25 patients (39.7%)	
	Council rental	1 patient (1.8%)	0%	
	With relatives	1 patient (1.8%)	11 patients (17.5%)	
Monthly income (per person in the family/household)¹	Below HUF100,000 (US\$450)	30 patients (53.6%)	46 patients (74.2%)	$P_{\text{fish}}=6.72$ $p=0.08$
	HUF100,001–150,000 (US\$450–670)	18 patients (32.1%)	10 patients (16.1%)	
	HUF150,001–200,000 (US\$670–900)	5 patients (8.9%)	2 patients (3.2%)	
	Above HUF200,000 (US\$900)	3 patients (5.4%)	4 patients (6.5%)	
Car ownership	Yes	48 patients (84.2%)	48 patients (80%)	$\chi^2=0.35$ $p=0.55$
Debts	No	22 patients (47.8%)	16 patients (29.6%)	$\chi^2=5.42$ $p=0.24$
	House	11 patients (23.9%)	13 patients (24.1%)	
	Car	5 patients (10.9%)	13 patients (24.1%)	
	Commercial credit	2 patients (4.3%)	5 patients (9.5%)	
	More than one type	6 patients (13%)	7 patients (13%)	

¹ date of currency exchange is 2012

Table 9. Medical conditions related to the underlying hematological disease and treatment in allogeneic and autologous HSCT patients (Janicsák H, 2023 p.6)				
		Autologous transplant patients (n=58)	Allogeneic transplant patients (n=63)	Comparison of autologous and allogeneic HSCT
Diagnoses	Acute lymphoid leukemia	1 patient (1.8%)	6 patients (9.5%)	
	Acute myeloid leukemia	5 patients (8.8%)	28 patients (44.4%)	
	Chronic lymphoid leukemia	1 patient (1.8%)	2 patients (3.2%)	
	Chronic myeloid leukemia	0%	7 patients (11.1%)	
	Hodgkin disease	10 patients (17.5%)	3 patients (4.8%)	
	Non-Hodgkin lymphoma	11 patients (19.3%)	5 patients (7.9%)	
	Myeloma multiplex	25 patients (43.9%)	4 patients (6.3%)	
	Other	5 patients (6.9%)	8 patients (12.8%)	
Bone marrow transplantation type ¹	Autologous	58 patients		
	Allogeneic related		36 patients	
	Allogeneic unrelated		23 patients	
Time elapsed since transplant (months)		22±36 (1–126)	28.87±38.68 (1–123)	U=2251.5 p=0.01
Duration of illness (months)		44±47 (4–224)	51.6±46.4 (6–228)	U=2039.5 p=0.2

Graft-versus-host disease (GVHD)	Acute		9 patients (14.3%)	
	Chronic		25 patients (39.7%)	
Phase of recovery ²	Complete remission	45 patients (77.6%)	25 patients (42.4%)	25.7 p<0.01 V=0.46 p<0.01
	Recovered	4 patients (6.9%)	29 patients (49.1%)	
	Active disease	9 patients (15.5%)	5 patients (8.5%)	
Active treatment		7 patients (12.1%)	23 patients (38.3%)	$\chi^2=10.73$ p<0.01 V=0.30 p<0.01
Medical comorbidity		19 patients (36.5%)	16 patients (27.6%)	P _{fish} =2.22 p=0.26
Psychiatric comorbidity		1 patient (1.9%)	2 patients (3.4%)	P _{fish} =1.35 p=0.79

¹ type of transplant was missing in four cases in the allogeneic HSCT group

² phase of recovery data were missing in four cases in the allogeneic HSCT group

Table 10. FACT-BMT scores of allogeneic and autologous patients

FACT-BMT scores	Autologous patients (n=58)	Allogeneic patients (n=63)
FACT-BMT total	142.55 ± 25.50	142.13 ± 28.70
Physical well-being	20.91 ± 5.39	20.56 ± 5.89
Functional well-being	17.55 ± 5.82	17.24 ± 7.21
Social well-being	21.47 ± 4.21	21.41 ± 5.06
Emotional well-being	19.14 ± 3.76	18.94 ± 4.90
BMT-specific complaints	63.48 ± 15.44	63.98 ± 11.72
FACT-G	77.64 ± 17.16	77.90 ± 18.71

FACT-BMT: Functional Assessment of Cancer Therapy-Bone Marrow Transplant Scale; FACT-G: Functional Assessment of Cancer Therapy; BMT: Bone Marrow Transplantation Subscale

4.2.2. Comparison of FACT-BMT, BDI and SSTAI scores between autologous and allogeneic patients

No significant differences were detected in the mean FACT-BMT ($p = 0.83$), BDI ($p = 0.24$), and SSTAI scores ($p = 0.69$) between the two groups.

The stepwise multiple regression analysis demonstrated that psychiatric comorbidity, depression, and anxiety significantly contributed to HRQOL deficit in both the autologous and allogeneic groups. Poor HRQOL was independently associated with depression and anxiety in both groups. Psychiatric comorbidity, anxiety, and CGI were the contributors to depression in the allogeneic sample and anxiety in the autologous sample. Functional limitation was independently associated with depressive symptoms in the allogeneic group. The significant results of the multiple regression analysis are listed in Table 11.

Table 11. Variables independently associated with H QOL and psychopathology (stepwise multiple regression analysis) (Janicsák H, 2023 p.9)

	FACT-BMT				BDI			
	Autologous		Allogeneic		Autologous		Allogeneic	
	beta	t(p)	beta	t(p)	beta	t(p)	beta	t(p)
Psychiatric comorbidity	0.3	4.61 (p<0.001)	-0.38	-3.79 (p<0.001)			-0.44	-5.37 (p<0.001)
CGI							0.23	3.38 (p=0.002)
BDI	-0.56	-5.62 (p<0.001)	-0.71	-5.04 (p<0.001)				
SSTAI			-0.42	-3.51 (p=0.01)	0.89	8.6 (p<0.001)	0.55	6.86 (p<0.001)
SSTAI “State” scale	-0.31	-3.1 (p=0.004)						

BDI: Beck Depression Inventory; SSTAI: Spielberger’s State and Trait Anxiety Scale; CGI: Clinical Global Impression

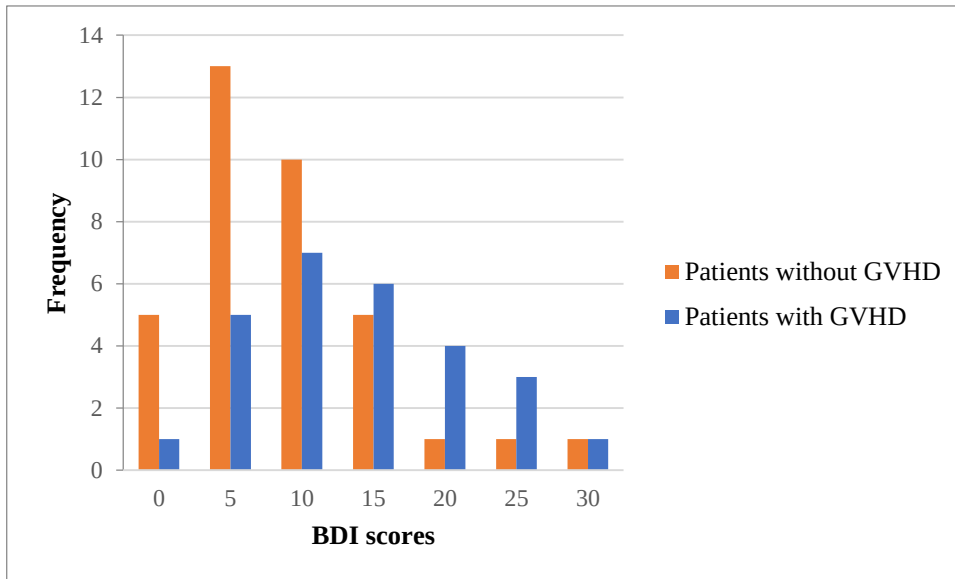
4.2.3. Comparison of FACT-BMT, BDI and SSTAI scores between autologous and allogeneic patients with or without GVHD symptoms

The medical characteristics and comparison of allogeneic patients with and without GVHD symptoms are summarized in Table 12. Comparison between groups recognized significant differences in the CGI ($p < 0.01$) and BDI ($p = 0.01$) scores (Figure 7.). The SSTAI Trait Anxiety scores were also significantly different ($p = 0.04$) between patients with and without GVHD (Figure 8.). Among the FACT-BMT domains, a significant difference in BMT-specific items ($p < 0.01$), in FACT-G scale ($p < 0.05$) and in total FACT-BMT ($p < 0.05$) scores was found between the GVHD groups (Figure 9.). Significant differences in sociodemographic and medical variables between patients with and without GVHD were not detected except immunosuppressive treatments. Allogeneic patients with GVHD symptoms received more immunosuppressive treatment than patients without GVHD (Table 9). Comparisons between autologous and allogeneic patients without GVHD did not explore significant differences in the FACT-BMT ($p = 0.17$), BDI ($p = 0.77$) and SSTAI ($p = 0.25$) scores. Comparisons between autologous and allogeneic patients with GVHD revealed significant differences in the CGI ($p < 0.01$) and BDI scores.

Table 12. Medical conditions related to the underlying hematological disease and treatment in allogeneic participants with GVHD and without GVHD undergoing HSCT (Janicsák H, 2023 p. 8)

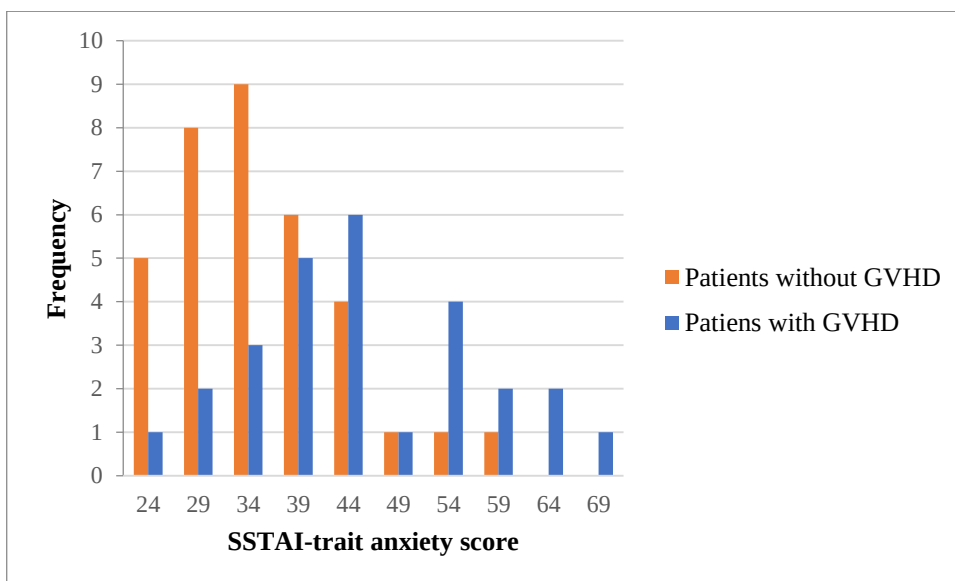
		Allogeneic HSCT with GVHD (n=25)	Allogeneic HSCT without GVHD (n=38)	Comparison of allogeneic HSCT with GVHD and without GVHD
Diagnoses	Acute lymphoid leukemia	3 patients (12%)	4 patients (10.5%)	
	Acute myeloid leukemia	9 patients (36%)	17 patients (44.7%)	
	Chronic lymphoid leukemia	1 patient (4%)	1 patient (2.6%)	
	Chronic myeloid leukemia	1 patient (4%)	6 patients (15.8%)	
	Hodgkin disease	1 patient (4%)	2 patients (5.3%)	
	Non-Hodgkin lymphoma	3 patients (12%)	2 patients (5.3%)	
	Myeloma multiplex	2 patients (8%)	2 patients (5.3%)	
	Other	5 patients (20%)	4 patients (10.4%)	
Bone marrow transplantation type ¹				
	Allogeneic related	9 patients (36%)	23 patients (60.5%)	
	Allogeneic unrelated	13 patients (52%)	14 patients (36.8%)	
Time elapsed since transplant (months)		27 (2-136)	30.1 (6-144)	U=533 p=0.51
Duration of illness (months)		52.44 (6-228)	51.15 (1-130)	U=467.5 p=0.79

Graft-versus-host disease (GVHD)	Acute	7 patients (28%)		
	Chronic	25 patients (100%)		
Phase of recovery ²	Complete remission	10 patients (40%)	15 patients (44.1%)	$P_{\text{fish}}=1.37$ $p=0.47$
	Recovered	14 patients (56%)	15 patients (44.1%)	
	Active disease	1 patients (4%)	4 patients (11.8%)	
Active treatment		17 patients (68%)	6 patients (17.1%)	$\chi^2=14.20$ $p=0.00$ $V=0.48$ $p=0.00$
Medical comorbidity		7 patients (30.4%)	9 patients (25.7%)	$\chi^2=0.00$ $p=0.95$
Psychiatric comorbidity		1 patient (4.3%)	1 patients (2.9%)	$\chi^2=0.04$ $p=0.84$



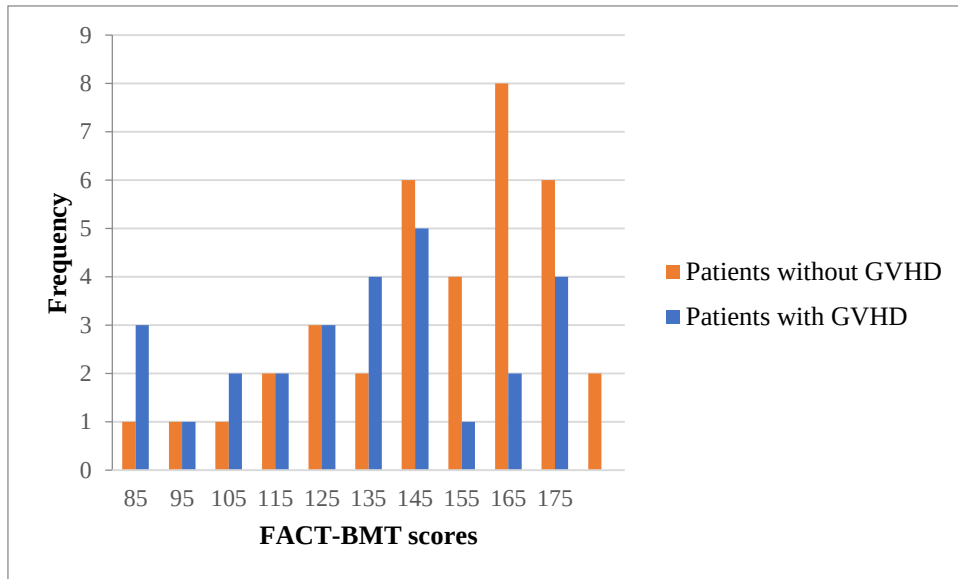
BDI: Beck Depression Inventory

Figure 7. Differences in BDI scores between allogeneic patients with GVHD and without GVHD symptoms



SSTAI: Spielberger's State and Trait Anxiety Scale; GVHD: Graft versus Host Disease

Figure 8. Differences in SSTAI Trait anxiety scores between allogeneic patients with GVHD and without GVHD symptoms



FACT-BMT: Functional Assessment of Cancer Therapy-Bone Marrow Transplant Scale; GVHD: Graft versus Host Disease

Figure 9. Differences in Fact-BMT total scores between allogeneic patients with GVHD and without GVHD symptoms

5. DISCUSSION

5.1. Health related quality of life and its socio-demographic and psychological determinants after HSCT

The study was performed at a mean of $26 + 37$ months after BMT. The one cross-sectional study (46) with comparable time frame, revealed poorer HRQOL than our findings. Reference FACT-BMT scores from that research were: FACT-BMT: 122 ± 15.64 ; physical well-being: 23.38 ± 3.79 ; functional well-being: 19.11 ± 4.18 ; emotional well-being: 20.27 ± 3.47 ; social well-being: 20.00 ± 4.99 ; relationship with the doctor: 6.72 ± 1.22 ; additional worries: 32.72 ± 6.08 (46). Other studies reported lower mean values at 6 months (110.95), 12 months (112.8) after HSCT (92). Longitudinal studies investigating HSCT patients' HRQOL at different time points have suggested poorer HRQOL at the time used in our study (55, 105). In this study only small proportion (47%) of eligible patients has managed to enroll. As research previously has confirmed, patients with more somatic and psychological difficulties were more likely to refuse participation in this research, and this attrition has been leading to potentially overestimated HRQOL (9, 62, 63). A set of differences in the sociocultural environment, sampling methods, and HRQOL measurement prevents direct comparison between our and previous investigations.

This study was unable to detect the general path of recovery proposed in the literature, This study was not able to identify the general trajectory of recovery suggested in the literature (87), often beginning with physical and functional well-being and ending with psychological and social re-adaptation. Our findings showed no relationship between HRQOL and the time elapsed since HSCT. A longitudinal study would have offered more adequate results in this regard.

5.1.1. Psychosocial determinants of HRQOL in HSCT patients

Attempts to clarify the relationship between psychosocial factors and HRQOL have produced inconsistent results due to differences in approach among research. Anxiety levels in the general Hungarian population were reflected in SSTAI scores [state anxiety for men: 38.40 ± 10.66 , trait anxiety for men: 40.96 ± 7.78 ; state anxiety for women: 42.64 ± 10.79 , trait anxiety for women: 45.37 ± 7.97] while BDI scores indicated mild

depression in this study (156). These results correspond with those of Syrjala et al. (70). Consistent with most research data exploring the relationship between HRQOL and depression and anxiety (106, 146) depressive and anxiety symptoms showed significant correlation with HRQOL in our study. This result implies that depressed and anxious patients perceive their HRQOL poorer than patients without such symptoms do. This study also found a significant correlation between pre-transplant psychopathology and HRQOL. This finding indicates that pre-transplant psychiatric illness could be a possible risk factor for poor post-transplant HRQOL. This study also found significant association between pre-transplant psychopathology and HRQOL. The findings, however, should be interpreted with caution because only three patients had psychiatric comorbidities prior to transplant.

Among the socio-demographic variables considered, only unemployment and gender influenced HRQOL. Female patients had more difficulties in managing HSCT-specific problems, which resulted in poorer HRQOL than for men, confirming the result of Heinonnen et al. on gender-related disparities in HRQOL after HSCT (73). The unique feature of our study is the thorough examination of the effect of economic factors in forming HRQOL in a Hungarian HSCT population. Unemployment was associated with poorer HRQOL following HSCT. HSCT implies significant financial burden on patients and their families, even in a free public health system, due to indirect costs of treatment such as providing proper hygienic conditions and nutrition at home.

5.1.2. Medical determinants of HRQOL in HSCT patients

Factors related to the medical condition, comprising chronic GVHD, have made negligible impact on HRQOL in the entire sample. GVHD did not correlate with HRQOL, even if it has influenced patients' somatic status. This is somewhat surprising, because previous studies reported a consistent adverse association between chronic GVHD and HRQOL (99, 157). As mentioned, numerous patients with somatic and psychological complaints refused participation in our study. The significant attrition, relatively small sample and its heterogeneity might explain the lack of this correlation. In addition the severe hematological condition has probably primarily affected patients' HRQOL, while the treatment and its negative effects had relatively insignificant impact in this regard.

5.2. Impact of the type of HSCT on HRQOL and psychopathology

5.2.1. Comparison of HRQOL and affective symptoms between autologous and allogeneic patients

This study found no direct impacts of the transplant type on the HRQOL anxiety or affective symptoms of patients. Both transplant strategies have specific diagnostic indications with different disease characteristics. Accordingly, our results showed significant differences between autologous and allogeneic patients in sociodemographic (e.g. age) and medical aspects (time elapsed transplant, disease status, active treatment) which impacts may have been equalized between groups indicating negligible differences in HRQOL anxiety and affective symptoms. However allogeneic patients experienced mild depression compared to autologous patients. Previous research also revealed inconsistent relationship between transplant type and HRQOL due to the differences in study methodology. Recovery is not a unidirectional progression with considerable disparities between autologous and allogeneic recipients and great individual variability in patients' physical and mental functionin.

Both earlier and our prior study found depressive and anxiety symptoms as significant risk factors for HRQOL deterioration following HSCT, suggesting that depressed patients assessed their HRQOL to be inferior (8, 157). The current study independently confirmed this relationship in patients receiving allogeneic and autologous transplant, exhibiting that adverse perceptions of HRQOL are unrelated to the transplant type.

5.2.2. Comparison of HRQOL and affective symptoms between autologous and allogeneic patients with or without GVHD symptoms

The direct comparison of allogeneic patients with and without GVHD found significantly worse somatic state and more transplant-related somatic complaints in allogeneic transplant recipients with GVHD and received more immunosuppressive treatments, impairing their HRQOL. Allogeneic transplant patients with GVHD symptoms had worse HRQOL than those without GVHD symptoms. A longitudinal study is recommended to thoroughly explore this association.

Additionally, our results demonstrated more severe depression with higher constant anxiety levels in patients with GVHD than those without GVHD, indicating that GVHD has a major impact on allogeneic transplant patients' affective symptoms through functional deficits and "somatic burden". Our findings supported the previously reported association between GVHD associated symptom burden, and functional deficits, affective symptoms and HRQOL deterioration in allogeneic recipients suffering from GVHD (11, 51, 131, 134, 137). Depression-related adverse perception among patients experiencing severe and persistent somatic symptoms derived from GVHD could further elevate the risk of depressive symptoms and, in turn, may affect several HRQOL components (51).

Our outcomes illustrate comparable HRQOL and psychosocial functioning in autologous and allogeneic transplant patients without GVHD symptoms. However, allogeneic transplant patients with GVHD symptoms experienced more depressive symptoms compared to autologous counterparts.

5.3. Limitations

The studies have methodological limitations that should be acknowledged. The major limitation was the cross-sectional design, which hindered the examination of causation of relationships between the risk factors in recovery trajectory. Given the variety and amount of clinical conditions that necessitate HSCT, the sample size was rather modest. As a clinical population, the study sample had heterogeneous characteristics in certain aspects (age, psychosocial factors, medical variables), and significant attrition rates, that may have influenced the results. Data of drop out patients with somatic and psychological difficulties may have confirmed the correlation between somatic and medical factors and HRQOL and may have impact on the perception of HRQOL. Furthermore, the quality of care provided by professionals, notably caretakers, and the family milieu were not investigated due to logistical constraints. The advancements in BMT and hematological care between 1994 and 2008 were also overlooked. Additionally, self-report surveys have inherent bias that may have been corrected via a comprehensive mental evaluation. Furthermore, not all variable could be gathered and tested in all cases.

6. CONCLUSIONS

Both study of the current research revealed specific correlations between psychosocial factors and HRQOL in the sample of Hungarian HSCT patients.

Our experiments focused on the following questions:

Regarding the goals of the first study on psychosocial and medical determinants of HRQOL after HSCT, the main finding was that unemployment and psychopathology, specifically depressive and anxiety symptoms, have a significant influence on HRQOL after HSCT.

- [1.] Results have not indicated HRQOL impairment, but confirmed mild depression in HSCT patients. Anxiety and affective symptoms predispose patients to perceive impaired HRQOL and further worsening anxiety and depressive symptoms.
- [2.] Unemployment was associated with poorer QOL after HSCT in this study. HSCT puts a heavy financial burden on patients and their families, even in a free public health system, due to indirect costs of treatment
- [3.] Our results confirmed previous data on gender differences in perceived HRQOL in HSCT patients. Female patients found it difficult to cope with HSCT-specific difficulties, which led to poorer HRQOL than for men.
- [4.] Somatic and medical factors surprisingly have not influenced patients' HRQOL presumably due to sample diversity.

Regarding the goals of the second study on the impact of transplantation type on HRQOL, anxiety and affective symptoms after HSCT the main finding was, that transplantation type has not impacted HRQOL and affective symptoms of HSCT patients.

- [1.] Results indicated similar HRQOL in allogeneic and autologous patients.
- [2.] The impact of anxiety and affective symptoms on HRQOL was also independent from transplantation type in this study.
- [3.] The impact of GVHD symptoms was examined separately in allogeneic patients to reduce sample diversity. Allogeneic transplant patients with GVHD symptoms indicated more depressive symptoms compared to autologous, and more depressive and anxiety symptoms compared to allogeneic counterparts

without GVHD symptoms. Additionally, GVHD symptoms and their treatment probably impair patients HRQOL through functional deficits and somatic burden and predispose them to develop affective symptoms and perceiving further HRQOL deficits [50]. These findings are consistent with the conclusion that allogeneic patients with GVHD and depressive and anxiety symptoms constitute a highly vulnerable population for poor functioning, impaired HRQOL, and HSCT-related mortality [141].

7. SUMMARY

Extensive research focused on the psychosocial challenges associated with HSCT. HRQOL, psychiatric comorbidities and affective symptoms of HSCT patients have been widely investigated. The issues deserved attention includes the examination of the correlations of various medical and psychosocial determinants, such as transplantation type, GVHD, socio-demographic and economic factors.

Therefore, we aimed to investigate the correlation of psychosocial status and health-related quality of life in Hungarian hematopoietic transplanted patients in this research with primary focus on the impact of various medical and psychosocial factors in shaping patients' HRQOL. Our research had a cross-sectional design. HSCT patients (n=121; auto-HSCT=58; allo-HSCT=63) were assessed with self-reported questionnaires for the measurement of HRQOL, affective symptoms, and medical and sociodemographic variables.

Our first study focused on the associations between HRQOL and psychosocial factors. Results have not indicated HRQOL impairment, but confirmed mild depression in HSCT patients. The main finding of this study is that unemployment, anxiety and affective symptoms have a significant influence on HRQOL after HSCT.

The distinctive feature of our study is the thorough examination of the effect of economic factors on HRQOL in a Hungarian BMT population. Unemployment was related to lower HRQOL following HSCT. HSCT places a significant financial burden on patients and close relatives, even in a free public health system, given to treatment's indirect expenses.

Our second study investigated the impact of transplantation type and concluded that the type of transplant has negligible impact on patients' HRQOL and psychosocial functioning. Analysis separately in the allogeneic transplant group revealed that GVHD symptoms impair patients HRQOL through functional deficits and somatic burden and predispose them to develop affective symptoms and perceiving further HRQOL deficits.

These findings support previous conclusion that allogeneic patients with GVHD and depressive and anxiety symptoms constitute a highly vulnerable subpopulation for poor functioning, impaired QOL, and HSCT-related mortality, and constitute a target population for consultation-liason psychiatrics and psychosocial support.

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9. BIBLIOGRAPHY OF PUBLICATIONS

9.1. Publications related to the thesis:

Janicsák H, Masszi T, Reményi P, Ungvari GS, Gazdag G. Quality of life and its socio-demographic and psychological determinant after bone marrow transplantation. *European Journal of Haematology* 2013; 91(2):135-40. [PMID: 23614507 DOI: 10.1111/ejh.12126]

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ΣIF of dissertation-related publications: 3.314

9.2. Publications not related to the thesis:

Janicsák H, Girasek H, Soós Alexandra, Dudás D, Reinhardt M, Gazdag G. A személyiségzavarok hátterében álló személyiségjegyek vizsgálata az MMPI-2 pszichodiagnosztikai teszttel. *Psychiatria Hungarica* 2023; 38:Supplementum I. 60.

Girasek H, Soós A, Janicsák H, Dudás D, Reinhardt M. Változások és újítások a Minnesota Multiphasic Personality Inventory-2 (MMPI-2) pszichodiagnosztikai tesztben. *Magyar Pszichológiai Szemle* 2023; 78(1):135-156. [DOI: 10.1556/0016.2023.00028]

Girasek H, Soós A, Dudás D, Reinhardt M, Janicsák H, Gazdag G. A szuicid veszélyeztetettség becslése az MMPI-2 pszichodiagnosztikai teszttel pszichiátriai fekvőbetegek körében. *Psychiatria Hungarica* 2023; 38:Supplementum I. 58.

Girasek H, Reinhardt M, Soós A, Dudás D, Janicsák H, Gazdag G. Az MMPI-2 teszt alkalmazhatósága a személyiségzavarok, kiemelten a borderline személyiségzavar esetében. *Psychiatria Hungarica* 2024; 39:Suppl. 22-23.

10. ACKNOWLEDGEMENTS

Above all, I would like to express my sincere appreciation to the patients who participated in this research.

I am expressing my deepest gratitude and appreciation to the following individuals for their invaluable support in completing this research project.

First and foremost, I am grateful to my primary advisor Gazdag Gábor for all the support, instructions, and encouragement I received throughout this research project. His insights and feedback have been helpful in shaping the scope and directions of this study.

I am also grateful to Gabor Ungvari and Masszi Tamás for their helpful insights and assistance with language proofreading and manuscript preparation. Their expertise enhanced the quality and credibility of the findings of this research.

I extend my appreciation to my colleagues at the Bone Marrow Transplantation Unit of Szent Laszlo Hospital in Budapest, for their support and collaboration.

Lastly, I am thankful to my family for their understanding, encouragement, and support.