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REVIEW ARTICLE

Sexuality and quality of life of patients with hematologic malignancy and hematopoietic stem cell transplantation: a critical review

Ioanna Tsatsou[1], Kyriaki Mystakidou[2], Eleni Panagou[3], Theodoula Adamakidou[4], Ioannis Kalemikerakis[4], Maria Vastardi[5], Ourania Gkovina[6]

[1]Oncology-Hematology Dept, Hellenic Airforce General Hospital, Athens, Greece. [2]Pain Relief and Palliative Care Unit, Dept of Radiology, Areteion Hospital, School of Medicine, National & Kapodistrian University of Athens, Athens, Greece. [3]Oncology-Hematology Dept, Hellenic Army General Hospital, Athens, Greece. [4]Department of Nursing, University of West Attica, Athens, Greece. [5]Manager of Quality, Research & Education, Cancer Hospital "Metaxa", Piraeus, Greece. [6]Dept of Nursing, University of West Attica, Athens, Greece.

Summary

Purpose: *This systematic review aims to investigate the relationship between sexuality and quality of life (QoL) of patients with hematological malignancies that underwent hematopoietic stem cell transplantation (HSCT).*

Methods: *A bibliographic search was carried out through PubMed database with the following terms for the years 2008 to 2019: sexuality, sexual function, quality of life, hematopoietic stem cell transplantation.*

Results: *Fourteen studies were included in the review. They present heterogeneity regarding measurement tools, time of measurement and type of HSCT. The common theme that emerged from most studies is that sexual dysfunction is reported after years of HSCT and it negatively impacts QoL. Women and allogenic HSCT with its consequences (graft versus host disease) were risk factors for sexual dysfunction. Sexual activity of HSCT patients was decreased at first but resumed after the first year. The most common sexual problems reported were erectile dysfunction for men and lack of desire for women. In the majority of studies the amelioration of physical, psychological symptoms and sexual function lead to improvement in QoL over time.*

Conclusions: *Sexuality and QoL of patients are affected by HSCT in varying degrees, and seems to be a significant and positive correlation between sexuality and QoL. However, with weaknesses and shortcomings in the revised studies' methodology (sample sizes, type of HSCT, attrition rates etc.), results are difficult to generalize.*

Key words: *sexuality,quality of life, hematological malignancy and hematopoietic stem cell transplantation*

Introduction

Autologous and allogeneic hematopoietic stem cell transplantations (HSCT) are curative procedures for patients with hematological malignancies, including lymphoma, multiple myeloma, acute and chronic leukemia. Alongside with many physical problems (pancytopenia, mucositis, Graft versus Host Disease –GVHD etc), patients experience a multitude of psychological and social issues, thus impairing their quality of life (QoL) [1].

World Health Organization (WHO) defines QoL as an individual's perception of its position in life in the context of culture and value systems in which they live in relation to their goals, expectations, standards and concerns. It is a broad concept

Corresponding author: Ioanna Tsatsou, RN, MSc, PhD. Oncology-Hematology Department, Hellenic Air Force General Hospital. P.Kanellopoulou 3 street, 115 23, Athens, Greece.
Tel: +30 6983525725, Email: itsatsou@uniwa.gr
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that incorporates a persons' physical health, psychological state, level of independence, sociability, personal beliefs and their relationship to salient features of the environment [2]. Sexuality has also been defined by WHO as a central aspect of being human throughout life which encompasses sex, gender identities and roles, sexual orientation, eroticism, pleasure, intimacy and reproduction [3,4]. Sexuality is characterized as a high priority issue by one to three quarters of cancer survivors and is classified as a major unmet need. Sexual dysfunction after cancer is consistently associated with poor QoL [5]. But unfortunately there are few empiric data that inform oncology professionals how to assess sexuality needs and how to care for patients regarding their sexual health. Sexuality is a central part of QoL [6].

In this context, HSCT can affect sexuality for both male and female transplant patients. Sexual dysfunction is frequently described in QoL studies after HSCT and is one of the most common long-term issues in HSCT. Chemotherapy, total body irradiation, other treatments for symptoms or side effects (e.g. anti-depressants, corticosteroids) and hormone system disorders often cause sexual dysfunction. Isolation, fatigue, distress, depression, body image alteration and conversioned relationships also contribute to sexual dysfunction [7]. As HSCT becomes more common and survivorship increases, it is important to evaluate the impact of sexual dysfunction on quality of QoL [8].

Despite the availability of systematic reviews examining separately sexuality [7-10] and QoL [11-14] in HSCT, there is no recent review studying both sexuality and QoL. Thus, the purpose of this systematic review was to present the literature for sexuality and QoL in patients with HSCT patients with hematological malignancies.

Methods

The systematic review methodology was based on PRISMA [15] guidelines. A search was conducted throughout PubMed database (November 23, 2019). The terms used were *sexuality, sexual function, quality of life, hematopoietic stem cell transplantation* (sexuality OR

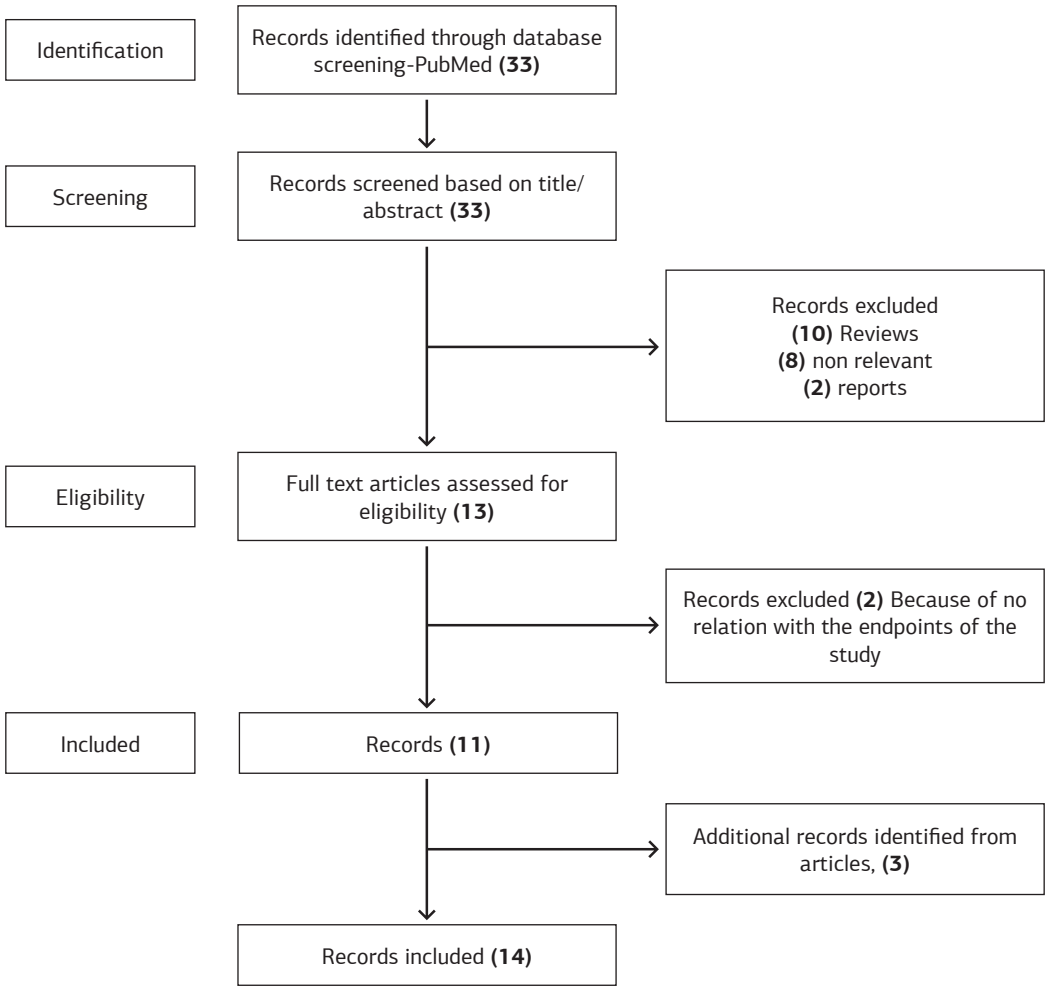

Figure 1. PRISMA flow diagram of literature reviewing process.

sexual function AND quality of life AND hematopoietic stem cell transplantation).

The inclusion criteria were as follows: studies published in English (case reports, clinical studies, clinical trials, pragmatic clinical trials, randomized controlled trials); studies between 2008 and 2019; and studies that assessed both sexuality and quality of life in adult patients with hematologic malignancies during or after HSCT (autologous and allogenic). Reviews, guidelines, letters, expert opinions and studies that evaluated solely sexuality or QoL in patients with hematologic malignancies and HSCT were excluded. All studies were evaluated according to the title and summary, while for the studies that met the criteria, a full text was searched and retrieved. A selection of studies is presented in Figure 1.

A total of 33 references were identified in PubMed as potentially relevant. Ten reviews, 2 reports and 8 articles of non-relevance to the subject were excluded. From the remaining 13 articles, 2 were excluded. One assessed only sexuality and the other one studied patients and partners (dyads). Eleven studies were eligible. After that, further investigation of the selected articles revealed 3 articles to be included in the review. Finally, 14 studies were included in this review.

Results

The research identified fourteen studies (Table 1) that met all the inclusion criteria. Five prospective studies [19,23,25,26,29], seven cross-sectional [16,17,20-22,27,28], one case report [18] and one retrospective study [24] were included. Two studies had mixed method design [17,19] and two were interventional [19,26]. The rest of the studies included solely assessments and quantitative analysis.

Regarding the type of transplant, two studies involved patients after autologous HSCT [16,28]. Seven studies involved patients after allogenic HSCT [18,19,21,22,24,26,29] and five studies had a mixed sampling process, including both patients after allogenic and autologous HSCT [17,20,23,25,27]. Two studies [18,23] included in their sample only women and one study [26] included adolescents and young adults (AYAs;18 to 25 years) after HSCT.

There was a widespread heterogeneity across studies in instruments used to measure sexuality and QoL and the time points of measurement. The most common used questionnaire to assess sexuality was the Female Sexual Function Index (FSFI) and for QoL, Functional Assessment of Cancer Therapy-Bone Marrow Transplant (FACT-BMT). Noteworthy, only 3 studies [20,24,26] evaluated patients shortly after treatment (1, 2 and 3 months). The rest of the researchers evaluated patients from 6 months to 30 years after HSCT. Studies focused mainly on the recovery period after HSCT.

The studies included patients and mostly survivors of hematologic malignancies after HSCT. But who is a cancer survivor? The National Cancer Institute defines the cancer survivor [30] as: "Someone who remains alive and continues to function during and after facing a serious or life-threatening illness. In cancer, a person is considered a survivor from the time of diagnosis to the end of life. "So, in this review we consider the terms patients and survivors identical.

Table 1 shows the characteristics of the studies. The results obtained from the studies were considered statistically significant at a p-value of 0.05 in the univariate analysis. The studies investigated the following regarding sexuality:

Sexual Activity (SA)

SA decreased before HSCT to 6 months afterwards for men and women, yet SA recovered sooner for men than women but remained below controls. For female controls and survivors across time, the most prevalent reason of sexual inactivity was lack of a partner followed by lack of interest or libido, without improvement over time. For males' controls and survivors, reasons for sexual inactivity varied (lack of partner and interest, fatigue etc.) [29]. Only the research of Wong et al [25] noted that women were more active than men, 3 years after their HSCT. Also, SA of allogeneic HSCT patients increased by 6.5% to 32.5% after the transplant and the monthly intervention for sexuality issues (assessment-education-intervention) [19]. At the case report included in the review [18], women's inactivity, severe genitalia chronic GvHD and vaginal obliteration led them to vaginal reconstruction that helped them resume SA and improve their sexual function (SF).

Sexual Function (SF)

Shortly after treatment, changes in SF were common and interest in having sex was negatively affected by the transplant [20,23,26,28]. At the first year following transplant, sexuality/fertility including precautions during intimacy is a major concern. Women reported absent to low desire and arousal, adequate lubrication less than half of the time, absent or rare orgasm, pain during vaginal penetration more than half the time and high to moderate dissatisfaction with overall sex life. Likewise, men reported erectile dysfunction and absent to low desire and arousal [20,23,26,28].

Long term survivors faced sexual dysfunction even many years after treatment [16,21,22,24,25,26,27,29] with SF being worse in women compared to men [21,22,24,25,27,29]. Men improved their function by 2 years, whereas women did not improve their functionality by 5 years. Both, male and female survivors were below con-

Table 1. Characteristics of included studies

Author team	*Study Design*	*Research Question*	*Sample*	*Qs-Assessments*	*Treatment*	*Results (Sexuality-QOL)*	*Limitations*
1. Georges et al 2019 [16]	Cross-sectional	Which are the late effects and what is the QOL of long-term survivors after autologous HSCT?	N=399 238 Lymphoma and 121 Multiple Myeloma Patients ≥5 years after HSCT (maximum 30 years)	-SF36 -Questions about medical conditions ever experienced and current medications	Autologous HSCT	The most commonly reported medical conditions (>10% incidence) included: sexual dysfunction, history of shingles, cataracts, osteoporosis or osteopenia, joint replacement, and skin cancer. Worse physical functioning was associated with older age, shorter time since HSCT, comorbidities, relapse and treatment for depression and/or pain. Better physical functioning was associated with younger age at time of questionnaire or AHCT (p=.029), no treatment for depression (p=.003), no comorbidities (p<.001), and no treatment for pain (p<.001), Better mental health was associated with older age (p<.001) and no medication for anxiety (p<.001), or depression (p<.001). 62% of lymphoma patients and 51% of myeloma patients reported sexuality problems (sexual desire, erection, ejaculation, vaginal dryness or pain). Sexual dysfunction was not found to significantly affect QOL. Lymphoma patients reported better health and QOL compared to multiple myeloma.	-important symptoms, such as cognitive functioning and fatigue, and current disease status were not captured -no pre-HSCT patient-reported outcomes were collected
2. Booker et al 2019 [17]	Cross-sectional Mixed methods study	What are the patients' experiences of sexuality following HSCT	8 male and 3 females up to 8 years post-HSCT	Semi-structured interviews FACT-BMT	-3 Autologous -8 Allogeneic HSCT	Qualitative themes that emerged included: changes in SF (such as desire and arousal), changes in relation to self(such as body image, sexual identity), changes in relation to others (such as current relationships, starting new relationships, fear of exposure to 'germs') and the experience of discussing sexual health concerns with healthcare providers. All participants stated that sexuality was important to them, even at times when they were quite unwell. The importance of sexuality to them had not changed after HSCT, but their expression of sexuality had changed. Both female and male participants reported changes in sexual desire and arousal, including physical changes in the body (such as vaginal atrophy and dryness and structural changes affecting the penis), reduced sexual response (such as decreased arousal, lubrication and erection) and changes in sexual interest. FACT-BMT overall scores ranged from 56 to 134 out of a possible 148. FACT-BMT revealed that participants reported low satisfaction with their sex life but remained interested in sex.	-diversity of sample -very few women -one-point measurement -probably researchers did not achieve saturation -self-selection bias -questions for the interview were adapted from palliative care setting.

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Author team	*Study Design*	*Research Question*	*Sample*	*Qs-Assessments*	*Treatment*	*Results (Sexuality-QOL)*	*Limitations*
3. Skorupska et al 2019 [18]	Case reports	What are the outcomes of two successful vaginal reconstructions on sexual function?	2 women following vaginal reconstruction surgery after vaginal obliteration due to BMT	-SF36 -FSFI -PISQ 12 -UDI-6 -IIQ-7 Before surgery 4 years after	Allogeneic HSCT	Patient 1 was sexually inactive for 9 years due to lack of a partner. When she found a new partner and tried to have intercourse, it was impossible due to complete vaginal obliteration and severe genital cGvHD. Patient 2 was sexually inactive for 3 years due to reduced libido and later due to marital problems. Then she discovered that she was unable to have sexual intercourse due to pain and vaginal narrowing and had severe genital cGvHD. The questionnaires revealed no troubles with urinary incontinence after surgery, improvement in quality of sexual life and mental state of general health. There were no changes observed in their physical aspects of life. After surgery, both patients were sexually active without any compromise due to vaginal obliteration. In addition, both patients used hormonal replacement therapy without any vasomotor symptoms due to premature ovarian failure. Vaginal sonography revealed no abnormalities	
4. El-Jawahri et al 2018 [19]	Prospective single-arm pilot design	Is SF improving through intervention?	47 HSCT survivors ≥3months post-HSCT with sexual dysfunction causing distress	-PROMIS-SF -FACT-BMT HADS PHQ-9 0(prior) -6 months post --intervention Intervention: monthly visits with a trained transplant clinician who 1) performed an assessment of the causes of sexual dysfunction2) educated and empowered the patient to address his/her sexual concerns3) implemented therapeutic interventions targeting the patient's needs.	Allogeneic HSCT	Participants reported improvements in satisfaction ($p<0.0001$), interest in sex ($p<0.0001$), and orgasm ($p<0.0001$), erectile function ($p<0.0001$), vaginal lubrication ($p=0.0001$), and vaginal discomfort ($p=0.0005$). At baseline, 32.6% of participants were not sexually active, compared to 6.5% post intervention ($p=0.0005$). Participants reported improvement in their QOL ($p<0.0001$), depression ($p=0.0002$), and anxiety ($p=0.0019$). There were no differences in the improvements in patient-reported QOL and mood by gender. All participants reported that the intervention was extremely helpful in addressing their sexual health concerns.	-small sample -one center - lack of a control group -no long-term data

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Author team	*Study Design*	*Research Question*	*Sample*	*Qs-Assessments*	*Treatment*	*Results (Sexuality-QOL)*	*Limitations*
5. Yasar & Akin, 2016 [20]	Cross sectional	-Does HSCT affect patients QOL? -What are the support needs and the symptoms experienced by patients after HSCT? -What are the sociodemographic, health and disease-related characteristics of the disease of patients who are undergoing HSCT?	100 patients (range:1–34 months post HSCT)	-FACT-BMT -Symptom checklist developed by the investigators	Autologous -Allogeneic HSCT	Changes in SF (N=59), loss of hair, loss of taste, loss of appetite and sleep disturbances were the most common symptoms. QOL was moderately affected, with the physical well-being in the most (SD:12.13 ± 6.88). Emotional and functional well-being was also moderately affected (12.70 ± 6.41 and 13.95 ± 4.61, resp). The emotional wellbeing subdimension scores were significantly higher in male patients than in females' patients (p = 0.001). FACT-BMT: I am interested in sex SD: 1.28±1.39. Being female, between 50-59 y, being single, having a chronic disease and having a history of hospitalization were associated with lower QOL.	-one center -small sample -one-point measurement
6. Gifford et al 2016 [21]	Cross-sectional	Which is the incidence and range of late complications and their association with the health and functional status of allogeneic HSCT survivors?	441 Survivors up to 10 years after HSCT	-Sydney Post-BMT -FACT– BMT, --DASS 2 -CGvhd Activity Assessment-Patient Self Report (Form B) -Lee cGVHD Symptom Scale -PTGI -FOR scale	Allogeneic HSCT	Sexual dysfunction was present at 66% females and 52% males. Similar percentages of males and females resumed SA post-HSCT (males 69.2%, females 68.5%) but both genders reported high incidences of sexual difficulties. Being female (p=0.01) increased the risk of post-HSCT sexual dysfunction, particularly for decreased pleasure (p<0.0001), libido(p=0.002) and dyspareunia (p<0.0001). 76.6% of males with sexual difficulties reported erectile dysfunction. After cGvHD, sexual dysfunction was the most adversely affected domain following HSCT reported by survivors. The correlation between subscale and summary FACT-BMT test scores was highest for functional well-being and lowest for social well-being. Mean QoL scores showed no significant differences when stratified by years from transplant (p=0.12). Lee cGVHD score showed a negative correlation with QoL measures (Pearson's correlation coefficient=−0.63).	- participation bias -One measurement - recall and misclassification biases -self reported Qs -The heterogeneity and restricted ethnic diversity of the population may limit the generalizability of these results to HSCT survivors in other countries and settings.

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Author team	Study Design	Research Question	Sample	Qs-Assessments	Treatment	Results (Sexuality-QOL)	Limitations
7. Dyer et al 2016 [22]	Cross-sectional study	What is SF and infertility post-HSCT?	441 adults allogeneic HSCT survivors Up to 10 years post HSCT	-Sydney Post-BMT -FACT– BMT, --DASS 2 -CGVHD Activity Assessment-Patient Self Report (Form B) -Lee cGVHD Symptom Scale -PTGI	Allogenic HSCT	Most HSCT survivors reported sexual difficulties. Men reported erectile dysfunction and decreased libido and women reported loss of libido, painful intercourse and less enjoyment of sex. Women also commonly reported vaginal dryness, vaginal narrowing and vaginal irritation. Women had much higher rates of genital cGVHD than men. Women, post -HSCT, also had significantly less enjoyment of sex (p< 0 0001), less sexual desire (p = 0 002) and more pain with intercourse (p< 0 0001) when compared to their male counterparts. Sexual problems arising from partner issues were similar between the two genders. Age and cGVHD were significantly associated with sexual dysfunction. Males who had not returned to sexual activity post-transplant had significantly lower scores on physical (p = 0,01), functional (p=0,009) and HSCT FACT subscales (p=0,003). Significantly lower scores on composite FACT scores (p=0,01) were also observed. Females who had returned to SA had significantly higher FACT BMT subscale scores, but did not have any significant differences across other FACT domains. Females who had resumed SA reported significantly higher rates of anxiety and/or depression (p=0,05).	-The heterogeneity and restricted ethnic diversity of the population may limit the generalizability of these results to HSCT survivors in other countries and settings. -Self reported Qs -Qs not specifically targeted at sexual function
8. Tierney et al 2015 [23]	prospective study	How is sexuality, menopausal symptoms, and quality of life affected in premenopausal women in the 1st y following HSCT?	63 premenopausal female recipients of HSCT	-FSFI -MEN- QOL -VAS for QOL pre-HCT 2–3, 6 ,12 months	-Autologous -Allogeneic -Autologous followed by allogeneic	1st year post-HSCT, women reported absent to low desire and arousal, adequate lubrication less than half of the time, absent or rare orgasm, pain during vaginal penetration more than half the time and dissatisfaction with overall sex life. Pain with vaginal penetration showed significant improvement in the first year (p=0.041). Women also reported moderate to severe vasomotor symptoms, including hot flashes, night sweats, and sweating. Across all four-time points assessments, women who received alkylating agents prior to HSCT had higher mean scores on the sexual domain, and this difference was statistically significant at pre-HSCT (p = 0.048). More than 1/3 of women reported that they were moderately to very dissatisfied with their overall sex lives. The percentage of women reporting low or absent desire and very to moderate sexual dissatisfaction decreased from pre-HCT to one-year post-HCT. During the 1st year,women showed significant improvement in QOL scores (p= 0.028). Moreover, women experienced a significant decline in psychosocial and physical symptoms, thus improving QOL.	- the sexual partner was not included -the study followed women only for a year -no controls -small sample -findings not generalizable

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Author team	*Study Design*	*Research Question*	*Sample*	*Qs-Assessments*	*Treatment*	*Results (Sexuality-QOL)*	*Limitations*
9. Gifford et al 2014 [24]	Retrospective	Which are the health issues that long-term survivors of allogeneic HSCT face, in an Australian center?	99 survivors up to 7 years post HSCT	FACT-BMT	Allogeneic HSCT	Ten females reported one or more symptoms in their genitalia. cGVHD symptoms were vaginal stenosis (n = 2), cervical stenosis (n = 1) vaginal scars and lichen planus-like features (n = 5). Other symptoms involving the genitalia were vaginal dryness, pain, dyspareunia and vulvovaginitis. One male patient reported decreased libido and two reported erectile dysfunctions. Patients' self-assessment of QOL as measured by the FACT-BMT found that the average score is 85.8% which is comparable with the FACT-G score of 85.9% for a general Australian population.	-single center -small sample - incomplete assessments of patients
10. Wong et al 2013 [25]	Prospective study	What is the sexual well-being before HSCT to 3 years and which are the predictors of post-HSCT sexual dysfunction?	131 Allogenic HSCT 146 Autologous HSCT	-DISF-SR -DSFI -GSSI -COH-QOL-HCT Before, 6 months, 1, 2, 3 years	-DISF-SR -DSFI -GSSI -COH-QOL-HCT Before, 6 months, 1, 2, 3 years -Allogenic HSCT -Autologous HSCT	Before HSCT, 61% of men and 37% of women were sexually active; the 3-year prevalence declined to 54% for men but increased to 52% for women. After HSCT, sexual satisfaction declined in both genders (p<.001), as did Orgasm and Drive/Relationship (p<.001) in men, but Sexual Cognition/Fantasy (p=0.01) and Sexual Behavior/Experience(p=0.01) improved in women. All sexual function domains were worse in women compared to men (p=0.001). Older age negatively impacted SF post-HCST in both genders (p<0.01). cGVHD was associated with lower Sexual Cognition/Fantasy (p=0.003) and Orgasm (p=0.006) in men and Sexual Arousal (p=0.05) and sexual satisfaction (p=0.005) in women. All male sexual functions declined with exposure to TBI (p<0.05). Sexual satisfaction was higher for sexually active participants compared to sexually inactive (p< 0.001). Male allogeneic HCT recipients reported significantly fewer sexual thoughts or fantasies and were less satisfied with their orgasmic quality than autologous HSCT recipients. Female allogeneic HSCT recipients also reported lower sexual satisfaction. For women and men sexual function raised as physical QOL improved, both pre-HSCT and post-HSCT. SF of men improved with psychological QOL post-HCT (p=0.03); no association was identified prior to HCT (p=0.20). Women's SF improved with psychological QOL post-HCT (p<0.001) but no association was identified prior to HCT (p=0.08).	-Low participation rate (51%) -Pre-HSCT treatment data were unavailable -Lack of controls

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Author team	Study Design	Research Question	Sample	Qs-Assessments	Treatment	Results (Sexuality-QOL)	Limitations
11. Cooke et al 2011 [26]	Mixed-methods longitudinal clinical trial	-What are the AYAs patients' experiences during the first year following allogenic HSCT -What are the effects of a standardized teaching intervention on QOL outcomes for allogeneic HSCT patients	24 AYAs: intervention group N = 10 and control N = 14 group	The quantitative data consisted of demographic, treatment, mortality, readmission, and complications data. The qualitative data was obtained from patients in the intervention group using information from post teaching debriefing tools, field notes, and extra session content recorded by the intervention nurses. At discharge, 3-, 6-, and 12-months post hospitalization	Allogeneic HSCT	Content analysis was used to classify comments into the four domains of the QOL model (physical, psychological, social, existential. Themes that emerged were: sexuality/fertility including precautions during intimacy, fatigue, depression/ poor coping/habits, adherence issues, use of technology, dependency issues, changes in roles/ relationships, issues with school/education, financial issues, family problems/issues, miscellaneous, religion/spirituality, fear of future, uncertainty, life, death, more life appreciation. Many of the patients brought up sexual concerns with the intervention nurses but felt uncomfortable with the physician.	-one center -small sample
12. Mosher et al 2011 [27]	Cross-sectional	What are the QOL, transplant-related concerns, and depressive symptoms and their demographic and medical correlates at 1 to 3 years following HSCT?	406 HSCT survivors	-FACT-BMT -FACT-G -BDI	-Allogenic HSCT -Autologous HSCT	The most common problems included fatigue (56%), worry for possibility of condition worsening (36%), lack of sexual interest and satisfaction (31% and 28%, resp), and changes in appearance (30%). 27% reported pain, concerns about keeping their job, including work at home and worry of transplant failure (25%). 1/4 of survivors were bothered by the side effects of treatment. 1/3 of survivors age 40 years and younger reported infertility concern. Unemployed survivors and those with lower incomes and worse functional status were more likely to experience poorer QoL in multiple domains. No gender differences were found for QOL and depressive symptoms but women reported more transplant-related problems than men. Functional impairment ($p < 0.001$) emerged as the only significant unique predictor of QOL. Allogeneic HSCT ($p < 0.05$) and greater functional impairment ($p < 0.001$) were unique predictors of higher transplant-specific problems and depressive symptoms.	-cross-sectional design -sample selection

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Author team	*Study Design*	*Research Question*	*Sample*	*Qs-Assessments*	*Treatment*	*Results (Sexuality-QOL)*	*Limitations*
13. Kav et al 2009 [28]	Cross-sectional	What is the QOL of patients after autologous HSCT?	67 patients (at least day 100+)	-EORTC QLQ-C30 -Long-term BMT recovery questionnaire -a specific questionnaire adapted from Bush BMT Symptom Inventory for measuring symptom severity and symptom distress related to AHSCT	Autologous HSCT	Sexual dysfunctions were reported from 32.2% of the sample. 76% of patients reported that their current QoL was the same or better than before HSCT and rated their current HRQoL as good to excellent. Financial difficulties, fatigue, sleeping problems and pain were the factors most rated, affecting QoL. Sexual dysfunction was not found to significantly affect QOL.	-small sample -self reported Qs
14. Syrjala et al 2008 [29]	Prospective Case-control study	How SF is affected in survivors after Allogenic HSCT during 5 years compared with case-matched controls at 5 years?	161 Survivors 77 controls	-SFQ -SF36 Survivors: Before 6 months, 1,2,3,5 years Controls: 5 years	Allogenic HSCT	Men and women differed in rates of being sexually active across time ($p<0.001$) and in overall SF ($p<0.001$). Both genders declined in rates of SA and SF before HSCT to 6 months afterwards ($p<0.05$). SA recovered for men by 1 year (74%) and for women by 2 years (55%). Men improved their 6-month nadir in SF by 2 years ($p=0.02$), whereas women did not improve by 5 years ($p=0.17$). Both male and female survivors were below controlling in rates of SA and SF at 5 years. Most women reported sexual problems (80% of survivor's vs 61% of controls, $p=0.11$); in contrast for men 46% of survivors versus 21% of controls ($p=0.05$) reported problems. For female controls and survivors across time, the most prevalent reason of sexual inactivity was lack of a partner. For males, reasons for sexual inactivity varied. The most common problem at 5years for sexually active male survivors was delayed ejaculation and for females lack of sexual desire. On the SF36 the controls had higher physical component t scores than 5-year survivors did ($p=0.01$).	-one transplantation center -SF before diagnosis was not known -Sample size was insufficient to examine problem-specific differences within groups beyond sex. -Results are not generalizable to autologous HC transplant recipients or other cancer survivors. -matched controls were not randomly designated

(Abbreviations: HSCT: hematopoietic stem cell transplantation ,QOL: quality of life, HRQOL: Health related quality of life ,SA: sexual activity, SF: Sexual function, FACT-G: Functional Assessment of Cancer Therapy-General, FACT-BMT: Functional Assessment of Cancer Therapy-Bone Marrow Transplant, AYA: adolescent and young adults , DASS: Depression Anxiety Stress Scale, BDI: Beck Depression Inventory cGvHD: chronic graft-versus-host disease ,PTGI : Post-Traumatic Growth Inventory , PROMIS-SF: Patient Reported Outcomes Measures Instruments: Sexual Function and Satisfaction, HADS: Hospital Anxiety and Depression Scale, PHQ-9: Patient Health Questionnaire, FOR: Fear of Recurrence, SF36: Short Form (36) Health Survey , FSFI : Female Sexual Function Index , PISQ 12: Pelvic Organ Prolapse/Urinary Incontinence Sexual Function Questionnaire , UDI-6: Urogenital Distress Inventory ,IIQ: Incontinence Impact Questionnaire, SFQ: Sexual Function Questionnaire, MEN- QOL: Menopause-Specific QOL questionnaire, DISF-SR: Derogatis Interview for Sexual Function-Self Report, GSSI: Global Sexual Satisfaction Index, COH-QOL-HCT: The City of Hope -Quality of Life - hematopoietic cell transplantation).

trolling in rates of SF at 5 years [29]. The most common long-term problem for sexually active male survivors was erectile dysfunction, delayed ejaculation and for females lack of sexual desire. Women also reported changes in sexual interest, loss of libido, painful intercourse, dyspareunia and less enjoyment of sex, vaginal dryness, vaginal narrowing and vaginal irritation [17,19,21,22,27,29]. Predisposing factors that negatively affected SF post-HSCT were older age, chronic GvHD and total body irradiation [21,22,25]. Additionally, survivors after receiving targeted monthly intervention for sexuality issues (assessment-education-intervention) reported improvements in satisfaction, interest in sex and orgasm, erectile function, vaginal lubrication and vaginal discomfort [19]. Furthermore, qualitative data stated that sexuality was important to survivors, even at difficult times, when they were not feeling well. The importance of sexuality for them had not changed after HSCT, while their expression of sexuality had changed [17].

Only one study [25] analyzed the differences of sexuality between autologous and allogenic HSCT recipients. Males who underwent allogenic HSCT had significantly fewer sexual thoughts or fantasies and were less satisfied with their orgasms than those who underwent autologous HSCT. Female patients after allogenic HSCT had also lower sexual satisfaction than females with autologous HSCT.

Relationship with QoL

Sexuality is acknowledged as important parameter for survivors' QoL, even at the first year post-HSCT [20,23]. In the majority of studies the amelioration of physical, psychological symptoms and SF lead to improvement in QoL over time [16,17,21-25]. Nevertheless, controls had higher physical QoL (measured with SF36) than did 5-year survivors [29]. Allogenic HSCT [20,21,25,27,29], sexual inactivity [18,22,29] and Chronic GVHD [18,21,24,25] had a negative correlation with QoL measures. On the other hand, autologous HSCT patients reported impaired SF but not significantly affecting QoL [16,28]. Moreover, after surgery of vaginal reconstruction, patients reported improvement in their quality of sexual life and mental state of general health and QoL [18]. At the retrospective study of Gifford et al, 2014 [24], allogeneic HSCT patients assessed their QoL at a percentage of 85.8% which is comparable with the score of 85.9% for a general Australian population. Finally, the "sexuality"-targeted intervention of El-Jawahri et al [19] helped patients report improvement in their QoL, depression and anxiety.

Discussion

This systematic review analyzed fourteen studies evaluating the relationship between sexuality and QoL in patients with hematologic malignancies and HSCT. The findings demonstrate the significant adverse impact of HSCT on sexuality and QoL, even many years after transplantation.

From the existing literature, the physical as well as the psychological effects after HSCT are known. Long-term survivors report fatigue, infections, GVHD, endocrine alterations, infertility, sexual dysfunction, conversioned relationships, anxiety, and depression. All these have a negative impact on QoL but most patients describe good to excellent QoL [14]. Sexuality problems are reported from survivors as one of the most common long-term issues following both allogeneic and autologous HSCT [31]. The long-term sexuality problems include decreased libido, vaginal problems (dyspareunia, dryness), erectile and ejaculatory dysfunctions, premature menopause, and hormone dysfunction [9]. HSCT has a negative impact at Sexuality and QoL even many years after treatment. Alterations in sexual health lead to poor QoL. This is commented in the literature from previous years [31-34].

Some shortcomings of the reviewed studies should be discussed.

Initially, the analysis of the reviewed studies reveals a variety of measurement tools for the two variables. The tools used to assess QoL, FACT-BMT [35] and City of Hope-QOL-HCT [36] were designed to measure specifically the QoL of HSCT patients. Some other common tools such as SF 36 [37] and EORTC QLQ-C30 [38] have been designed for general and patient populations, or for multidimensional measurement of QoL in cancer patients. In general terms, the measurement tools for QoL must be suitable for the intended purpose. The existing general measures target broad aspects of QoL, thus, they lack sensitivity to specific changes of cancer for patients. Nevertheless, these instruments also allow group comparison assessment of the overall impact of disease and treatment on QoL. On the other hand, the disease-specific tools include a more detailed symptom assessment and important concerns for the specific cancer patient group being studied. However, these instruments do not easily allow comparisons between groups. It is suggested that a more complete and accurate approach would be the combination of both types of measurement tools (for general QoL and cancer-specific QoL) [39].

Although the tools for the assessment of sexuality are different (The Female Sexual Func-

tion Index (FSFI), Sexual Function Questionnaire (SFQ), Derogatis Interview for Sexual Function-Self Report (DISF-SR), The Global Sexual Satisfaction Index (GSSI) of the Derogatis Sexual Functioning Inventory, Patient Reported Outcomes Measures Instruments (PROMIS), Sexual Function and Satisfaction, they cover similar aspects of sexuality (activity, arousal, orgasm, pain, satisfaction, interest, desire). Moreover, we have the FACT-BMT, which includes only two questions for sexuality regarding satisfaction and interest ("I am satisfied with my sex life", "I am interested in sex"). Therefore, the studies that used only the FACT-BMT [17,20-22,24] to measure both sexuality and QoL seem to be deprived of crucial aspects of sexuality in their analysis.

The studies revealed that sexual inactivity had a negative correlation with QoL and SA decreased after HSCT but improved over time for both genders. SA and enjoyment are considered to be important components of QoL for adults of all ages in general and patient populations [40]. Wong et al [25] found that women were more active while men were less active after HSCT, 3 years later. This increase may be explained by the improvement in female participants' psychological QoL post-HSCT. In this study, the reduction of SA was present at men autologous HSCT recipients or men who had relapsed. Lastly, this study is the only one to make comparisons between allogenic and autologous HSCT recipients.

The female gender and allogenic HSCT with its consequences (GvHD) were risk factors for sexual dysfunction. This is in the same line with earlier studies and reviews. Married female and allogeneic HSCT recipients were less satisfied with their sexual life, had less interest in sexual relationships and were less sexually active compared with married males [41]. From 13% to 33% of women with leukemia experienced vaginal dryness, decreased sexual interest, or less sexual satisfaction [42]. In 1997 Schover et al stated that the more types of cancer treatments a woman has, the more likely she is to have sexual dysfunction [43]. Thus, a woman with hematologic malignancy that underwent chemotherapy, radiotherapy and transplantation was more susceptible in long-term sexual dysfunction. After chronic GvHD, sexual dysfunction was the most adversely affected domain following HSCT reported by survivors, thus significantly affecting their QoL. According to the systematic review of Braamse et al in 2012, female gender, GVHD and younger age are predictors of various aspects of health-related QoL following HSCT. The treatment of chronic GVHD includes high dose of corticosteroids and prophylactic administration of medications to prevent opportunistic infection. These are a further cause of sexual dysfunction and have a profound adverse effect on recovery. GVHD is a unique entity that severely affects QoL after HSCT. Nonetheless, on average, physical and emotional function after resolution of GVHD are similar to controls [44].

Noticeably, homosexuals are not represented. This is not a surprise since this is a medically underserved and understudied population [45]. Sexual orientation and gender identity data are often not collected, but nowadays these should be made clear when assessing patients' needs, including sexual and relationship needs.

In addition, there were only two interventional studies. The intervention focused on evaluation and education around sexual matters. Both interventions aid to the improvement of QoL of the participants. But unfortunately, the current lack of randomized trials of interventions on sexual dysfunction is a major problem for psychosocial oncology. It is time to shift from the causes, prevalence of sexual dysfunction to creating, evaluating and integrating practical cost-effective programs for sexual rehabilitation [46].

Although we know that, after HSCT, adults face a multitude of psychological and social issues, there is a gap in the literature about the AYAs HSCT population [26]. The AYAs cancer population is a particularly vulnerable group due to a variety of social, psychological and developmental reasons. They endure body image changes and sexuality problems that have an adverse impact on their QoL. Only Cooke et al [26] focused on them. Sexuality issues alongside with fatigue, were the most common physical symptoms acknowledged by AYAs. These, coupled with alterations in relationships, have affected their sexuality.

Limitations of this review are as follows: the strict criteria used for the selection of studies, the heterogeneity of the studies regarding the study design, the research question, the sample and the measurement tools and the relatively small sample of most studies, with the possibility of nonsignificant results due to a lack of statistical power (type II error). The included studies in this review may be biased because unpublished studies have not been identified (publication bias). A number of methodological problems limit the applicability of the available research and need to be addressed.

On the other hand, we used the PRISMA guidelines to conduct the review. In addition, this article is the first systematic review of the literature of the last decade on sexuality and QoL in patients with hematological malignancies and HSCT.

Conclusions

The main purpose of this systematic review was to investigate the correlation of sexuality and QoL in patients with hematologic malignancies and HSCT in published studies of the last decade. Overall, compared to the general population, sexuality and QoL of patients are affected by HSCT in varying degree and there appears to be a significant and positive correlation between sexuality and QoL. However, with weaknesses and shortcomings in the revised studies' methodology (sample sizes and attrition rates, type of HSCT, etc.), results are difficult to generalize.

Recommendations for future research

Evidence suggests that sexual dysfunction is one of the most prevalent and persistent long-term problems after HSCT affecting their QoL, but there are still gaps in the research that need to be filled in. The limited literature on this subject identifies the urgent need to address sexuality issues of patients after HSCT. Few studies have examined the nature of this dysfunction or followed survivors over time to determine whether sexual function improves, stabilizes or declines at prolonged survivorship. The following research should also include partners and homosexual couples and the development and testing of interventions to address sexuality.

Implications for clinical practice

Despite its limitations, this systematic review brings insight into the literature on sexuality and QoL of patients after HSCT. There seems to be a significant correlation between sexuality and QoL. This finding may act as a trigger for research activity, taking into account the directions just mentioned. In addition, it can increase awareness in health care professionals in the fields of sexuality and QoL problems of these patients, which are often underestimated and undertreated. Patients require specific sexual care to overcome the physical and emotional sexual problems resulting from HSCT. Sexuality and QoL should be systematically monitored by multidisciplinary teams and interventions should be implemented through integrated care to improve them.

Conflict of interests

The authors declare no conflict of interests.

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