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REVIEW

Predictors of health-related quality of life in patients treated with auto- and allo-SCT for hematological malignancies

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Identifying factors that predict health-related quality of life (QOL) following hematopoietic SCT, is important in estimating patients' abilities to adjust to the consequences of their disease and treatment. As the studies that have been published on this subject are scattered, the present study aimed to systematically review prognostic factors for health-related QOL after auto- and allo-SCT in hematological malignancies. A systematic, computerized search in Medline, EMBASE, PsycINFO and the Cochrane Library was conducted from 2002 to June 2010. The methodological quality of the studies was assessed using an adaptation of Hayden's criteria list. Qualitative data synthesis was performed to determine the strength of the scientific evidence. In all, 35 studies fulfilled the selection criteria. Strong–moderate evidence was found for GVHD, conditioning regimen, being female, younger age, receiving less social support and pre-transplant psychological distress as predictors of various aspects of health-related QOL following hematopoietic SCT. The results of this review may help transplant teams in selecting patients at risk for experiencing a diminished health-related QOL following hematopoietic SCT. Follow-up treatment can be provided in order to promote QOL.
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Introduction

In the treatment of hematological malignancies, the number of auto- and allogeneic hematopoietic stem cell transplants (HSCT) increases each year. Also, the number of indications for which HSCT is considered appropriate expands, for instance to older patients and patients with comorbidities. HSCT has become standard care for many patients, and in 2006, almost 45 000 HSCT-procedures for hematological disorders were reported worldwide.[1] Although these intense procedures lead to improved long-term survival, they are associated with physical morbidity and psychological distress, potentially threatening patients' quality of life (QOL).[2–5] The World Health Organization defines QOL as 'individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns.[6] Health-related QOL refers to those domains of QOL directly affected by changes in health, and can be defined as the functional effect of an illness and its consequent therapy upon a patient, as perceived by the patient. Health-related QOL consists of several broad domains, including physical and occupational functioning, psychological functioning, social interaction, and somatic sensation.[7]

Reviews of health-related QOL after HSCT generally indicate that the functioning of patients after HSCT is diminished.[8–10] A distinction should be made between auto- and allo-SCT, as these different procedures may have a differential impact on health-related QOL. In auto-SCT, patients are impaired in their QOL before as well as directly after transplantation, due to the conditioning regimen and their disease. Patients experience impaired physical, emotional and role functioning compared with population norms. In the months and years after auto-SCT, these aspects of QOL reach or surpass pre-transplant levels, although continuing long-term impairments are observed for physical functioning, role functioning and overall health-related QOL.[8–10] Following allo-SCT, in which patients are transplanted with stem cells from a sibling or matched unrelated donor, approximately 30–70% of patients experience acute or chronic GVHD,[11] which can last for many years. Other serious somatic complications such as infections and damage to the liver and lungs can also occur. As in auto-SCT, the time before allo-SCT is characterized by specific impairments in QOL. Patients

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experience diminished physical functioning, high levels of emotional distress, impaired social functioning and lower role functioning compared with population norms. Immediately after allo-SCT, all QOL aspects decline rapidly but improve gradually toward pre-SCT levels in the years following transplantation. Compared with other non-cancer comparison groups, however, all aspects of health-related QOL continue to be impaired in the long term.[8–10]

Individual differences in health-related QOL depend on somatic as well as psychosocial factors. Identifying factors that predict health-related QOL following HSCT is important for the prediction of patient ability to adjust to the consequences of their disease and treatment. This information may guide the transplant team in selecting patients who need additional (psychological) care before, during and/or after HSCT, and in evaluating what kind of care patients require. As the studies that have been published on prognostic factors are scattered, the present study aims to systematically review prognostic factors for health-related QOL after HSCT in hematological malignancies, focusing on biomedical factors, and physical, psychological, social and sexual functioning.

Materials and methods

Literature selection

A systematic, computerized search of Medline, EMBASE, PsycINFO and the Cochrane Library was conducted. As HSCT-protocols have been changing (for example, since 2000, the so-called reduced-intensity regimens have been introduced in allo-SCT, which differ substantially from the very intensive treatment regimens before 2000), we focused on more recent studies and limited the literature search to articles published from January 2002 to June 2010. In collaboration with a librarian, the authors developed the following search strategy for Medline, which was modified correspondingly for each of the databases: the Medical Subject Headings (MeSH) terms 'hematologic neoplasms', 'lymphoma', 'leukemia' and 'myeloma' were combined with the MeSH terms 'hematopoietic SCT', 'BMT', 'SCT' and 'peripheral blood SCT'. These were combined with the MeSH terms 'QOL', 'health', 'pain', 'physical fitness', 'exercise', 'depression', 'anxiety', 'stress, psychological', 'adaptation, psychological', 'affective symptoms', 'life change events' and 'social support'.

The search was supplemented with a free keyword search of the terms 'hematologic malignanc*', 'hematological malignanc*', 'hematopoietic malignanc*', 'HSCT', 'SCT', 'BMT', 'BMT*', 'SCT*', 'hematopoietic transplant*', 'hematopoietic cell transplant*', 'QOL', 'HRQOL', 'functional status', 'physical*', 'psycholog*', 'psychological distress', 'well-being', 'social*', 'sexual*', 'depression', 'anxiety', 'mood' and 'psychological stress' (in titles and abstracts). Finally, the search was limited to studies focusing on adult populations. References of included studies were checked for additional literature.

Study selection

A study was included if: (1) the study population consisted of adult subjects ($\geqslant$18 years of age) with hematological malignancies (at least 50% of the diagnoses in a single study), treated with HSCT; (2) it concerned a prospective study with at least one assessment before transplant and one assessment after transplant; (3) the study evaluated health-related QOL (symptoms or physical, psychological, social and sexual functioning) as an outcome measure, assessed with at least one quantitative multi-item measure; (4) the article was published between January 2002 and June 2010, and inclusion of patients did not start before 1995; and (5) the article was published in English, Dutch or German. Only full-text articles were included.

In the first selection stage, all references were screened by the first author (AB) based on title and abstract. During this phase, studies were included in case of doubt. In the second selection stage, the full-text articles of all selected abstracts which fulfilled the selection criteria were read for the final inclusion (AB and MG). Disagreements were discussed and resolved during a consensus meeting.

Categories of predictors and outcome measures

According to the domains of health-related QOL, the predictors were categorized into the following domains.

(1) Biomedical: symptoms (pain); disease; treatment.
(2) Physical functioning: instrumental activities of daily living ((I)ADL); exercise physiology (VO2 max); sleep and fatigue.
(3) Psychological functioning: cognitive; emotional; psychiatric symptoms.
(4) Social functioning: social relations, support; education/socio-economic status (SES); work.
(5) Sexual functioning.
(6) Other.

Outcome measures were categorized into the same domains, with the exception that disease and treatment (biomedical domain) were only predictors and no outcome variables.

Assessment of methodological quality

The methodological quality of the selected studies was assessed by two independent reviewers (AB and MG) using a standardized predefined list of quality criteria (Supplementary A), based on a list by Hayden,[12] which was adjusted to the goals of this review. Following Hayden's recommendations, we evaluated 14 domains addressing six potential biases: bias related to study participation, study attrition, measurement of prognostic factors, measurement of and controlling for confounding variables, measurement of outcomes, and analysis approaches. For example, to assess risk for bias related to study attrition, we took into account the amount of loss to follow-up, reasons for loss to follow-up, differences between completers and non-completers on key characteristics and the information the authors gave on drop outs, completers and non-completers. The risk for bias was judged to be high if a study failed (to report) on these items and consequently, there was a distortion in study results due to a relationship between the prognostic factor and outcome being different for completing and non-completing participants. A study was identified as a high-quality study, if all six areas were rated as low

or moderate risk of bias. If a study had a high risk for any area of bias, it was defined as being a low-quality study. Disagreements between the reviewers were discussed and resolved during a consensus meeting.

Data extraction

The following data were extracted from each paper: (a) sample demographics at baseline; (b) disease type; (c) type of transplant; (d) risk factors/predictors; (e) outcome variables; (f) instruments used for assessing predictors and outcome variables; (g) timing of assessments; (h) results.

Method of analysis: levels of evidence

Because the studies included in this review were heterogeneous with respect to the prognostic factors and outcome measures, a qualitative data synthesis was performed. To determine the strength of the scientific evidence, a rating system was applied which consists of five levels of evidence (strong, moderate, weak, inconclusive and inconsistent) based on the quality and the outcome of the studies, adapted from Licht-Strunk *et al*. (Table 1).[13] Strong evidence could only be established by two high-quality studies showing consistent associations. Without a high-quality study showing consistent associations, low-quality studies lead to weak evidence at best.

Results

Description of included studies

The literature search identified 4438 articles. Examination of titles and abstracts resulted in 152 publications that were considered for inclusion. After full-text assessment, 35 articles met the inclusion criteria and were included in this review (Figure 1).

An overview of the studies included is provided in Table 2 (an extended version of this table is available in Supplementary B). The number of patients varied from 19 to 320. All studies had a longitudinal design (in line with our inclusion criteria), and follow-up measurements ranged from a few days to 3 years post transplant. In all, 11 studies focused only on allo-SCT patients, 3 studies focused on auto-SCT patients only and 21 studies included both. Of these studies with mixed samples, one provided separate analyses for auto-SCT and allo-SCT patients, whereas the other studies analyzed all patients together.

The results of the assessment of methodological quality are presented in Table 2. The two reviewers agreed on 81% of the scored items. In all, 27 studies were considered to be of high quality and eight studies were of low quality.

Factors predicting health-related QOL

Predictors of pain or symptoms. Allo-SCT. One study focused on predictors of pain and symptoms: patients treated with myeloablative conditioning had worse outcomes than those treated with reduced-intensity conditioning (weak evidence).[16]

Auto-SCT. Comparing patients with non-Hodgkin lymphoma and multiple myeloma, one study reported that patients with non-Hodgkin lymphoma had more severe lack of appetite at nadir. Furthermore, at nadir, patients with non-Hodgkin lymphoma reported more pain, whereas patients with multiple myeloma reported more pain at day 30 post transplant (weak evidence).[15]

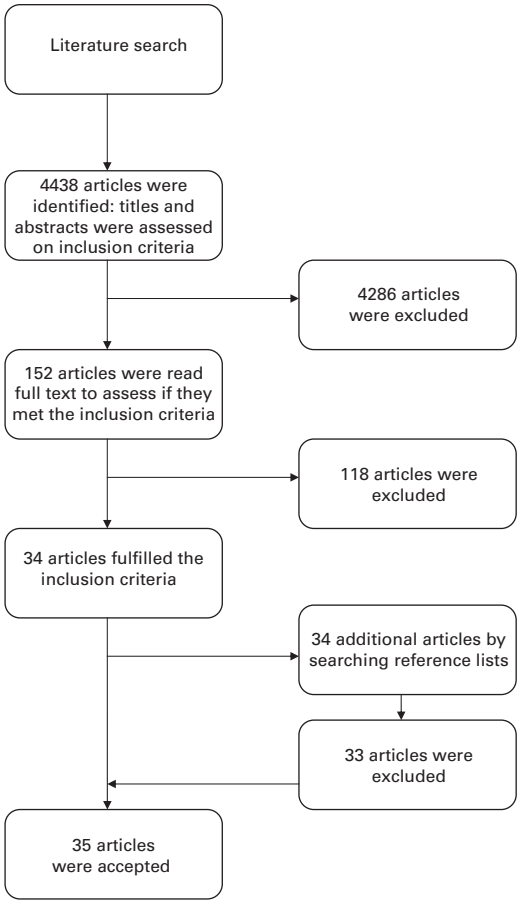

Figure 1 Article selection.

Table 1 Level of evidence for prognostic factors for outcome after SCT

Levels of evidence	
Statistical significant associations	
Strong	Consistent associations found in at least two high-quality studies
Moderate	Consistent associations found in one high-quality study and at least one low-quality study
Weak	Association found in one high-quality study or consistent associations found in at least three low-quality studies
Inconclusive	Association found in less than three low-quality studies
Inconsistent	Inconsistent findings irrespective of study quality

Table 2 Overview of the included studies

Reference	*Sample demographics at baseline*	*Disease type*	*Type of transplant*	*General results*	*Study quality*
Altmaier *et al.*[14] (2006)	$N=309$, 55% male, mean age $\approx$ 33 years	44% CML, 25% AML, 21% ALL, 6% MDS, 3% other leukemia, 1% NHL	100% allo-SCT	There were no differences in QOL or depression at 1 year between the treatment arms.	High
Anderson *et al.*[15] (2007)	$N=100$, 60% male, mean age = 53.6 years	34% NHL, 66% MM	100% auto-SCT	There was a time-by-cancer-diagnosis interaction with respect to fatigue severity, sleep disturbance, lack of appetite and pain severity. For lack of appetite, patient's reported QOL and mood disturbance at baseline were significant covariates.	High
Andersson *et al.*[16] (2009)	$N=57$, 51% male, mean age $\approx$ 45 years	32% AML, 16% ALL, 16% CML, 4% CLL, 11% lymphoma, 2% MM, 7% MDS, 5% myelofibrosis, 2% Walderström's macroglobulinemia, 2% aplastic anemia, 5% solid tumors	100% allo-SCT	Over time, patients receiving myeloablative conditioning scored lower on social functioning and higher on appetite loss, financial problems and change of taste. A month post transplant, MAC patients scored worse on sleep disturbance, financial impact, skin irritations, soreness in mouth and change of taste. At 1 year post transplant, patients with myeloablative conditioning reported a dry mouth more often.	High
Andorsky *et al.*[17] (2006)	$N=320$, 52% male, mean age = 47 years	6% ALL, 11% AML, 7% CLL, 26% CML, 3% HD, 6% MDS, 19% MM, 22% NHL, 2% other	37% auto-SCT, 63% allo-SCT	Gender, marital status, disease risk, GVHD, transplant type, pre transplant overall health and mental health were predictive of agreement with statements regarding recovery from transplant and social functioning at 6 months post transplant. At 12 months, baseline mental health, self-reported overall health and physical health were important predictors of recovery.	Low
Basinski *et al.*[31] (2010)	$N=52$, 56% male, mean age $\approx$ 40 years	52% CML, 15% ALL or AML, 15% breast cancer or ovarian cancer, 8% MDS or MM, 10% NHL	19% auto-SCT, 81% allo-SCT	At 6 months post transplant, patients with a previous delirium episode reported more fatigue, cancer and treatment distress, worse physical health-related QOL, and worse neuropsychological functioning. At 1 year post transplant, patients with a previous delirium episode reported more mental health distress, including depression, PTSD symptoms and worse mental health (SF-12) as well as more fatigue, cancer and treatment distress and worse neuropsychological functioning.	High
Bevans *et al.*[37] (2008)	$N=76$, 67% male, mean age = 40 years	17% acute leukemia, 38% chronic leukemia, 29% lymphoma/MM, 12% MDS, 4% non-hematological malignancy	100% allo-SCT	Younger patients experienced more distress. A low-disease risk predicted low symptom distress.	High
Bevans *et al.*[20] (2006)	$N=76$, 67% male, mean age $\approx$ 40 years	17% acute leukemia, 38% chronic leukemia, 28% lymphoma/MM, 12% MDS, 4% non-hematological malignancy	100% allo-SCT	On the FACT and SF-36, there were no differences found between treatment groups in QOL. Only time was a predictor of physical and mental functioning on the SF-36.	High
Chang *et al.*[21] (2005)	$N=84$, 57% male, mean age = 44 years	CML	100% allo-SCT	Time was a significant predictor for QOL. Significantly higher depression scores were found in women, but otherwise, only time was a significant predictor.	High
Diez-Campelo *et al.*[22] (2004)	$N=117$, mean age $\approx$ 54 years	13% AML, 3% ALL, 4% CML, 6% MDS, 28% NHL, 9% HD, 5% breast cancer, 25% MM, 3% CLL, 1% amyloidosis	60% auto-SCT, 40% reduced-intensity conditioning allo-SCT	Auto-SCT patients experienced more fever episodes, mucositis and nausea/comiting compared with allo-RIC patients. Auto-SCT patients experienced worse physical functioning in the 1st year post transplant until day 180; more lack of energy, more need for rest and nausea. Allo-RIC patients experienced more GVHD symptoms like itching, ocular or mouth disturbances. GVHD predicted worse physical and functional well-being.	Low

Table 2 Continued

Reference	*Sample demographics at baseline*	*Disease type*	*Type of transplant*	*General results*	*Study quality*
Fann *et al.*[19] (2007)	$N=90$, 60% male, mean age $\approx$ 42 years	42% CML, 28% ALL or AML, 12% BR or OV, 11% MDS or MM, 7% NHL	19% auto-SCT, 81% allo-SCT	Age distinguished between patients with and without a delirium episode. At 30 days post transplant: delirium episode predicted anxiety, depression and fatigue. At 80 days post transplant: delirium episode predicted worse mental health functioning, anxiety, fatigue, cancer and treatment distress and executive/frontal functioning. Regarding delirium severity, the same associations were found. Exceptions had no relationship with delirium severity and either 30-day fatigue or 80-day mental functioning and a significant positive relationship between delirium severity and 80-day depressive symptoms.	High
Fann *et al.*[24] (2002)	$N=61$, 51% male, mean age = 49 years	42% CML, 28% ALL or AML, 12% breast cancer or ovarian cancer, 11% MDS or MM, 7% NHL	19% auto-SCT, 81% allo-SCT	Biomedical variables (BUN, malignancy diagnosis category, magnesium level, alkaline phosphatase level) and cognitive functioning (TMT-B, MMSE) predicted delirium. Biomedical variables (malignancy diagnosis category, TBI, magnesium level, creatinine level, alkaline phosphatase level), demographic variables (age, gender) prior alcohol or drug abuse and MMSE-score predicted delirium severity.	High
Friedman *et al.*[25] (2009)	$N=117$, 60% male, mean age = 45 years	6% ALL, 9% AML, 3% CLL, 15% CML, 14% HD, 30% NHL, 19% myeloma, 3% MDS	50% auto-SCT, 50% allo-SCT	Disease stage did not predict cognitive performance.	Low
Grulke *et al.*[26] (2005)	$N=53$, 68% male, mean age = 40.3 years	51% AML, 26% CML, 23% other diagnoses	100% allo-SCT	POMS-vigor decreased over time and showed lower scores for the radioimmunotherapy-group. The radioimmunotherapy-group had significantly more physical distress during the recovery period.	High
Harder *et al.*[27] (2007)	$N=101$, 61% male, mean age = 42 years	29% lymphoma, 4% HD, 27% AML/ALL, 17% CML/CLL, 17% MM, 3% MDS, 3% other	34% auto-SCT, 66% allo-SCT	TBI predicted poorer psychomotor functioning.	High
Harder *et al.*[28] (2006)	$N=25$, 64% male, median age = 47 years	4% ALL, 8% AML, 8% CLL, 28% MM, 8% MDS, 12% HD, 16% NHL, 16% severe aplastic anemia	20% auto-SCT, 80% allo-SCT	Time and age predicted memory. In other cognitive domains, there were no associations found. Higher education predicted better QOL. A time effect was found for emotional functioning. Females had better overall health at 6 months post transplant.	High
Hochhausen *et al.*[29] (2007)	$N=87$, 53% male, mean age $\approx$ 35 years	Leukemia	100% allo-SCT	GVHD predicted lower BMT-specific and general physical well-being. Social support, optimism, self-efficacy were predictors of QOL and depression.	High
Humphreys *et al.*[30] (2007)	$N=79$, 53% male, mean age = 34.5 years	45% CML, 25% AML, 22% ALL, 6% MDS, 3% other leukemia, 1% NHL	100% allo-SCT	Women experienced more overall sexual problems. At year 3 post transplant, baseline depression predicted total sexual problems and sexual desire problems. Furthermore, at year 3, women reported more sexual physical functioning problems.	High
Jenks-Kettmann *et al.*[31] (2008)	$N=86$, 55% male, mean age = 35 years	Hematological malignancies	100% allo-SCT	Pre-transplant depression predicted post transplant depression. Pre-transplant social support predicted post transplant depression.	Low
Kirchhoff *et al.*[43] (2010)	$N=197$, 42% male, mean age $\approx$ 42 years	39% CML, 18% AML, 8% lymphoma, 10% MDS, 4% MM, 21% other	19% auto-SCT, 81% allo-SCT	Women returned to work less often and later than men. In female patients, In women, TBI conditioning predicted less work return in the first 18 months post transplant.	Low

Table 2 Continued

Reference	*Sample demographics at baseline*	*Disease type*	*Type of transplant*	*General results*	*Study quality*
Langer *et al.*[32] (2009)	$N=80$, 68% male, mean age = 57 years	45% acute leukemia, 28% MDS, 6% lymphoma, 5% CML, 5% MM, 5% CLL, 3% aplastic anemia, 4% other	5% auto-SCT, 95% allo-SCT	Buffering predicted less satisfaction with relationship and worse mental health (received). The more highly motivated patients were to protect their partners relative to themselves, the greater was their adjusted post transplant relationship satisfaction. The motivation index was inversely related to relationship satisfaction among caregivers.	High
Larsen *et al.*[34] (2007)	$N=41$, 34% male, median age = 44	19% acute leukemia, 27% chronic leukemia, 7% MM, 37% breast cancer, 10% other	56% auto-SCT, 44% allo-SCT	High number of symptoms predicted poor general health at T1 and T4. At 1 year post transplant, a significantly larger proportion of patients in the poor general health-group reported tiredness, loss of appetite, anxiety, depression, skin changes, changed body image, shivers and constipation.	High
Larsen *et al.*[23] (2004)	$N=43$, 40% male, mean age = 45 years	21% acute leukemia, 23% chronic leukemia, 14% MM, 33% breast cancer, 9% other	60% auto-SCT, 40% allo-SCT	Anxiety predicted symptom distress at T5 and T6.	High
Lee *et al.*[36] (2006)	$N=96$, mean age = 46 years	Hematological malignancies	100% allo-SCT	Acute and chronic GVHD predicted the trial outcome index of the FACT-BMT, a composite of the physical, functional and transplantation-specific subscales. Relapse of disease predicted lower TOI. Time and the time by GVHD interaction were significantly associated with TOI-scores.	High
Lee *et al.*[33] (2005)	$N=61$, 51% male, median age = 49 years	Hematological malignancies	44% auto-SCT, 56% allo-SCT	Patients who were distressed pre-transplant were more likely to screen positive for distress post transplant.	Low
Lee *et al.*[11] (2003)	$N=313$, 52% male, age = 46.5 years	11% AML, 5% ALL, 26% CML, 7% CLL, 6% MDS, 20% NHL, 4% HD, 18% MM, <1% other leukemia, 1% other	35% auto-SCT, 65% allo-SCT	Optimistic expectations did not cause differences in physical or psychological functioning.	Low
Prieto *et al.*[41] (2006)	$N=220$, 59% male, mean age $\approx$ 41.5 years	23% AML, 13% ALL, 15% CML, 21% NHL, 9% HD, 12% MM, 7% other	59% auto-SCT, 41% allo-SCT	Baseline energy level predicted subsequent measures of energy level. Baseline energy level had no effect on predicting depression at T2, T3 and T4. Baseline depression was found to significantly predict T3 energy level.	High
Prieto *et al.*[39] (2005)	$N=220$, 59% male, mean age $\approx$ 41.5 years	15% CML, 13% ALL, 23% AML, 21% NHL, 9% HD, 12% MM, 7% other	59% auto-SCT, 41% allo-SCT	Women experienced more anxiety, depression and systemic symptoms. Higher disease risk status predicted lower energy level. Allo-SCT patients reported higher levels of systemic symptoms at T4. Auto-SCT patients experienced poorer functioning at T1 and T2, but had a more pronounced recovery and reported better physical functioning and energy level at T4.	High
Rischer *et al.*[40] (2009)	$N=50$, 74% male, mean age = 53 years	36% AML, 22% MM, 14% NHL, 10% MDS, 10% osteomyelofibrosis, 8% other	22% auto-SCT, 78% allo-SCT	An interaction between time and type of transplant was found.	High
Schulz-Kindermann *et al.*[46] (2007)	$N=19$, 63% male, mean age = 46.5	21% AML, 16% CML, 11% MM, 11% lymphoma, 11% MDS, 16% osteomyelofibrosis, 5% ALL, 5% CMML, 5% severe aplastic anemia	100% allo-SCT	In various degrees of GVHD, no differences in cognitive functioning were found. compared with patients who received an unrelated transplant, recipients of related transplants scored better on the digit-span-backwards-task. RIC patients scored significantly better on a reasoning task compared with patients receiving standard conditioning.	High

Table 2 Continued

Reference	*Sample demographics at baseline*	*Disease type*	*Type of transplant*	*General results*	*Study quality*
Schulz-Kindermann *et al.*[42] (2002)	$N = 63$, 65% male, mean age = 40 years	22% AML, 10% ALL, 49% CML, 13% myeloma, 6% other	16% auto-BMT/SCT, 84% allo-BMT/SCT	Week 1: depression, pain-related avoidance and support seeking behavior predicted mouth pain. Week 2: TBI/chemo predicted less mouth pain and mucositis predicted more mouth pain. Week 3: BMT-related distress predicted more mouth pain. BMT-related distress before BMT predicted anxious mood. Week 1 and week 3: coping (diverted attention) predicted mouth pain, and more resources in daily life or living together predicted less anxiety.	Low
Sherman *et al.*[45] (2009a)	$N = 94$, 62% male, mean age = 56 years	MM	100% auto-SCT	Positive religious coping predicted greater transplant-specific concerns. Negative religious coping predicted poorer functioning on anxiety, depression, emotional well-being and transplant-related concerns. An interaction between positive and negative religious coping predicted physical well-being.	High
Sherman *et al.*[44] (2009b)	$N = 94$, 62% male, mean age = 56 years	MM	100% auto-SCT	Older age predicted better social well-being. Patients who had undergone a previous HSCT experienced less anxiety. The diagnosis MM predicted QOL. Biomedical variables (treatment with thalidomide, LDH level) predicted QOL and depression.	High
Syrjala *et al.*[34] (2004)	$N = 319$, 56% male, mean age = 36 years	28% CML (chronic phase), 14% CML, (accelerated or blast phase), 18% acute leukemia in remission, 20% acute leukemia in relapse or *de novo*, 6% lymphoma in remission, 14% lymphoma in relapse	17% auto-SCT, 83% allo-SCT	Higher education predicted slower decline in distress post transplant. Females experienced more anxiety and depression. Pre-transplant treatment, diagnosis, chronic GVHD, depression and less satisfaction with support were predictors of distress, depression and physical limitations. Medical risk and physical limits did not predict distress, although medical risk did predict physical impairments. Return to work was significantly delayed for women.	High
Wells *et al.*[18] (2009)	$N = 214$, 52% male, mean age = 51 years	55% MM, 15% NHL, 7% breast cancer, 6% AML, 5% HD, 4% CML, 4% ALL, 2% ALL-MDS, 1% testicular cancer, 4% other	80% auto-SCT, 20% allo-SCT	Women experienced more depression and anxiety and used other coping strategies than men. Pre-HSCT depression predicted post-HSCT depression when combined with gender. Pre-HSCT anxiety predicted post-HSCT anxiety when combined with gender and belonging social support.	High
Wong *et al.*[47] (2010)	$N = 312$, 55% male, mean age = 48 years	28% NHL, 21% AML, 19% MM, 8% HD, 7% ALL, 6% myeloproliferative disorder, 11% other	54% auto-SCT, 46% allo-SCT	Several demographic and clinical variables were predictive of QOL and return to work. A distinction is made between patients who underwent autologous and allogeneic transplantation.	High

Abbreviation: BR = breast cancer; BUN = blood urea nitrogen; HD = Hodgkin's disease; MDS = myelodysplastic syndrome; MM = multiple myeloma; MMSE = mini mental status examination; NHL = non-Hodgkin's lymphoma; OV = ovarian cancer; TMT-B = trail making test B; QOL = quality of life.

Mixed. Evidence for the prediction of mouth pain is inconclusive.[42] Compared with patients undergoing allo-SCT with reduced-intensity conditioning, auto-SCT patients reported more fever episodes, more mucositis and nausea and less GVHD-like symptoms[22] (inconclusive evidence). Furthermore, auto-SCT patients had less systemic symptoms than allo-SCT patients (weak evidence).[39]

Predictors of global QOL. Allo-SCT. Strong evidence exists for an association between GVHD and global QOL: patients with GVHD experienced worse QOL post transplant.[29,47] Conditioning regimen, depression, self-efficacy, optimism and social support were only studied once as possible predictors for global QOL, whereby the evidence remains weak.[16,21,29]

Auto-SCT. Treatment with thalidomide, only used in patients with multiple myeloma, predicted worse functional well-being (weak evidence).[44]

Mixed. Higher education level was associated with higher QOL (weak evidence).[28]

Predictors of physical functioning. Allo-SCT. Strong evidence suggests that patients with chronic GVHD experience worse physical functioning post transplant.[29,36,47] Higher BMI and reduced-intensity conditioning were related to better physical functioning post transplant (weak evidence),[26,47] whereas myeloablative conditioning and the diagnosis of acute lymphatic leukemia or Hodgkin's disease predicted worse physical functioning (weak evidence).[16,26,47]

Auto-SCT. Only weak evidence was found for predictors of physical functioning. A study focusing on the comparison between patients diagnosed with multiple myeloma and non-Hodgkin lymphoma, showed that patients with non-Hodgkin lymphoma reported higher levels of fatigue than patients with multiple myeloma at day 30 post transplant. Patients diagnosed with multiple myeloma reported lower levels of sleep at the time of transplantation and at nadir.[15,17] Another study found that patients with a high score on both negative and positive religious coping had worse physical well-being.[45]

Mixed. Inconsistent results were found for GVHD as a predictor of general health, physical limits and the feeling to be recovered from the transplant at 6 months; having chronic GVHD and having acute GVHD predicted worse physical functioning,[17] whereas another study found no association.[34] Evidence for other predictors of general health/physical limits was weak (gender,[28] number of symptoms,[24] medical risks, history of radiotherapy, depression[34] and previous delirium episode[38]), inconsistent (type of transplant[22,47]) or inconclusive (marital status and health[17]).

Disease risk status,[39] pre-transplant energy level, depression,[41] previous delirium episode and delirium severity[38] were studied as possible predictors for energy level, fatigue and sleep quality, but the evidence was weak. The factors predicting delirium episode, delirium severity and sustaining a delirium episode, were only studied once and therefore showed weak evidence.[19,31,38]

Predictors of psychological functioning. Allo-SCT. Conditioning regimen predicted neuropsychological functioning: patients who underwent reduced-intensity conditioning performed better on neuropsychological tasks than patients who underwent myeloablative conditioning (strong evidence). Patients pretreated with myeloablative conditioning decreased substantially more in the first month post transplant, and patients who underwent reduced-intensity conditioning performed better on a reasoning task.[16,46] Depression was predicted by lower social support (moderate evidence).[29,35] Other alleged predictors of psychological functioning, including age, gender, BMI, diagnosis, disease risk, GVHD, optimism and self-efficacy (weak evidence)[21,29,37,46,47] as well as pre-transplant depression (inconclusive evidence)[35] were studied only once.

Auto-SCT. The evidence for diagnosis as a predictor for psychological functioning is inconsistent.[45,47] Other potential predictors that have been studied are treatment with thalidomide, having undergone a previous HSCT, elevated lactate dehydrogenase level, decline in BMI and religious coping.[44,45,47] The evidence for these predictors is weak.

Mixed. Women were more likely to suffer from depression post transplant (strong evidence).[18,39] Furthermore, strong evidence suggests that pre-transplant psychological distress predicted post transplant psychological distress (anxiety, depression and symptom distress).[18,23,33,42] The evidence for other predictors of psychological functioning or distress is weak (type of transplant,[47] diagnosis, anti-cancer treatment before HSCT,[34] previous delirium episode, delirium severity,[19,31] protective buffering of the partner and being buffered by the partner,[32] satisfaction with social support[34]) or inconclusive (education,[43] coping with pain, amount of resources in daily life and living alone[42]).

Evidence for predictors of the feeling that life returned back to normal, enjoying normal activities and the feeling to have put their illness behind them, remained inconclusive.[17] Finally, weak evidence was found for predictors of neuropsychological functioning (age, previous delirium episode and conditioning with TBI).[19,27,28]

Predictors of social functioning. Allo-SCT. Negative associations were found between biomedical predictors (BMI decline, chronic GVHD and pre-transplant conditioning) and social functioning (weak evidence).[16,47]

Auto-SCT. Older age predicted better social functioning post transplant (strong evidence).[44,47] Further evidence regarding the prediction of social functioning is weak. One study reported treatment with thalidomide to predict worse social well-being and the diagnosis of multiple myeloma to predict better social functioning. Another study reported that higher BMI predicts worse social functioning.[44,47] Patients who underwent HSCT in the fourth or fifth decade of life were less likely to return to work (weak evidence).[47]

Mixed. Single studies focused on predictors for enjoying socializing with friends or family or satisfaction with the marital relationship. Patients who underwent auto-SCT (compared with allo-SCT), had better physical functioning, and better mental health were found to enjoy socializing with friends or family more (inconclusive evidence).[17] One study focused on protective buffering, defined as withholding or denying cancer-related thoughts and concerns

from one's partner, hiding dispiriting information and acquiescing to avoid conflict. Patients who protectively buffered their partner or were being buffered by their partner and patients who had less motivation to protect their partner relative to themselves, had lower satisfaction with their marital relationship, whereas caregivers who were highly motivated to protect their partner, experienced decreases in their own relationship satisfaction over time (weak evidence).[32] With respect to returning to work, moderate evidence suggests that women return to work less often and later compared with men.[34,43] For other factors predicting return to work (TBI, physical functioning), the evidence is inconclusive.[43]

Predictors of sexual functioning. Allo-SCT. Sexual functioning was predicted by pre-transplant depression and by gender: 1-year post transplant, women experienced more overall sexual problems than men and more sexual physical functioning problems 3-years post transplant (weak evidence).[30]

Predictors of other outcome measures. Allo-SCT. Chronic GVHD negatively predicted spiritual well-being (weak evidence).[47] Patients treated with myeloablative conditioning had more financial problems than patients treated with reduced-intensity conditioning (weak evidence).[16]

Auto-SCT. Spiritual well-being was higher for patients who underwent only one HSCT compared with patients who underwent two or more transplants (weak evidence).[47] A summary of the main results is provided in Table 3.

Discussion

This study aimed to review the prognostic factors for health-related QOL after HSCT. In all, 35 studies that evaluated predictors of (aspects of) health-related QOL were included in this review. Strong evidence suggests that GVHD predicts worse overall health-related QOL,[29,47] and that chronic GVHD predicts diminished physical well-being.[29,36,47] Furthermore, in allo-SCT patients, there is strong evidence for the conditioning regimen being a predictor for neuropsychological functioning: patients receiving myeloablative conditioning (compared with reduced-intensity conditioning) showed more impairments on various neuropsychological tasks.[16,46] Being female (strong evidence, mixed patient group)[18,39] and receiving less social support (moderate evidence, allo-SCT patients)[35,29] predict depression, whereas pre-transplant distress (strong evidence, mixed patient group) predicts psychological distress post transplant.[18,23,33,42] Female patients returned to work less often and later compared with male patients in mixed patient samples.[34,43,47] Finally, in auto-SCT patients, strong evidence was found for older age predicting better social functioning.[44,47] The other evidence found is weak, inconclusive or inconsistent.

Our results suggest that certain subgroups of patients have more difficulties adjusting to their disease and treatment, and consequently experience a more impaired health-related QOL post transplant compared with other patient subgroups. Suffering from (chronic) GVHD leads to problems with overall QOL and physical well-being. This concurs with our expectations, as GVHD is a major cause of morbidity and mortality following HSCT.[48] Other subgroups of patients that are at risk for lower health-related QOL, and specifically for worse psychological and social functioning, are female patients, patients receiving low social support and patients experiencing pre-transplant psychological distress. This is consistent with other research on psychological and social functioning in cancer patients. Receiving low social support has been shown to increase the risk for depression and anxiety.[49,50] A history of depression or anxiety is a risk factor for distress, and previous distress and was found to be a predictor of health-related QOL.[51,52] Regarding gender differences in the prevalence of depression in cancer patients, previous studies have yielded conflicting results. Some studies report higher prevalence rates of depression in female patients, whereas other studies found no gender differences.[53]

The present study has certain strengths and limitations. First, a strong characteristic of this review is that we only included prospective studies. Consequently, information about causal relationships between predictors and outcome variables can be more reliably inferred compared with cross-sectional studies. Second, we were able to draw distinctive conclusions from this review, because of the large number of high-quality studies: the quality of 27 of the 35 included studies was considered to be high. Third, health-related QOL is a broad concept, which is reflected by the many predictors and outcome measures included in this review. Because of the multiplicity of the study variables, there are only a few studies focusing on the same predictors and outcome variables, which makes it hard to draw any definite conclusions. There is, for example, a study focusing on variables (gender, pre-transplant depression) influencing sexual functioning post transplant.[30] However, as there has been no attempt to replicate these results, the evidence for these associations remains weak. Fourth, a limitation of this review is that, due to the heterogeneity of the studies, we have not been able to pool data to quantify the strength of the associations between predictors and outcome variables. The studies evaluated were not uniform in their populations, in their measurement of predictors and outcomes and in the timing of measurements. To strengthen the evidence on specific predictors and outcomes, studies should focus on the same set of predictors and outcomes in homogeneous patient groups, measured with identical assessment methods on standardized moments in time. With respect to the patient groups, future research should separate auto-SCT patients from allo-SCT patients. As the treatment procedures are different and may have a differential impact on health-related QOL, it would be more informative to analyze these patient groups apart. A core set of questionnaires would contribute considerably to reducing heterogeneity. One option is a core set containing the European Organisation for Research and Treatment of Cancer (EORTC)- or Functional Assessment of Cancer Therapy (FACT)-questionnaires, and/or the MOS-SF-36 for measuring health-related QOL; the Hospital Anxiety and Depression Scale or Profile of Mood States for measuring emotional functioning; and the MOS-Social Support Scale (MOS-SSS) for

Table 3 Predictors of aspects of health-related quality of life (QOL)

	Pain/ symptoms	*Global QOL*	*Physical functioning*	*Psychological functioning*	*Social functioning*	*Sexual functioning*	*Other QOL aspects*
Allo-SCT							
Demographic/clinical factors				*W*		*W*	
Biomedical factors	*W*	*W*	*W*	*W*	*W*		*W*
Myeloablative conditioning (vs reduced intensity conditioning)				Myeloablative conditioning predicts poorer neuropsychological functioning (strong evidence)			
GVHD (chronic)		GVHD predicts worse overall QOL (strong evidence)	Chronic GVHD predicts diminished physical well-being (strong evidence)				
Physical functioning							
Psychological functioning		*W*		*W/ICC*		*W*	
Social functioning		*W*					
Social support				Receiving less social support predicts depression (moderate evidence)			
Sexual functioning							
Other QOL aspects							
Auto-SCT							
Demographic/clinical factors				*ICS*			
Age					Higher age predicts better social functioning (moderate evidence)		
Biomedical factors	*W*	*W*	*W*	*W*	*W*		*W*
Physical functioning							
Psychological functioning			*W*	*W*			
Social functioning							
Sexual functioning							
Other QOL aspects							
Mixed: allo-SCT and auto-SCT							
Demographic/clinical factors		*W*	*W/ICC*	*W/ICC*			
Being female				Being female predicts depression (strong evidence)	Being female predicts returning to work less often and later (moderate evidence)		
Biomedical factors	*W/ICC*		*ICS/W/ICC*	*W*	*ICC*		
Physical functioning			*W/ICC*	*W/ICC*	*ICC*		
Psychological functioning	*ICC*		*W*	*W/ICC*	*W/ICC*		
Psychological distress				Psychological distress pre-transplant predicts psychological distress post transplant (strong evidence)			
Social functioning				*W/ICC*			
Sexual functioning							
Other QOL aspects							

Abbreviations: ICC = inconclusive evidence; ICS = inconsistent results; QOL = quality of life; W = weak evidence.
Empty cell = no information available.
For further details, refer to text.
Bold values indicate main categories of predictors.

assessing social functioning. Furthermore, studies should standardize the timing of the measurements. The timing could be set as follows: a pre-transplant measurement, assessments during hospital stay, and 3 months, 6 months, 1, 3 and 5-years post transplant. This is essential for comparing the results of various studies.

Finally, although this review focuses on patients with malignancies, some of the studies included also reviewed non-malignant indications. However, as the percentages of patients with non-malignant indications are generally very small in these studies (0.5–5%)[16,17,27,32,41,46,47] except for one (16%),[28] we feel that this is not likely to have influenced our results substantially.

The results of this review have clinical implications for the treatment of patients undergoing HSCT. Our conclusions may help transplant teams in selecting patients who are at risk for experiencing a diminished health-related QOL following HSCT. Patients presenting with pre-transplant distress, patients receiving little social support and younger and female patients could be monitored and offered psychological care if impairments in QOL occur. The same applies to risk factors like GVHD and conditioning regimen: clinicians should be alert, inform their patients of possible consequences and offer psychological care or rehabilitation in case the patient indeed experiences impairments.

Furthermore, to estimate survival probabilities after allo-SCT, at present scoring systems like the hematopoietic cell transplantation comorbidity index (HCT-CI)[54] and the Glucksberg Seattle criteria[55] are used. As the importance of health-related QOL as an outcome measure is increasingly being recognized, the development of a scoring system estimating risk factors for (impaired) health-related QOL would be a logical next step. The results of this review could be used to develop such a scoring system.

In conclusion, strong–moderate evidence has been found for GVHD, conditioning regimen, being female, younger age, receiving less social support and pre-transplant psychological distress as being predictors of various negative aspects of health-related QOL following HSCT.

Conflict of interest

The authors declare no conflict of interest.

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