REVIEW ARTICLE

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Haematological malignancy: Are we measuring what is important to patients? A systematic review of quality-of-life instruments

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Abstract

The wide range of health-related quality-of-life (HRQoL) instruments used in haematology makes it challenging for haematologists and other care team members in practice to select, use and understand the scoring system and finally interpret the results. The main objectives of this study were to: (a) provide a comprehensive list of quality-of-life issues important to patients suffering from haematological malignancies, identified through the literature; (b) provide a list of health-related quality-of-life (HRQoL) instruments used in haematological malignancies in both daily clinical practice and research; and (c) evaluate the relevance and comprehensibility of the identified instruments in haematological malignancies. Systematic literature review of two databases, followed by addition of articles by manual searching, was carried out. The articles focusing on the primary studies, which have used semi-structured/structured interviews or surveys to identify issues important to HM patients, and other studies describing the results of testing measurement properties, such as reliability, validity and responsiveness of the instruments currently used to evaluate the HRQoL in different HMs, were included. Fifty-seven studies reported development and validation of 30 HRQoL instruments, which have been used in haematology. Twenty-four studies were identified using qualitative methods to report HRQoL issues and symptoms from a patient's perspective. No identified instrument captured all the issues identified from the qualitative studies. None of the instruments reviewed appeared to have been developed for use in clinical practice and specifically for patients with HM, except MyPOS. Furthermore, measurement properties were established, largely, in clinical trial scenarios. There is a need for development of a new HRQoL instrument entirely based on involvement of patients with haematological malignancies.

KEYWORDS
clinical practice, clinical research, haematological malignancy, HRQoL, PRO, QoL

1 | INTRODUCTION

"Haematological malignancies (HM) are type of cancers that originate in blood forming tissue such as bone marrow or in the cells of the immune system".[1] They are mainly of three types: leukaemia; lymphoma; and myeloma. Leukaemia types consist of acute lymphoid leukaemia (ALL), acute myeloid leukaemia (AML), chronic lymphoid leukaemia (CLL) and chronic myeloid leukaemia, whereas lymphomas are either Hodgkin or non-Hodgkin (with indolent or aggressive non-Hodgkin lymphomas). The UK has an incidence of 66.1 (annual rate per 100 000)

as per HMRN 2004-14,[2] with expected cases per year of 38730 for all haematological neoplasms and the reported median age at diagnosis is 70.8 years.[2] There have been advances in the treatment of haematological cancers, and it has led to improvement in survival, with an overall 5-year relative survival of 69.2%.[2] The improvement in survival with HM has put emphasis on the long-term effects of the disease and its treatments. There is evidence that health-related quality of life (HRQoL) of HM patients is greatly affected in both short term and long term.[3-8] Difficulty with physical and psychosocial activity, living with uncertainty, worrying about future and relapse and impact on work life are evident in survivors of HM and bone marrow transplant.[3,9-12] The high-dose chemotherapy has a detrimental effect on many patients' bone marrow which is usually followed by bone marrow transplant (BMT),[13,14] and this might have further complications such as graft-versus-host disease (GVHD).[15-17] Most of these studies which focus on identifying the quality-of-life (QoL) issues important to HM patients and evaluating their QoL have used the standard HRQoL instruments from the shelf for such purpose. There are a wide range of HRQoL instruments which are currently used in haematology to understand such impact, some are general to oncology, and others are specific to a type of haematological disease. Furthermore, some of the instruments which are developed and used for patients with solid tumours (ST) are also used in haematology. However, the most important questions are as follows: Are the quality-of-life issues, the impact of the disease and treatment and patient needs the same for patients with ST and HM? There is evidence suggesting that this is not the case. In general, the psyche of patients with HMs is different to that of patients with ST, and consequently, the conceptual model for the two would be different based on the fundamental philosophical notion of "normative standard." Thus, conceptually, patients make assessment/perception of their HRQoL with reference to their "normative standard" to which no one except patients themselves have access. For example, compared to solid tumours, patients with HMs: experience significant challenges with emotional/psychological disturbances[18-21]; experience prolong periods of neutropenia[22]; have more frequent visit to intensive care unit or inpatients[19]; are more likely to die in the hospital, and use intensive care during the last days of their life[23,24]; receive less information on sexual side effects of the treatment as well as treatment information[25]; and are much less likely to be referred to the specialist palliative care later in the course of their illness.[26-28] Moreover, most of these instruments have been developed and validated for use in clinical trials, but the need of patient-reported outcome (PRO) measures in clinical practice has been reported.[29,30] The PROs intended for such purpose can be used to assist in clinical care and gather valuable information related to patient experiences. The wide range of HRQoL instruments makes it challenging for the clinical care team to select, use and understand the scoring system and finally interpret the results.

Several systematic reviews have been conducted in the past which only describes the HRQoL issues important to patients with different HMs,[31-33] but none except Osborne et al (2012) have assessed the content of the HRQoL instruments against these HRQoL issues. Furthermore, no systematic review has provided a comprehensive conceptual framework of the HRQoL themes and sub-themes for patients with HMs. According to FDA, the adequacy of any HRQoL instrument depends on its characteristics including conceptual framework.[34]

The aim this systematic review was to identify the important HRQoL components to patients with HM required for developing a conceptual framework based on published literature to support the need for development of a new instrument to assess the HRQoL of such patients in clinical practice as well as research. The main objectives of this systematic review were to: (a) provide a comprehensive list of quality-of-life issues important to patients suffering from haematological malignancies, identified through the literature; (b) provide a list of health-related quality-of-life (HRQoL) instruments used in haematological malignancies in both daily clinical practice and research; and (c) evaluate the relevance and comprehensibility of the identified instruments in haematological malignancies.

2 | METHODS

This systematic review focuses on the primary studies which have used semi-structured/structured interviews or surveys to identify issues important to HM patients and other studies describing the results of psychometric testing of the instruments currently used to assess the HRQoL in different HMs.

2.1 | Search strategy

The literature search was carried out for both published and unpublished studies. A 3-step search strategy was used. For the first step, search was carried out using MEDLINE, followed by additional search using SCOPUS with the same search string. In the third step, the reference list of all identified and included papers were scanned for any additional studies, followed by the manual search of the articles in the last step. The literature search was confined to only two databases due to limited access to other databases. All the studies in English languages, involving adult (18+ age) patients and published between 1 January 1990 and 31 December 2016 were considered for the inclusion in the review. The search terms were kept as inclusive as possible to identify all the relevant studies. Since there are wide range of different haematological malignancies with wide range of published and ongoing research in haemato-oncology, it might result in a number of irrelevant studies to the current research question. Hence, to narrow down the search period to a more relevant timeline and to process the most relevant identified studies, Osborne et al[35] paper was used as a guide. The publication period of 26 years considered for this systematic review is defined based on the reference list from Osborne et al.[35]

2.2 | Search terms

The search terms were finalised after discussion between the two reviewers (PG and YK) and were kept as inclusive as possible for the
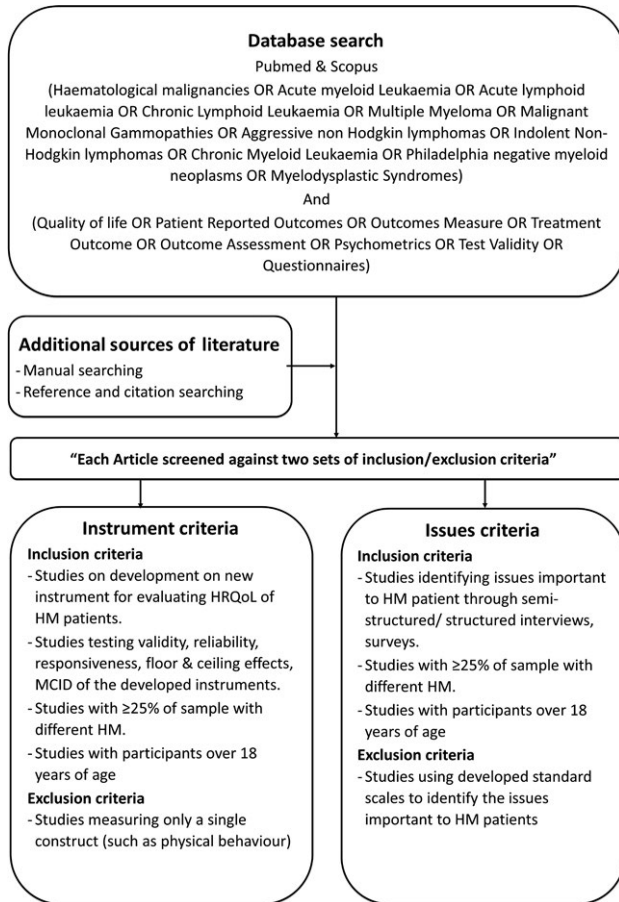
Database search

Pubmed & Scopus

(Haematological malignancies OR Acute myeloid Leukaemia OR Acute lymphoid leukaemia OR Chronic Lymphoid Leukaemia OR Multiple Myeloma OR Malignant Monoclonal Gammopathies OR Aggressive non Hodgkin lymphomas OR Indolent Non-Hodgkin lymphomas OR Chronic Myeloid Leukaemia OR Philadelphia negative myeloid neoplasms OR Myelodysplastic Syndromes)

And

(Quality of life OR Patient Reported Outcomes OR Outcomes Measure OR Treatment Outcome OR Outcome Assessment OR Psychometrics OR Test Validity OR Questionnaires)

Additional sources of literature
- Manual searching
- Reference and citation searching

"Each Article screened against two sets of inclusion/exclusion criteria"

Instrument criteria

Inclusion criteria
- Studies on development on new instrument for evaluating HRQoL of HM patients.
- Studies testing validity, reliability, responsiveness, floor & ceiling effects, MCID of the developed instruments.
- Studies with ≥25% of sample with different HM.
- Studies with participants over 18 years of age

Exclusion criteria
- Studies measuring only a single construct (such as physical behaviour)

Issues criteria

Inclusion criteria
- Studies identifying issues important to HM patient through semi-structured/ structured interviews, surveys.
- Studies with ≥25% of sample with different HM.
- Studies with participants over 18 years of age

Exclusion criteria
- Studies using developed standard scales to identify the issues important to HM patients

FIGURE 1 Outline of methods and inclusion and exclusion criteria

identification of the studies (Figure 1). The term "clinical practice" refers to any consultation activity and provision of care that take place routinely in an outpatient setting.

2.3 | Study identification & screening

In the systematic review, all the experimental and epidemiological studies focusing on HM patients' HRQoL were included irrespective of the study design. A novel approach used by Osborne et al[35] in a review published for myeloma patients was used to screen every identified study for two different sets of inclusion and exclusion criteria. The two reviewers agreed on the two sets of the inclusion and the exclusion criteria (Figure 1). The "issues criteria" were designed to identify the studies which focus only on the areas which are reported important by the patients themselves rather than using any standardised instruments. Studies using only inductive methods (qualitative) were included. The "instruments criteria" were designed to focus on the studies which describe the development and measurement properties of the instruments with respect to different domains rather than focus on any single construct such as physical ability. Studies with a sample consisting >25% of patients with HM were included. This means studies with a mixed sample with different type of cancers (breast cancer, lung cancer, pancreatic cancer, etc.) were included only if more than 25% of the total sample were diagnosed with any haematological malignancy. The systematic stepwise approach of inclusion and exclusion of the studies was adopted as per PRISMA guidelines.[36]

2.4 | Data collection and synthesis

The standardised data extraction tool from Cochrane collaboration was adopted for extracting the data. All the information was extracted by two reviewers (PG and YK) with consensus. Any unresolved discrepancies were then discussed with the third reviewer, the adjudicator (SS), to reach consensus. A summary table of all the articles identified as per issues criteria was developed to summarise the HRQoL issues reported by the patients in such studies. The quality assessment of all the articles included under "issue criteria" was carried out using a critical appraisal tool developed by Hawker et al[37] for qualitative studies. Hawker's checklist was used to rate the nine components (abstract and title; introduction and aims; method and data; sampling; data analysis; ethics and bias; results; transferability or generalisability; and implications and usefulness: How important are these findings to policy and practice?) for each article as "good" (score 3), "fair" (2), "poor" (1), or "very poor" (0), with maximum possible score of 27 for each article where higher score mean reflects better quality. The Hawker's tool was chosen because it provides clear description of ratings, that is, "good," "fair," "poor" and "very poor," and has been designed to assess quality of studies covering a variety of research paradigms. All the issues identified were then divided into two broad categories after reaching consensus between the two reviewers: "HRQoL issues" and "Signs and Symptoms" (including disease-related symptoms and treatment side effects). The classification of the identified HRQoL issues in the literature into respective themes and sub-themes was entirely based on the underlying theoretical construct. The themes and sub-themes generated were discussed among all three reviewers to reach consensus.

A second summary table of all the articles included in the instruments criteria was developed to summarise the QoL instruments and their measurement and psychometric properties for use in patients with HM.

3 | RESULTS

The two databases search resulted in 39 656 articles. All the identified studies were screened by two reviewers (PG and YK) against two set of criteria. After a systematic inclusion and exclusion of articles, 24 articles were included as per the issues criteria and 57 articles were included as per the instruments criteria. The PRISMA flow chart, presented in Figure 2, shows the different steps of identification and screening of the selected articles and reasons of exclusion. Three articles reporting development and validation of on myelodysplastic syndrome (MDS), leukaemia and myeloma-specific instrument (QoL-E, Fact-Leu and EORTC-MY24) were included in both sets.[38-40]
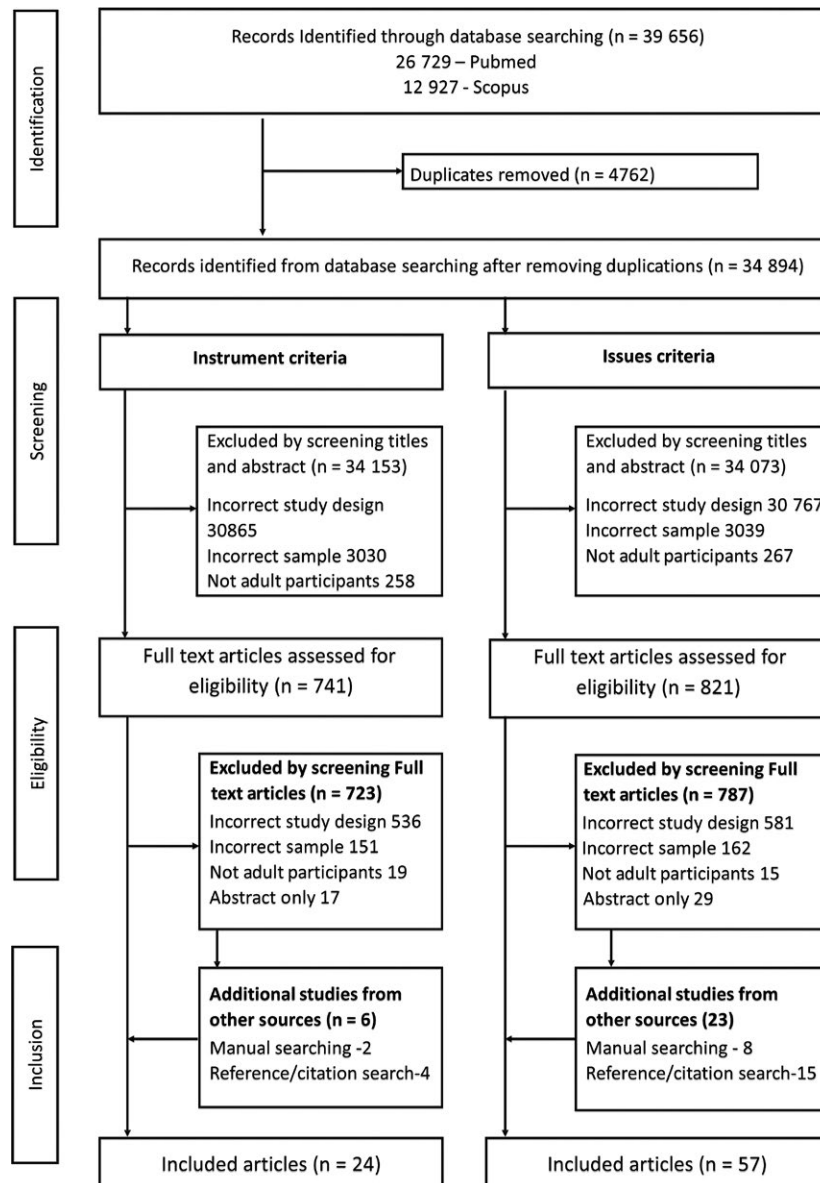
FIGURE 2 Prisma flow chart for the systematic review

3.1 | HRQoL issues reported important by patients

Twenty-four articles were identified meeting the inclusion/exclusion criteria, using inductive method to identify HRQoL issues reported as important by patient with HMs. A total of six articles focused on leukaemia patients, ten on multiple myeloma (MM), six on patients with HMs undergone BMT, two on lymphoma and two MDS patients. A total of 14/24 articles focused on exploring lived experience with disease, three on lived experience with SCT, two on response and psychological impact of intensive treatment, one on sexuality post-SCT and three on development of disease-specific instrument. A total of fifty different disease-related symptoms and treatment side effects were identified from the selected articles and classified as "Signs and Symptoms" (Table 1). Overall, 21 HRQoL issues were reported important by the patients with different HMs

(Table 1). The most highly reported disease- and treatment-related symptoms across all included studies were as follows: tiredness; fatigue; feeling ill; nausea; and weakness. The most highly reported HRQoL life issues were as follows: impact on daily life; living with uncertainty; and financial impact.

Almost all the identified studies used purposive sampling for data collection without using sampling to redundancy approach, which is an important consideration in the qualitative research,[41] except three articles where inpatients were interviewed until saturation was achieved.[39,42,43]

3.2 | HRQoL instruments identified

Thirty different HRQoL instruments were identified from 57 included articles as per instruments criteria. Of these, four were

TABLE 1 Summary of HRQoL issues and signs and symptoms reported important by patients in the literature

		Sign & Symptoms			
HRQoL issues[a]	N		n		n
• Coping with disease	22	• Fatigue	16	• Lethargy during treatment	2
• Disease and Treatment related symptoms	21	• Nausea	9	• Neutropenia	2
• Performance ability	21	• Feeling ill	8	• Restlessness/agitation	2
• Psychological well-being (emotional and cognitive)	18	• Infections	5	• Shortness of breath	2
• Burden of disease & treatment (long hospital stays, invasive diagnostic and treatment procedure)	15	• Swollen limb	5	• Weight loss	2
		• Bleeding	4	• Bruising	1
• Living with uncertainty	14	• Bone aches	4	• Chest pain	1
• Physical well-being	14	• Hair loss	4	• Chills	1
• Social well-being/ participation	13	• Loss of appetite	4	• Clotting disorders	1
• Healthcare/healthcare professionals	11	• Tiredness	4	• Cough	1
• Support factors	11	• Weakness	4	• Disturbed taste	1
• Financial impact	10	• Anaemia	3	• Hip pain	1
• Impact on job/work life/ role change	10	• Cognitive impairment	3	• Heartburn	1
• Insecurity/body image	9	• Constipation	3	• Lymph node lumps/swelling	1
• Interpersonal relationships	9	• Fever	3	• Mouth sores	1
• Sexual problems/infertility	8	• Fractures	3	• Night sweats	1
• Information about the disease and treatment	7	• General pain	3	• Numbness	1
• Insurance problems	4	• Insomnia	3	• Peripheral neuropathy	1
• Socio-economic impact	4	• Back pain	2	• Renal failure	1
• Knowledge about the disease	3	• Bone lesion	2	• Shoulder pain	1
• Self-esteem	3	• Brittle or broken bones	2	• Sore eyes	1
• Spiritual well-being	3	• Diarrhoea	2	• Stomach area pain	1
		• Drowsiness	2	• Thirst	1
		• Dry mouth	2	• Tingling	1

n, number of studies reporting the issues/sign and symptoms.

[a]All the studies identified and included in the systematic review to extract the HRQoL issues and signs and symptoms had used the same conceptual definition of health-related quality of life.

general measures used in oncology (EORTC-QLQ-C30, FACT-G, FACT-AN and QAHL); twelve were disease-specific [*three BMT specific (EORTC BMT module, FACT-BMT and QoL-BMT); four multiple myeloma specific (EORTC-QLQ-MY24 & MY20, FACT-MM and MyPOS); three leukaemia specific including one specific for chronic myeloid leukaemia (EORTC Leu, FACT-Leu and EORTC-QLQ-CML24); one specific to MDS (QoL-E); and one specific for lymphoma (FACT-Lym)].* Moreover, two were chemotherapy treatment specific (EORTC-QLQ-HDC 19 & 29). Fact-Fatigue was the only fatigue instrument identified used as HRQoL for patients with HMs. Eleven other instruments were generic QoL instruments used across different

diseases (SF-36, SF-12, EQ-5D, 15D, LIP, QLI, SUNS, SF-SUNS, SeiQoL-DW, POMS, POMS-SF). One full article eligible to be included as per the instruments criteria was inaccessible and hence excluded from the final list of included articles (LIP[44]). All the identified instruments were developed and validated by collecting data from patients on different chemotherapy clinical trials or patients undergone/undergoing allogenic/autologous stem cell transplant, except MyPOS which has been developed and validated by collecting data from patients in palliative setting. MyPOS has been validated for use for myeloma patients[45] and follicular lymphoma patients[46] in clinical practice.

TABLE 2 Content analysis of the HRQoL instrument for the identified HRQoL issues from the literature

HRQoL Issues vs Instruments	QoL-BMT	QAHL	EORTC QLQ-C30	EORTC BMT	EORTCQLQ-MY24	EORTC QLQ-MY20	EORTC QLQ-HDC19	EORTC QLQ-HDC29	EORTC QLQ-CML24	EORTC Leu	FACT-G	FACT-LEU	FACT-AN	FACT-BMT	FACT-LYMPH	FACT-FATIGUE	FACT-MM	SF-36	SF-12	EQ-5D	15D	QLI	QoL-E	SUNS	MY POS	SF-SUNS
Burden of disease & treatment (long hospital stays, invasive diagnostic and treatment procedure)	✓							✓	✓					✓									✓		✓	
Coping with disease	✓		✓					✓	✓	✓	✓	✓	✓	✓	✓	✓	✓						✓	✓	✓	✓
Disease and Treatment related symptoms	✓		✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓				✓		✓		✓	
Financial impact	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			✓					✓	✓		✓	✓
Healthcare/Healthcare professionals	✓																							✓		
Impact on Job/work life/ Role change	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓		✓		✓	✓	✓	✓	✓
Information about the disease and treatment					✓	✓			✓															✓	✓	
Insecurity/ Body image	✓		✓		✓		✓	✓			✓						✓					✓	✓	✓	✓	
Insurance problems	✓																							✓		
Interpersonal relationships	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓
Knowledge about the disease	✓																							✓	✓	
Living with uncertainty	✓		✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Performance ability	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Physical well-being	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Psychological well-being (emotional and cognitive)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Self-esteem	✓				✓						✓							✓	✓		✓				✓	
Sexual problems/Infertility	✓	✓	✓			✓	✓		✓		✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	
Social well-being/ Participation	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Socioeconomic impact																								✓		✓
Spiritual well-being	✓																								✓	
Support factors	✓				✓			✓	✓		✓	✓	✓	✓	✓	✓	✓					✓		✓	✓	✓

3.3 | Content validity of HRQoL instruments

The ability of each instrument to capture the quality-of-life issues identified from the 24 qualitative studies is shown in Table 2. Seven EORTC modules were identified which are used for different haematological malignancies along with the core EORTC-QLQ-C30 questionnaires. Similarly, six FACT modules were identified which are used together with the core FACT-G questionnaire. Content of all the available questionnaires was checked for the identified HRQOL issues presented in Table 1. Subsequently, a number of HRQoL issues were identified from individual studies appraised for content validity of the employed HRQoL instruments (Table 3).

None of the instrument captured all the 22 identified HRQoL issues. QoL-BMT with its total 84 items was the most comprehensive instrument in covering the identified issues.

The important issues not captured by most of the thirty instruments reviewed were as follows: burden of the disease and the treatment (9); issues related to healthcare and healthcare professionals (5); information about the disease and the treatment (5); feeling insecure and body image (10); issues related to insurance (2); socio-economic impact (2); and spiritual well-being (2).

All the generic instruments (SF-36, SF-12. EQ-5D) were missing the important identified issues. Sei-QoL-DW is an open questionnaire with no predefined items, and only five most important issues can be reported by a respondent. The POMS, POMS-SF and LIP could not be obtained for content analysis, hence not being included in Table 2.

3.4 | Psychometric properties of the identified HRQoL instruments

A summary of the psychometric properties of the identified HRQoL instruments is presented in Table 4 based on the criteria reported by Gruenewald et al[47] and Osborne et al[35] The table gives information about the sample used for development and validation of the instrument, validity (content, criterion, convergent and divergent), reliability (internal consistency, test-retest), responsiveness, sensitivity to change and minimal clinically important difference (MCID).

Twenty-three studies were identified extensively reporting the measurement/psychometric properties for the EORTC-QLQ-C30 general oncology measure,[4,48-70] followed by EORTC-MY24 module[38,63,71-73] and SF-36 generic measure.[74-79] Most of the studies provided evidences for internal consistency, convergent/divergent validity, floor/ceiling effect and responsiveness.

Content validity was reported for only five instruments, either represented as level of agreement between raters and items reported missing by the patients. All the studies reported internal consistency of >0.7 for different instruments, but none reported for SF-12, EQ-5D and 15-D in the study population. The evidence for minimal clinically important difference and prognostic power of the instrument were identified for only eight instruments (EORTC-QLQ-C30, EORTC-QLQ-MY24, EORTC-QLQ-CML24, FACT-AN, FACT-Lym, EQ-5D, 15D and QLI; Table 4). Most of the studies had patient population from Europe (mainly Sweden, Germany and UK), followed by the USA.

The psychometric properties for EORTC-QLQ were tested in wide range of patient population with different disease diagnosis, majority from MM, lymphoma and leukaemia. Only one study recruited patients with other neoplasm, and none reported recruiting patients with MDS. The psychometric properties of FACT-G have been tested with 100% lymphoma patients in two studies and mixed sample of patients with different HMs in another two studies including only 0.5% MDS and no patients with MPN. The SF-36, SF-12, EQ-5D, 15D, LIP, POMS and POMS-SF also had focused on majority patients with myeloma, followed by leukaemia, and lymphoma. None of the identified studies had patients with MDS and MPN. Disease-specific instruments EORTC (MY24, MY20, HDC-19, HDC-29 and CML-24), FACT (Leu, AN, BMT, Lymph and MM), QoL-E, QoL, BMT and MyPOS had recruited patients with respective type of haematological malignancy. Hence, none of the instruments have undergone complete psychometric evaluation in patients with all types of haematological malignancies.

3.4.1 | Instruments for myeloma patients

EORTC-QLQ-C30 and its myeloma modules (MY-24 & revised MY-20), followed by FACT-G and its myeloma module (FACT-MM), have been extensively validated with myeloma clinical trial patients. As reported by Osborne et al,[35] the EORTC recommends MY20 which has been revised after removing the social subscale from MY24, which is an important issue identified from the 24 qualitative studies included as per issues criteria in this review Table 1. Only one instrument, that is MyPOS, has been recently developed to be used in daily clinical practice. MyPOS total score is reported to be negatively correlated to the EORTC-QLQ-C30.[45,46]

3.4.2 | Instrument for lymphoma patients

FACT-G and its lymphoma module FACT-Lym have been identified for lymphoma patients. One study reporting the psychometric properties of the FACT-Lym was carried out only with non-Hodgkin lymphoma patients from USA. It is also noteworthy that no correlation was found between FACT subscales and social desirability scale.[80] Validation of FACT-G was carried out with mixed patient groups. No instrument has been validated to be used in daily clinical practice. Ceiling effect has been reported for 4 items from FACT-G scale (nausea, feeling ill, forced to spend time in bed and losing hope in fight against illness).[81]

3.4.3 | Instruments for leukaemia patients

Out of 23 studies reporting psychometric properties of EORTC-QLQ-C30, only five studies recruited patients with leukaemia (acute and chronic), the majority of these patients were diagnosed with AML. One study focused 100% on AML patients.[69] Only one study has been identified reporting the psychometric properties

TABLE 3 Summary of qualitative studies for identifying the HRQoL issues

Disease type	Author, year, aim	Method used	Sample	Summary of themes and issues generated	Quality score

Acute and chronic leukaemia	Bertero C, Eriksson BE et al (1997)[43] 'To explain the different profiles in QOL, described from the patients' perspective, as experienced by adults with acute and chronic leukaemia, respectively.'	Qualitative live interviews. Questions asking about their experience of QoL and if and how the disease had affected their QoL.	Sweden, n = 23, with Acute leukaemia [n = 8, 5 female, 3 male, mean age 44.125 (18.79, median 41(22-73)] and chronic leukaemia [n = 15, 6 female, 9 male, mean age 62.33 (12, 10), median age 64 (39-82)]	1. Uncertainty about disease
				   Living with a life-threatening disease and do not know how long life will be.
				2. Uncertainty with working lives
				3. Changing lifestyle—all according to the disability caused by disease
				4. Not feeling secure
				   Being in doubt, not being in control, being undecided.
					22/27

Acute myeloid leukaemia (AML)	Schumacher A et al (1998)[86] 'To monitor QL and subjective well-being of those patients actually responding to intensive treatment.'	Questionnaire administration during first four course of chemotherapy during inpatient treatment, before and after drug-induced myeloaplasia. Semi-structured face-to-face interviews during first cycle of maintenance therapy. Questions asking individual perception of their disease and therapy.	Germany, n = 28 (23 interviews), with AML 16 female, 12 male mean age 46, median age 47 (25-69)	1. Long hospital stays
				   Lack of privacy, bothered by boredom, lack of entertainment facilities while staying the hospital for such a long time, insufficient quality of food
				2. Psychological well-being
				   Undergoing treatment for such a long time makes it difficult for the patients to cope with their disease.
				3. Uncertainty and inability to plan things in advance
				   Hard to set up daily routine at home as they have to go to the hospital for several courses of inpatient treatment, the monthly course of therapy means an interruption of their everyday routine such as work, family, household task. Uncertainty about long-term remission is another threat to a patient's psychological well-being.
				4. Leading a normal life
				   Leading a plain, ordinary life, back to daily routine is a highly desired aim for most patients.
				5. Fear of relapse
				6. Emotional support
				   Relying for emotional support not only on family, but also from nurses and medical staff.
					18/27

Chronic leukaemia	Bertero C et al (1997)[87] To gain a deeper understanding of what individuals with chronic leukaemia consider QOL to be and to give the concept of QOL a theoretical and empirical significance relevant to nursing care.	Qualitative live interviews until saturation. Question related to patient perception of QoL, how has it changed since diagnosis and how nursing staff can help improve their QoL.	Sweden, n = 15, with chronic leukaemia 9 males, 6 females, aged between 39 and 82 y. Had diagnosis for 2-20 y	Life satisfaction.
				1. Self-esteem
				2. Interpersonal relationships
				   Needing someone and being needed, to feel secured and Have a companion
				3. Performance ability
				   Being able to do something which felt meaningful
				4. Social ability
				   Leisure time activity, intellectual stimulation and financial security
				5. Coping with disease
				   Denial of the diagnosis and hope for improvement
				6. Knowledge about the disease
				   To have power to go on living and to be capable of taking responsibility for their lives
					20/27

TABLE 3 (Continued)

Disease type	Author, year, aim	Method used	Sample	Summary of themes and issues generated	Quality score
Haematopoietic cell transplant (HCT) (HM)	Cooke Liz et al (2011)[88] 'To 1) describe the allogeneic transplant experience for AYA transplant patients during the first year following transplantation including demographic and treatment characteristics, 2) present AYA data obtained during and following a six-part post-transplant discharge study, 3) illustrate typical AYA experiences using case studies and 4) propose AYA intervention strategies within Erickson's Stages of Psychosocial Development.	Qualitative Interviews of the intervention patient group. Questions were focused on QoL of HCT survivors.	USA, n = 24 (a subset of bigger trial group), with acute leukaemia (20), HL (2), chronic leukaemia (1) and MDS (1). Intervention (n = 10) & control (n = 14) 13 females, 11 males Mean age 21.5 (19-24). 19 Caucasians & 5 Asian.	1. Physical Sexuality/fertility issues including precautions during pregnancy and fatigue 2. Psychological Depression/poor coping habits, adherence Issues, use of technology for distraction: music, iPod, phones, and texting, computer and dependency issues 3. Social Changes in roles/relationships, issues with school/education, financial Issues, changes/losses/being in limbo, family problems/issues and miscellaneous: How can the patient vote in an election when he is in isolation? 4. Existential/Spiritual Religion/spirituality, fear of future, uncertainty, life and death, meaning in life and role/more appreciate in life, "don't sweat the small stuff"	23/27
Chronic myeloid leukaemia (CML)-BMT	Molassiotis A & Morris PJ (1998)[89] 'To identify the patients' perceptions of their QOL not only by defining the content domain of QOL, but from a wider perspective by asking about certain post-BMT difficulties and leaving space for inclusion of positive alterations in the patients' lives.'	Survey with questions related to patients QoL, how is it different from before the transplant, and how could health care professional improve their QoL.	UK, n = 28, with CML 13 females, 15 males mean age at BMT 31.6 (17-48 y) Mean survival = 41.2 mo (13-92 mo)	1. Perception of quality of life Having a normal life, enjoyment and fulfilment with life, being healthy, independence and restrictions of activities, having family and relationships, having work, having social life, happiness, having material support 2. Impact of transplant Negative impact of the transplant (increased fatigue and weakness, decreased energy, loss of work, restriction in daily activities, problems with family. Positive impact—revaluation and appreciation of life, less contact with hospital, start education, decrease physical symptoms. 3. Difficulties after transplant Coping physical symptoms, coping with family, frustration on inabilities to perform/ function in daily life, returning to work, and fear of dying and getting ill again, infertility, problems with social life, increased dependency on others, planning for future, coping with memories and dealing with financial restrictions 4. After coming home Future concerns related to health, relapse, concerns on Long-term effects of transplant, financial concerns and infertility, planning about future, concerns about the normalisation process and coping with family. 5. What healthcare professionals could do to improve their QoL Provision of psychological support, advice on medication and treatments, discover a cure for GvHD and invent a new drug, more help with physical symptoms and improve research	23/27

TABLE 3 (Continued)

Disease type	Author, year, aim	Method used	Sample	Summary of themes and issues generated	Quality score

Hodgkin Lymphoma (HL)	Kornblith AB et al (1992)[10] 'To understand the nature and extent of psychosocial problems within a single disease site and identifying illness and sociodemographic factors associated with good and poor adaptation.'	Semi-structured telephone interviews 7-10 d after questionnaires concerning their psychological, social, vocational and sexual functioning were mailed to them.	USA, n = 273, with advanced HL accrued from 9 clinical trials, median age 37, 164 males, 109 Females. White 95%, Black 4%, Asian 1%	1. Job discrimination
				   Fires, demoted or encouraged to leave job
				2. Insurance problems
				   Denial of Life and Health Insurance
				3. Sexual problems
				   Sexual problems affected by illness 85(31%), one or more sexual problems 95(37%), infertile when tested 71(26)
				4. Conditioned nausea
				   Nausea largely in response to sights and smells that were reminders of chemotherapy
				5. Negative socio-economic effect (36%)
				6. Vocational problems 30(11%)
				7. Psychological distress
				   Increase in distress due to spectrum of physical and psychosocial issues
				8. Problems in sexual functioning
					25/27

HM	Richardson JL et al (1988)[90] 'To describe the adverse physical effects experienced in a sample of cancer patients in terms of frequency, difficulty, and level of interference with normal daily activity. Also, to examine how these relate to age, complexity of treatment regimen, disease severity.'	Qualitative Interviews, at the initiation of therapy and 6 mo later. Questions related to frequency and difficulty of unpleasant physical effects experienced.	USA, n = 107, with MM, acute/chronic leukaemia, indolent/aggressive lymphoma and HL. Median age 42 (18-86), 66 males and 41 females 55% Hispanic/Latin, 27% Black and 14% non-Hispanic	1. Physical effects Hair loss, nausea, loss of appetite, fever, weakness, pain, bleeding, infections 2. Distress from experienced symptoms	23/27
Hematopoietic stem cell transplant (HSCT)	Hog GL et al (2002)[91] 'To assess: 1) the changes in sexuality in terms of satisfaction, orgasm, sexual desire and frequency, 2) QOL in physical, psychological, social and spiritual domains and 3) the correlation between sexuality and QOL.'	Qualitative Interviews after completing self-administered questionnaires. Questions focussed on sexuality and general QoL	Korean, n = 38, who remained disease free after HSCT 26 female, 12 male, mean age 39 y (range 28-57) HM(57.89%)—[AML-11, CMI-6, MDS-2, NHL-2 & MM-1]	1. Avoid sexual contact due to fatigue 2. Decreased sexual desire 3. Anxiety about infections caused by sex, diminished vaginal secretion, change of appearance, anxiety about bleeding. Weakness, difficulty in erection	21/27

TABLE 3 (Continued)

Disease type	Author, year, aim	Method used	Sample	Summary of themes and issues generated	Quality score
HSCT (HM)	Beeken RJ et al (2011)[92] 'To describe adjustment post-HSCT from the theoretical basis of the response-shift model, through (1) identifying the antecedents and mechanisms that patients find helpful for adjustment and (2) exploring whether patients report response shifts in describing their adjustment.'	Semi-structured interviews. Open-ended questions focusing on HRQoL and patient's experience since diagnosis.	UK, n = 28, with CML 13 females, 15 males mean age at BMT 31.6 (17-48 y) Mean survival = 41.2 mo (13-92 mo)	1. Medical variables Initial diagnosis, treatment, time post-transplant, frequency of appointments, satisfaction with care, additional complications. 2. HRQOL and Response shift Overall QOL, change in values, recalibration, reconceptualisation. 3. Physical HRQOL Self-care, mobility, strenuous activities, differences, fatigue, sexual activity. 4. Social HRQOL Activities, family, friends, relaxation, differences, confidence. 5. Emotional HRQOL Anxiety, depression, anger/bitterness, differences. 6. Cognitive HRQOL Employment ability/status, employment satisfaction, employment help, concentration, memory, differences. 7. Management post-transplant Optimism, social support, social comparisons, changing expectations, setting goals, avoidant coping.	25/27
HSCT (HM)	Neiderbacher S et al (2012)[93] 'To (1) quantitatively measure the QOL of the random sample and (2) qualitatively describe the subjective experiences of some of the patients after the allogeneic HSCT'	Semi-structured, problem-oriented interviews. 'Question focussed on various aspects of life-threatening disease, radical therapy and its effects'	Italy, Germany, n = 7 (7/44 randomly selected) 4 Females, 3 males, mean age 45.27 (11.85; 17-67) time elapsed from HSCT 39.68 mo (35.07; 5-140)	1. Dependence versus Independence Change in work life, being independent, cannot drive, need someone to accompany, inability to have steady work, loss of independence, premature retirement, dependent on others 2. Relationships Support from family, friends, partner, siblings and true friendship grew stronger and less important friends turned away, change in interpersonal relationships, trust issues and lack of confidence 3. Shift in Priorities Difficult to accept changes because of disease, physical and mental experience leading to negative and positive consequences, increase in self-esteem and pride in one's coping abilities. Facing death 4. Dealing with the disease and its consequences Positive thoughts and demoralisation after the initial 'shock'	25/27
Leukaemia	Cella D et al (2012)[39] 'Develop and validate a health-related quality-of-life measure for patients with acute and chronic leukaemia.'	Semi-structured interviews. Questions focused on how leukaemia may affect physical status, emotional well-being, functional well-being, family/social issues, sexuality/intimacy, work status and future orientation.	Argentina, Brazil, France, Germany, Poland, Russia and USA, n = 29. Acute leukaemia (19) and chronic leukaemia (10).	1. Symptoms Fevers, bleeding, general pain, stomach area pain, chills, night sweats, bruising, lymph node lumps/swelling, weakness, tiredness, weight loss, appetite, shortness of breath, mouth sores and diarrhoea. 2. HRQoL Issues Functional ability, lack of concentration, emotional/social concerns (frustration with activity limitation, discouraged by illness, future planning, uncertainty, worry about illness, emotional ups and downs, isolation, concern about infertility, worry about family and worry about infections.	24/27

TABLE 3 (Continued)

Disease type	Author, year, aim	Sample	Method used	Summary of themes and issues generated	Quality score
Leukaemia and Lymphoma	Jones WC et al (2015)[94] 'Provide insight into how lifespan stage shapes the nature of distress in a post-treatment survivor population with representation across the lifespan by tapping the experiences of leukaemia and lymphoma survivors.'	USA, n = 51, with NHL (29), HL(10), AML(2), ALL(3), CLL(2) & MM(1) post-treatment. 28 female, 23 male, mean age 50.3 (20-82 y). Two with BMT. White (45), Non-White (6).	Qualitative face-to-face interviews. Questions focused disclosure of distress and lifespan factors influencing adjustment.	1. Physical After-effects Chronic and late effects of cancer—Fatigue, neuropathy, change in appetite, altered functioning Fertility challenges and concerns—Change in energy level and day-to-day function, concern related to difficulty in conceiving, fear related to perceived or confirmed infertility, fear of birth defects, pregnancy or complications. 2. Emotional after-effects Anger and depression, persistent worry or anxiety, fear of recurrence, anticipatory anxiety regarding follow-up care and concerns regarding future plans 3. Economic after-effects Financial burden, health insurance concerns, medical debt, employment challenges, return to work challenges/inability to work. 4. Employment discrimination.—revealing cancer-related gaps in their employment history and regaining employment after an extended time out of the work force.	25/27
MDS	Thomas ML (2012)[95] 'To explore how MDS impacts QoL of those living with the disease.'	USA, n = 70, with MDS Mean age 69 (9), median time since diagnosis 26.5 mo (2-276)	Qualitative focus group discussions. Open-ended discussion on how MDS impacts QoL.	1. Physical Well-being Symptoms related to anaemia (such as difficulty climbing stairs and dyspnoea on exertion), symptoms related to treatment (pain, nausea, malaise, fatigue, fevers and asthenia) 2. Functional Well-being Decreased ability to function, fatigue, work associated with administering therapy, work associated with interpreting and managing symptoms, side effects and complications. 3. Social Well-being Activity restrictions, time associated with office visits, relinquishing roles, Planning for future 4. Emotional Well-being Shock at diagnosis, anger and frustration, Depression, anxiety and fear, uncertainty 5. Spiritual Well-being Renewed appreciation for life, renewed appreciation for relationships, enhanced faith and beliefs	25/27
MDS	Oliva E et al (2013)[40] 'The development and validation of a psychometric questionnaire assessing HRQoL in MDS patients (QOL-E©).'	Italy, n = 10, MDS	Qualitative interviews with focus group of MDS patients. Questions focusing on impact of MDS on patients' QoL.	1. HRQoL Issues: General well-being, ability to perform daily activities, difficulty in staying awake, physical well-being, sexual functioning, fatigue, perception of being a nuisance to family members, relationship with healthcare practitioners, myelodysplastic syndromes-related disturbances (frequent hospital visits, transfusions, inability to travel, dyspnoea when climbing stairs, worry and stress.	17/27
MM	Stead et al (1999)[38] 'To develop a questionnaire with a maximum of 30 items to assess the disease-specific symptoms of myeloma and their impact on daily life, and treatment-related issues, mainly side effects of chemotherapy'	UK, Norway, Denmark & Sweden, n = 40, MM. female 20, male 20.	Relevant issues generated by literature review and 'informal interviews'. Questions focusing on frequency of symptoms, troubles they may cause.	1. Treatment Side effects Drowsiness, thirst, feeling ill, dry mouth, hair loss, tingling in hands and feet, restlessness/agitation, heartburn, sore eyes. 2. Disease Symptoms Bone aches, back pain, hip pain, shoulder pain, arm pain, chest pain. 3. Social Support Relationships with doctors, care received from doctors, information about illness, feeling of being listened to, physical attractiveness, thinking about illness. 4. Future perspective Worried about dying, worried about health in the future.	21/27

TABLE 3 (Continued)

Disease type	Author, year, aim	Method used	Sample	Summary of themes and issues generated	Quality score
MM	Dahan JF et al (2006)[96] 'To understand the emotional impact of multiple myeloma, as well as the impact of its principle treatment, peripheral blood stem cell transplant PBSCT.'	Semi-Structured Qualitative Interviews. Questions related to time leading up to diagnosis, reaction at diagnosis, transplant experience, personal relationships, support, impact on significant others, sexuality, body image and changes to self.	USA, n = 6, MM Mean age 57.3 (50-66 y) 3 Female, 3 males. 5 Caucasian, 1 African American. Post-HSCT.	1. Catalyst to diagnosis Feeling unwell, or in pain, frustration and delayed diagnosis, looking death in face, deciding on plan of action 2. Treatment Reaction to transplant, physical immobilisation, violation and dehumanisation, sense of vulnerability, burden on family 3. Network of safety Confidence in doctor, appreciation for cancer centres, overwhelming social support, strong family presence, relating to other cancer patients, personal coping. 4. Recuperation Strengthened body and spirit. 5. Reflection/New Existence Changed body (weight gain, short-term memory loss, insomnia, fatigue and painful neuropathy), less hope for future treatments, enduring threat of relapse, anticipating loss, acceptance, identifying resilience in oneself, strengthened connection to others, living while dying.	24/27
MM	Maher & De Vries. (2001)[97] 'To explore the experience of living with relapsed myeloma, specifically to explore how the experience of living with relapsed myeloma had affected the quality of the lives of these individuals.'	Unstructured interviews conducted using conversational manner in order to elicit narrative data.	UK, n = 8, MM 3 female, 5 male. Age range 48-74. Purposive sampling.	1. Living with Uncertainty Not being able to plan things, Impact of day-to-day life, uncertainty due to treatment and disease, worrying about test results. 2. Intuitive knowing Knowing that disease has relapsed before being told by the consultant. 3. Maintenance of normalcy Living a normal life appeared to be vital as a means of preventing cancer becoming dominant. 4. Adjustment to Illness Adjustment to illness and managing their lives accordingly, support from family members, withholding information about disease to protect family and friends, physical and psychological stress, increased dependency on others for daily activities, lack of mobility, psychological distress and depression, anxiety and social isolation. 5. Hope Dealing with uncertainty, belief in an afterlife, spiritual beliefs, and hope for new treatment provided an 'illusion of safety. 6. Effects of Treatments Large unpleasant toxicities—fatigue, tiredness, nausea 7. Trusting healthcare professional Concerned about wasting healthcare professional's time, conscious about other people waiting which prevented them in raising questions and concerns 8. Receiving the bad news Patients believed that it was important to be brave when receiving bad news. 9. Positive: hope and positive thinking.	16/27

TABLE 3 (Continued)

Disease type	Author, year, aim	Method used	Sample	Summary of themes and issues generated	Quality score
MM	Vlossak & Fitch (2008)[98] 'To explore, in a qualitative manner, the impact of a diagnosis of multiple myeloma on the patient and family.'	Qualitative telephone interviews. Questions focusing on personal experience during the diagnosis and treatment, impact of disease and treatment on patient and family life and how this disease may have changed their hopes for future.	Canada, n = 20, MM 7 female, 13 male. Length of time since diagnosis range 10 mo–6 y.	1. Diagnosis was shocking and unexpected. 2. Long Hospital stays and expensive parking tickets 3. Little time to weigh treatment options. 4. Negative information available online. 5. Few options for treatment. 6. Worrying about family and how they will handle diagnosis. 7. Time of psychosocial transition. 8. Inadequacy in carrying usual task (in house or outside). 9. Feeling being burden to family & friends. 10. Dependent on other for informational needs. 11. Treatment is difficult, long and very complex. 12. Pain during treatment 13. Side effects from steroids (mood swings, emotional volatility, increasing stress) Other side effects: Fatigue (most common), lethargy and severe constipation. 14. Loss of independence (going to work, daily chores, shopping, socialising) 15. Change is self-image/self-concept 16. Worrying about relapse 17. Worrying about future (goals and dreams)	18/27
MM	Wagner LI et al (2012)[99] 'To develop a disease-specific, patient-reported outcome (PRO) measure for the assessment of HRQL among patients with MM as part of the Functional Assessment of Cancer Therapy (FACT) measurement system.'	Semi-structured interviews. Questions focused on how MM impacted their lives.	N = 13, with MM, 6 female, 7 male, mean age 57 y (9), White 12, Asian 1.	1. Definition of HRQL Performing ordinary day-to-day activities, enjoying life and able to do enjoyable activities, absence of pain, feeling emotionally well and having energy. 2. Important HRQL issues Emotional distress, daily normal physical activities, pain, recreational activities and fatigue	23/27

TABLE 3 (Continued)

Disease type	Author, year, aim	Method used	Sample	Summary of themes and issues generated	Quality score
MM	Molassiotis A et al (2011)[100] 'To explore the experience of living with myeloma after completion of treatments in patients and their informal caregivers.'	Semi-structured interviews. Questions focussed on QoL issues with MM and why and how these issues occurred.	UK, n = 20, with MM 12 female, 8 male, mean age 61.8 y. Mean time post-diagnosis 5 y (range, 1-11.5 y). None receiving any active treatment, 5 relapsed, 2 awaiting treatment, 3 on treatment break.	1. Current and future concerns Not active as used to, frustration, rely on others, not able to do self-care and care for family, transition from abled to 'disabled', future concerns related to health problems, constipation, losing height, anxiety about relapse, worrying about protein levels in blood/urine, uncertainty about future. 2. Effects of myeloma in daily life Tiredness, back pain, long-term effects—cataracts, neuropathy, hearing loss and graft-vs-host disease affecting legs., lack of energy & mobility, inability to do housework, inability to walk far or play with grandchildren, being housebound, not socialising, given up work as a result of illness, could not cope with demands of the previous job, diagnosis affecting partner's life, 3. Practical, functional and emotional coping use of aids to maintain independence and functional well-being or ease of symptoms, housebound, refused to use wheelchair because it is embarrassing, eager to gather knowledge about myeloma, maintaining healthy body, being active in order to stay well for children, difficulty in self-management, covering (concealing) and, not discussing illness with friends, cheating in hospitals by wearing heavy clothes while weighing. Psychological coping mechanism like avoiding, denial, staying positive, using comparisons with others, normalising, distraction and stoicism. 4. Unmet needs Limited expressed needs, limited help from outside agencies, lack of continuity of care, seeing the person in the patient.	27/27
MM	Potrat B et al (2011)[42] 'To gain greater insight into the symptoms and distressing experiences of patients living with myeloma.'	Semi-structured Interviews. Question focused on symptom experience and distress from their illness overall.	UK, n = 15, MM Mean age 58.2 y (42-75) Median survival time 4-5 y. Female 33.3%, male 67.7%. White 73.3%. Eleven received SCT.	1. Distress from experienced symptoms Brittle or broken bones, tiredness, nausea, pain and lethargy during treatment.—distressing, difficulty with mobility's, long time wait for disability allowances from social services, out-of-pocket expenses for mobility equipment's 2. Distress from body image changes Weight loss/gain, hair loss—distressing 3. Distress caused by family and Friends Substantial financial burden for young patients with no regular income, moving back to live with parents, and distress due to enquires from family and friends. 4. Distress from myeloma-related information Too much negative information, relying on friends or appointed person for information. 5. Distress from stem cell transplant Various symptoms like nausea, insomnia, inability to swallow and mucositis, period as looking or being somehow dead, and fear of dying	23/27
MM	Kelly & Dowling (2011)[101] 'To explore patients' lived experience of being diagnosed with myeloma.'	Qualitative Interviews. Questions focusing on living with myeloma.	Ireland, n = 11, MM. 4 female, 7 male. Mean age 63 (42-83) y. Time since diagnosis range 1.5-4 y.	1. Lived Body: a changed body Alopecia, Fatigue 2. Lived Space: living in limbo living with unknown cancer, stigma of cancer, loss, feeling Lucky. 3. Lived time: time is precious Fear of recurrence, Limited time with healthcare professional. 4. Lived relations: significance of support Family support, protecting others	24/27

TABLE 3 (Continued)

Disease type	Author, year, aim	Method used	Sample	Summary of themes and issues generated	Quality score
MM	Osborne T et al (2014)[102] 'To (1) explore the issues important to QOL from the perspective of people with multiple myeloma, and (2) explore the views of patients and clinical staff on existing QOL questionnaires and their use in clinical practice.'	Semi-structured Interviews. Questions focused to explore the issues important to QoL from the patients' perspective.	UK, n = 20 (issues Interviews), with MM 10 female, 10 male, median age 66(41-78). White British 13, White other 1, Black African/ Caribbean 5, other 1. Newly diagnosed (7), Stable/plateau phase (7), and relapsed (6).	1. Biological Status Anaemia, bone lesion, clotting disorders, fractures, hyperglycaemia, infections, neutropenia, para-proteins, peripheral neuropathy, renal failure, spinal cord 2. Treatment Factors Bone marrow aspiration, chemotherapy, clinic visits, dialysis, Hickman line, hospital and admissions, injections and blood test, radiotherapy, stem cell transplant, steroids, surgery, tablets and other medication, transfusions, X-rays and scans 3. Symptom status Appetite change, bleeding, breathlessness, cognitive impairment, constipation, cough, diarrhoea, disturbed taste, dry mouth, fatigue or drowsiness, hair loss, incontinence, insomnia, nausea and vomiting, Pain, swollen limb, syncope, tingling and numbness, tremor 4. Activity and Participation Ambulation and mobility, Family and family life, friendship and social life, independence, leisure and hobbies, self-care, activities of daily life and usual activity, sex and intimacy, work life 5. Emotional Status Body image and bodily violation, distress and shock at diagnosis, embarrassment, fear of dying, fear of fracture, fear of infection, fear of relapse, frustration and anger, isolation, low mood and depression, perceived burden on others, personal growth and positive effects, uncertainty, worry and anxiety 6. Support Factors Accessible health care, care & respect from professional, communication and information, competency of professional, consistency of health care, financial, housing, support from employer, support from friends and family and transport 7. Expectations 8. Adaptation and coping 9. Spirituality	26/27
MM	Baz R et al (2015)[103] 'To explore the burden of MM symptoms and treatment and the impact of these on HRQoL.'	Open-ended Semi-structured telephone Interviews. Questions focussed on symptoms and their impact, followed by the overall impact of MM on HRQoL	USA, n = 20, with MM. 11 female, 9 male, mean age 60.4 y (48-77), White Caucasian (20).	1. Reported Symptoms Pain/discomfort, fatigue/lack of energy, bone damage/ fractures, anaemia, nausea, aches, cognitive issues, neuropathy, infections, shortness of breath/breathing problems. 2. HRQOL Issues • Impact of pain on daily activities—pain limited walk and physical activity • Impact of fatigue on work.—Fatigue made them alter their plans, affects everyday cleaning and gardening and other daily activities. Change in working patterns to incorporate regular rest periods. • Impact of pain on family and leisure activities • Impact of fatigue on everyday activities. • Impact of fear of injury on leisure activities. • Impact on independence. Wife or partner has become caretaker. • Impact of symptoms—fear of fractures and restricted sports activities and other leisure activities. travel was affected, depression. • Impact of MM treatment—Clinic visits (frequency and commuting). Blood test regularly even if travelling and finding a testing centre. • Mode of administration—IV every month, scares on arms. • Treatment burden—Inconvenience, Financial, mode of administration, monitoring	24/27

TABLE 4 Summary of psychometric properties of the identified HRQoL instruments

Instrument name	Subscales and total Items	Sample details	Validity	Reliability	Responsiveness and floor/ceiling effects	Minimal important difference and prognostication
QoL-BMT[104]	Four Domains; Physical Well-being & Symptoms; Psychological Well-being; Social Well-being; Spiritual Well-being. Total 30 items.	HM patients undergone Allogenic BMT (n = 179, CML (40), AML (38), NHL (29), SAA (23), HL (18), ALL (13), MDS (5), LL (3), Other (10).[104]	**Content validity** A level of 90% agreement was for acceptance of the item content. The time period of 1-3 y post-BMT was significant predictor of QoL as compared to the length of survival or 0-1 y or >3 y post-BMT. Happiness—a strong indicator in the psychological well-being dimension-accounted for over half of the variance ($r^2 = 0.59$ for single QOL item, $r^2 = 0.64$ for the mean QOL total score).[104] **Criterion validity** Happiness, strength, satisfaction, enjoyment, affection, control, useful, adjustment, appearance, sleep had item correlation with $r > 0.5$ showing strong correlation among items.[104]	**Test-retest reliability** Pearson's correlation coefficient r = 0.71 ($P < 0.001$) showed strong consistency over time. **Internal consistency** Over all Cronbach's alpha = 0.85 ($P < 0.01$). Subscales alpha ranged from 0.40 for physical well-being to 0.86 for psychological well-being.[104]		
QAHL[105]	Two Scales; A quality of health-scale (items 1, 4, and 9), and quality-of-life scale (items 2, 5, 10, 11, & 12). And four single items. Total 12 items.	Patients with HM. Czech, German, Hungarian, Italian, Croatian, Polish, Romanian and Slovakian. Mixed disease stages (n = 1104, Acute Leukaemia's (14.7%), Hodgkin (11.3%), NHL (29.5%), MDS (4.9%), MPN (15.9%), MM (8.5%) and other diagnosis (15.2%).[105]		The reliability for QoH-scale reached an alpha of 0.73, for the QoL-scale alpha is 0.80.[105]	The possible range of the QoH-scale of 0 to 14 points and that of the QoL-scale of 0 to 22 points together with the fact that both distributions are well-centred with means close to the middle of each scale show the potential for good discrimination. Each extreme category contains about 1% of the answers (data not shown), and therefore, ceiling effects are not probable in comparable samples. Hence, two important requirements for sensitivity to change are fulfilled.[105]	

(Continues)

TABLE 4 (Continued)

Instrument name	Subscales and total Items	Sample details	Validity	Reliability	Responsiveness and floor/ceiling effects	Minimal important difference and prognostication
EORTC QLQ-C30[4,48-70]	5 functional scales; Physical, role, emotional, cognitive, & social. Two global health and QoL items. 3 symptom scales and six single items.	**Trial data:** BMT patients (n = 125, Acute leukaemia(40%), aplastic anaemia (34%), chronic leukaemia (20%), other (6%< lymphoma, myeloma & other neoplasm)[48] **Trail data:** Mexico (n = 98, 100% MM)[50] **Trial data:** Greece (n = 90, MM 100%)[49] Europe (n = 274, 100% MM)[51] (n = 145, 41% lymphoma, 40% MM, 3& AL, 2% CL)[52] (n = 79, 58.2% MM, and 25.3% NHL)[53] (n = 96, 58.3% MM, 33.3% lymphoma, 2% AML)[54] (n = 504, 100% MM).[55] (n = 424, 100% MM)[56] (n = 131, 23.7% AML, 10.7% CLL, 1.5% ALL, 10.7% HL, 19.1% NHL, and 28.2% MM)[58] (n = 239, 100% MM)[60,61] (n = 1956, 10% lymphomas, 22% myeloma)[62] (n = 92, 100% MM)[4] (n = 12. 100% MM)[63] (n = 202, 100% MM)[64] (n = 22, 4.5% HL, 18% NHL, 27% AML, 54% MM)[65] (n = 521, %100 MM)[66] (n = 745, 100% MM)[67,68] **Trial data:** German (n = 101, 100% AML)[69] Trial data: USA HSCT patients (n = 20 at baseline, n = 17 post-transplant[57] Trial data: USA (n = 132, 100% MM)[70]	**Convergent and divergent validity** Correlation between item and own scale >0.3 (0.3-0.7). Good discriminant validity in majority of scales[50] The 0.4 item scale correlation criteria were satisfied.[49,62] Convergence in 23/24(95.8%) criteria were satisfied.[49] Item discrimination successful in 149/192(77.6%).[49] Criterion of discriminant well satisfied for 6 scales, PRF, E4-E7 & E9 have only scaling success.[62] **Criterion validity** Psychosocial QoL Scales (role, emotional, and social function-ing) weakly associated with disease as compared to physical scale (mean R^2 8.8% vs 15.7%).[4] Good association with MDASI-MM for physical, role, cognitive, social and emotional-functioning subscales (all $P < 0.001$).[70] **Construct validity** For physical functioning, patients had decreased score from 67% to 48% for 10th percentile of the reference population and 43% to 20% for global QoL and for pain 46% had higher scores.[56] All subscales significantly impaired compared to reference population.[4]	**Internal consistency** High Internal consistency with Cronbach's alpha = 0.92. Six of 9 subscales were reliable, alpha range = 0.7-0.91. Three had questionable reliabilities (physi-cal = 0.57, social = 0.38, nausea/vomiting = 0.48)[48] Cronbach's alpha >0.7 for all the scales except Nausea and vomiting with alpha value 0.356 and cognitive (0.597)[50] Cronbach's alpha >0.7 for all subscales except cognitive function (alpha = 0.57),[49] except for social functioning in one group[57,62,66]	**Floor/ceiling effects** Nausea and Vomiting scale had a floor value of 50 in 3.1% of cases, remaining scales of floor value of zero and mean ceiling values of 100. Five QlQ-C30 symptom scales had ceiling value in >50% of patients.[50] High floor score (>50%) for five symptom scales/items, that is, nausea/vomiting, appetite loss, constipation, diarrhoea and financial difficulties. No ceiling effect.[49] Very small overall floor & ceiling effect. Only few patients achieved the lowest or highest possible score.[60] **Responsiveness** Sensitivity to change in five scales after 1 mo[50] Changes for subscales over time[51,52,54,55,59,63,65-67,69] No difference in outcomes over time.[58] **Responsiveness** responsive with SRM 0.32 for improved and 0.57 for deteriorated.[60]	**Floor/ceiling effects** Difference of 6-17 points as clinically important for patients.[59] Univariate analysis shows role function-ing, emotional functioning and fatigue significantly associated with overall survival ($P < 0.0031, P < 0.034$ and $P < 0.0034$). All other scales not related to overall survival.[4,64,68] Multivariate analysis showed only two variables as significant predictive variables.[64] **MID** Change of score from 7.6 to −12.1 was important to patients.[60] Absolute change of scores from 6.2 to 14.7 for improved patients in physical function, 8.6 (fatigue)-17.3 (pain), and 12.2 to 27 for patients who deteriorated.[61]

TABLE 4 (Continued)

Instrument name	Subscales and total Items	Sample details	Validity	Reliability	Responsiveness and floor/ceiling effects	Minimal important difference and prognostication
EORTC BMT module[48]		BMT patients (n = 125, acute leukaemia(40%), aplastic anaemia (34%), chronic leukaemia (20%), other (6%<lymphoma, myeloma & other neoplasm)[48]		**Internal consistency** Cronbach's alpha for BMT module = 0.87 with category alpha ranging from 0.71 to 0.89 with four exceptions (skin = 0.55, mouth/throat = 0.69, infections = 0.32, fear of relapse/dying = 0.66) QLQ-C30 and BMT highly correlated (r = 0.77, P < 0.001)[48]		
EORTC QLQ-MY24[38,63,71-73]	EORTC-QLQ-30 items. Additional 24 items in four scales (two symptom scales: disease symptoms, side effects of treatment, one functional scale: future perspective and a social support scale) and one single item: body image). Total 54 items.	Patients on 10 trial: UK, USA, Germany, Sweden, Norway, Denmark, and Czech Republic (n = 240, 100% MM) 255- Newly diagnosed and 15 relapsed/refractory disease.[71] Trial data: Europe (n = 116, 100% MM)[38] Trial data: (USA (n = 202, 100% MM)[72] (n = 12. 100% MM)[63] Trial data: UK (n = 132, 100% MM)[73]	**Content validity** 10%-18% of patients felt there were missing items.[71] **Convergent and divergent validity** The correlation between an item and its own hypothesised scale was higher than 0.4 for all the subscales except side effects of treatment which ranged from 0.17 to 0.72. At the baseline. At the follow-up, the correlation was again higher than 0.4 for all the scales accept the improved correlation of 0.33-0.62 for side effects of treatment. The social support scale was removed dues to high ceiling effect.[71]	**Internal consistency** Cronbach's alpha >0.7 in all scales at both time points.[71]	**Responsiveness** Improvement in score for disease symptoms and future perspectives. Significant difference between the three groups.[72] **Floor/ceiling effect** Low scores for some subscales.[73]	**Predictive validity** Univariate analysis showed that higher level of Karnofsky performance status, albumin, platelet count, and haemoglobin associated with survival.[72] Fatigue, pain, sleep disturbance and treatment adverse effect related to death.[72]

TABLE 4 (Continued)

Instrument name	Subscales and total Items	Sample details	Validity	Reliability	Responsiveness and floor/ceiling effects	Minimal important difference and prognostication
EORTC QLQ-MY20[49,50,70,71]	EORTC-QLQ-30 items. Additional 20 items in four scales (two symptom scales: disease symptoms, side effects of treatment, one functional scale: future perspective) and one single item: body image). Total 50 items.	Trial data: Patients on 10 trial: UK, USA, Germany, Sweden, Norway, Denmark and Czech Republic (n = 240, 100% MM) 255- Newly diagnosed and 15 relapsed/refractory disease.[71] Trail Data: Mexico (n = 98, 100% MM)[50] Trial data: Greece (n = 90, MM 100%)[49] Trial data: USA (n = 132, 100% MM)[70]	**Convergent and divergent validity** Correlation between item and own scale >0.2 (0.2-0.7). Low for items in disease symptoms and side effects of treatment. Good discriminant validity in majority of scales.[50] The 0.4-item scale correlation criteria were satisfied. Convergence in 13/18(72.2%) Item discrimination successful in 21/36(58.3%).[49] **Construct validity** Low correlation with QLQ-C30 functioning scales (Spearman's r < 0.4) in 11/18 comparison. But high correlation with QLQ-C30 symptoms scale (r = 0.74).[49] **Criterion validity** Pain and bone-aches items from MDASI-MM correlated with QLQ-MY20 disease symptom scale (0.71 & 0.69 (P < 0.001)[70]	**Internal consistency** Cronbach's alpha >0.7 for all scales[50] Cronbach's alpha >0.7 for all scales[49]	**Floor and ceiling effects** mean ceiling values of 100. Functional scale with >50% of patients with ceiling effect.[50] Ceiling effect in body image scale.[49] **Responsiveness** Disease symptoms (P −0.001) and body image (<0.0001) significantly decreased over time. The side effects of treatment increased significantly (P = 0.0036)[71] Sensitive to change in three scales after 1 mo (P > 0.01)[50]	
EORTC QLQ-HDC 19[52,106]	Items covering circulation, mouth and skin problems, pain, anxiety, sexuality, social support and perspectives regarding future health. Total 19 + 30 items.[106]	Trial data: Swedish Patients who accepted SCT (n = 202, lymphoma (32%), MM (28%), acute leukaemia (15%), chronic leukaemia (7%), solid tumours (7%) and other (9%).[106] Trial data, Swedish (n = 145, 41% lymphoma, 40% MM, 3& AL, 2% CL)[52]	**Convergent and divergent validity** Mean correlation between hypothesised scale and items >0.7 at all time lines for Health worries items and sexual functioning. For joint, muscle pain and 2 items for skin irritation had mean correlation of >0.4 at all items. 100% of items correlating higher or significantly higher with their hypothesised scale than with competing scale.[106] **Criterion validity** Changes in score similar to EORTC-QLQ-C30 score changes[52]	**Internal consistency** At inclusion Cronbach's alpha >0.8 for health worries and sexual functioning. **Test-retest** Intra-class correlation coefficient was high for scales (0.96-1.00). For joint and muscle pain (0.59) and 0.62 for skin irritations.[106]	**Floor/ceiling effect** All scales highly skewed with skin irritations, increased mucous production, soreness in mouth and worries about sterility responding at floor.[106] Floor effect for symptom and functional scales.[52] **Responsiveness** Most changes found between baseline and 1 mo after transplantation with SRM ranging from 0.00 to 0.94.[106] Statistically significant score for functioning scales and some symptom scales from baseline to 1 mo after SCT.[52]	

TABLE 4 (Continued)

Instrument name	Subscales and total Items	Sample details	Validity	Reliability	Responsiveness and floor/ceiling effects	Minimal important difference and prognostication
EORTC QLQ-CML24[82]	EORTC-QLQ 30 items. CML24: Four multi-item scale; symptom burden, impact on worry/ mood, impact on daily life and satisfaction with care and information. Two single items; body image problems and satisfaction with social life.	Trial data: Online Survey (n = 107, CML 100%)[82]	**Construct validity** Weak correlation between Satisfaction with care and information and satisfaction with social life scales with QLQ-C30 ranging 0.01-0.37. High correlation between symptom burden and impact on daily life scales from module and fatigue scales from core questionnaire (0.64 and 0.65).[82]	**Internal consistency** Cronbach's alpha ranged from 0.73 to 0.83.[82]		Statistically significant differences in all scales in the expected directions. Comparisons between responders and non-responders showed better HRQoL outcomes for patients responding to therapy.[82]
EORTC Leu[83]	EORTC-QLQ 30 items. Four additional subscales with 20 items.	Trial data: EORTC GIMENA AML8A and MRC AML10 Trial (n = 388, 100% AML)[83]	**Content validity** 20/32 items were retained and rest deleted after factor analysis.[83]	**Internal consistency** Cronbach's alpha >0.7 for both the factors.[83]	**Responsiveness** Significant difference between allograft and other two modalities (P < 0.0001) and factor two (P < 0.01).[83]	
SUNS[107]	Five domains; Financial concerns, emotional health, access & continuity of care, information, and relationships. Total 89 Items	Trial data: Australian (n = 715, 59% NHL, 19% leukaemia, 16% myeloma, 6.2% other lymphoma)[107]	**Construct validity** 5-factor model based on parallel analysis.[107] **Convergent and divergent validity** Correlation coefficient >0.4 for all domains with three subscales of DASS-21.[107] Higher score for younger (<60 at diagnosis) than older survivors.[107]	**Internal consistency** Cronbach's alpha >0.9 for all domains.[107] **Test-retest** Weighted kappa coefficient ranged 0.25-0.76. ICC ranged 0.61-0.77.[107]	**Floor/ceiling effect** Floor effect for all five domains and ceiling effect for 4 domains.[107]	

(Continues)

TABLE 4 (Continued)

Instrument name	Subscales and total Items	Sample details	Validity	Reliability	Responsiveness and floor/ceiling effects	Minimal important difference and prognostication
FACT-G (functional Assessment of Cancer Therapy—general)[39,80,81,108]	Four Subscales: physical well-being, social/family well-being, emotional well-being and functional well-being. Total 27 Items.	Trial data: USA (n = 611, 100% lymphoma).[81] Trial data: USA (n = 182, NHL (36%), HL (8%), CML (7%), AML (11%), ALL (2%), CLL (1%), MM (2%), MDS (0.5%).[108] Trial data: USA (n = 79, AML (27), ALL(5), APML (3), CLL (25), CML (15), HCL (4))[39] Trial data: USA (n = 84, NHL 100%)[80]	**Criterion validity** Twelve items had item-total correlation ≥0.4 for at least one subgroup and time point. Correlation at 36 mo between FACT-G total score and ECOG PS ($r = -0.43$, n = 177), B-POMS ($r = -0.63$, n = 201), STAI ($r = -0.57$, n = 226), and LASA QoL ($r = 0.63$, n = 229) was moderate to large in magnitude with statistical significance (all $P < 0.001$).[81] **Construct validity** Performance status highly correlated with physical well-being (−0.58) and functional well-being subscale (−0.47).[108]	**Internal consistency** Cronbach's alpha >0.7 at all time points. Alpha >0.9 at all assessments for total scale.[81] Cronbach's alpha >0.9 at all time points.[39] Cronbach's alpha >0.7 at all three Times.[80] **Test-retest** ICC = 0.806 between at all times.[39] ICC = 0.84 for the scale.[80]	**Floor/ceiling effects** Floor effect less than 5% for all items in each of the three subgroups. Ceiling effect most apparent for nausea, feel ill, forced to spend time in bed, losing hope in fight against illness.[81] **Sensitivity to change** FACT-G total score and subscale scores demonstrated very good sensitivity to change in ECOG PS and LASA QoL.[81] Statistically significant results for the overall scale ($P < 0.001$).[108]	
FACT-LEU[39,76]	FACT-G and 27 item Leu subscale. Total 44 Items	Trial data: USA (n = 79, AML (27), ALL(5), APML (3), CLL (25), CML (15), HCL (4))[39] Japanese HSCT patients (n = 36)[76]	**Content validity** Generally positive, confirming face and content validity. Item relevant, comprehensive and easy to understand. 10 Items eliminated from initial 54 items for being too generic.[39] **Convergent and divergent validity** High correlation with POMS-SF with FACT-G and Leu scale. Crowe Social desirability[39]	**Internal consistency** Cronbach's alpha >0.7 at all time points for all scales. 17 item Leu subscale in combined acute and chronic sample Alpha = 0.86 (T1), 0.88(T2), and 0.87(T3).[39] Cronbach's alpha >0.7[76] **Test-retest** ICC >0.7 for all scales at all times.[39]	**Responsiveness** Significantly different scores among three performance status change groups for FACT-leu subscale ($P < 0.001$)[39]	

(Continues)

TABLE 4 (Continued)

Instrument name	Subscales and total Items	Sample details	Validity	Reliability	Responsiveness and floor/ceiling effects	Minimal important difference and prognostication
FACT-AN[109-111]	FACT-G 27 items (4 domains) 13 Item Fatigue scale and 7 non-fatigue anaemia specific items. Total 47 Items.	Trial data: Canada, Australia and Europe (n = 303, 5.9% HL, 28.7% NHL, 16.5% CLL, 48.8% MM)[110] Trial data: Europe & Russia; (n = 349, 30.3% NHL, 36.1% CLL, 33.5% MM.[111] Trial data: USA, Europe (n = 85, 100% MPN)[109]	**Construct validity** Item scale correlation significantly lower for physical well-being and significantly higher for social well-being.[109] Improvement in Fatigue (P < 0.001) for all scales except social scale (P = 0.148)[110]	**Internal consistency** Cronbach's alpha ranged from 0.7 to 0.87 for all domains.[109]	**Floor/ceiling effects** No evidence of scale-level floor or ceiling effects.[109] **Responsiveness** Improved in score over time.[110,111]	Responders showed greater improvement in PWB across all visits compared with non-responders. The per cent of responders achieving clinically important differences increased from cycle 2(37.9%) to cycle 3 (44.8%) and remained >28% throughout the study. The per cent of non-responders meeting clinically important differences decreased from cycle 2 (37.5%) to cycle 3 (22.5%) and fell to <=7.5% thereafter.[109]
FACT-BMT[76,108,112,113]	FACT-G and 12 item bone marrow transplant subscale. Total 47 items.	Trial data: USA (n = 182, NHL (36%), HL (8%), CML (7%), AML (11%), ALL (2%), CLL (1%), MM (2%), MDS (0.5%).[108] USA HSCT patients (n = 94, 100% MM)[112] Spanish (n = 70, 5 AML, 1 ALL, 2 MDS, 27 NHL, 7 HD, 18 MM, 3 CLL and 1 amyloidosis)[113] Japanese HSCT patients (n = 36)[76]	**Construct validity** Correlation of FACT-BMT with individual scales ranged from 0.24 to 0.62. Correlation with Brief-POMS −0.57.[108] Total score SF-36 correlated with FACT-BMT (r > 0.4)[76] **Divergent validity** BMTS correlates highly with FACT-G physical (0.60) and functional well-being (0.60) and less with relationship with doctors subscale (0.24) and MOS social support survey (0.29)[108]	**Internal consistency** Cronbach's alpha 0.74-0.90 for two assessments.[112] Cronbach's alpha >0.7.[76] Cronbach's alpha for 12-items BMTS ranged from 0.52-0.60. 10 Item BMTS ranged from 0.54-0.63. Cronbach's alpha for total FACT-BMT (FACT-G + 10 items BMTS) ranged from 0.85 to 0.92.[108]	**Sensitivity to change** Statistically significant results for t10 item BMTS (P = 0.0183). For overall scale P < 0.0001[108] **Responsiveness** Physical well-being improved 1 y post-transplant.[113]	

TABLE 4 (Continued)

Instrument name	Subscales and total Items	Sample details	Validity	Reliability	Responsiveness and floor/ceiling effects	Minimal important difference and prognostication
FACT-LYM[80]	FACT-G 27 items and 22 Lymphoma subscale. Total 49 items	Trial data: USA (n = 84, NHL 100%)[80]	**Content validity** Items were content valid, relevant, comprehensive, and self-explanatory[80] **Convergent and divergent validity** Moderately high correlation with POMS total score (0.42–0.68), as with SF-36 MCS (r = 0.48, $P < 0.001$) and PCS (r = 0.62, $P < 0.001$). Correlation between FACT subscales and social desirability (MC-10 score) was zero. Highest coefficient (0.16) between social desirability and social family well-being[80]	**Internal consistency** All subscales and aggregated score showed high internal consistency. Cronbach's alpha >0.7 at all three times. The 15 items Lymp had alpha 0.79, 0.85 and 0.84 at Times 1, 2 and 3 resp.[80] **Test-retest reliability** ICC ranged for 0.61–0.87 for all subscales and overall ICC for FACT-Lym = 0.87.[80]	**Sensitivity to change** FACT-Lym differentiated patients in each of the three groups ($P < 0.001$).[80]	Distribution based MID between 0.33 and 0.50 SD ranges. This corresponds to 206-3.9 point for Lymp. SEM is 3.0. Anchor-based group differences and change scores ranged from 4.5-8.1. MID range for the Lymp is approx. 3%–5% or 5%–8% of the scale range (0-60).[80]
FACT-FATIGUE[114]	EORTC-QLQ-C30 with 30 items and 3 items for Fatigue scale. Total 33 items.[114]	Clinical trial patients with HM (n = 128, NHL (56), HL(37), & leukaemia (35)[114]	The FA scale correlated between 0.49 and 0.75 at all assessment points with both PF and MF scales of the FQ.[114] **Construct validity** A two-factor solution was found, explaining 64%-74% of variance.[114]		A ceiling effect indicating extreme scores of fatigue was observed for with fatigue scale as compared to FQ (10.9% versus 2.9%, PF in FQ), and a floor effect was observed in cancer survivor groups with fatigue scale as compared to FQ (24% vs 0%).[114] **Sensitivity to change** t-statistics of the pF scale (t = 2.33 versus 0.79) and the low t^2 ratio (0.11) indicating PF differentiates better between diagnosis tic groups than FA.[114]	
FACT-MM[99,115]	FACT-G with 27 items and additional 14 items for MM subscale.	Trial patients with MM (n = 13).[99]	**Construct validity** Significant correlation with FACT physical and functional well-being at baseline (r = 0.72), cycle 5 (r = 0.64) and end of treatment (r = 0.72)[115]	**Internal consistency** Cronbach's alpha ranged from 0.79 to 0.89[115]		

TABLE 4 (Continued)

Instrument name	Subscales and total Items	Sample details	Validity	Reliability	Responsiveness and floor/ceiling effects	Minimal important difference and prognostication
SF-36[74-79]	Eight Scales: mental health, physical functioning, role physical, role emotional, social functioning, bodily pain, general health perceptions and vitality. Total 36 items.	Netherlands (n = 50, 100% MDS)[74] UK HSCT patients (n = 58, leukaemia (32%), lymphoma (27.6%), myeloma (32.8%))[75] Japanese HSCT patients (n = 36)[76] USA HSCT patients (n = 17, 13 autologous BMT, 4 allogenic BMT)[77] Dutch (n = 120, 27.5% (AML, ALL, MD), 29.16%-(NHL, HL), 26% MM.[78] Canada (n = 231, 36% CML, 30% AML, 11% ALL, 4% NHL, 3% MM)[79]	**Construct validity** Lower mean scores of subjects from the Dutch general population of similar age and sex.[74] Lower mean scores compared to general population[75,78] **Criterion Validity** Total score SF-36 correlated with FACT-BMT (r > 0.4[76]	**Internal consistency** Cronbach's alpha ranged from 0.75 to 0.89 for all the scales.[74] Cronbach's alpha >0.7[76] **Test-retest reliability** ICC ranged from 0.62 to 0.95 for all scales.[79]	**Responsiveness** Statistical significant ($P < 0.05$) improvements for SF-36 physical functioning and physical role functioning subscales.[76] Statistically significant difference between the groups.[78]	
SF-12[116,117]	Physical functioning, mental health functioning Total 12 items.	USA HSCT patients (n = 213, 100% MM)[116] USA HSCT patients (n = 61, 100% MM)[117]	**Construct validity** Physical functioning and mental health functioning worse than general population for 53.45% and 22.41%.[117] Physical functioning, mental health, energy and pain worse than general population (59.4%, 28.3%, 80.7% and 57.6%), respectively.[116]			
EQ-5D[60,63]	Mobility, Self-care, usual activities, pain/discomfort, anxiety/depression. Total 5 items.	Trial data: Norway (n = 239, 100% MM)[60] Dutch (n = 12, 100% MM)[63]			**Floor/ceiling effects** Very small overall floor & ceiling effect[60] **Responsiveness** Most responsive SRM 0.43.[60] Changes for subscales over time.[63]	Change of score from 0.08 to −0.10 was important to patients.[60]

TABLE 4 (Continued)

Instrument name	Subscales and total Items	Sample details	Validity	Reliability	Responsiveness and floor/ceiling effects	Minimal important difference and prognostication
15D[60]	Breathing, mental function, communication, vision, mobility, usual activities, hearing, eating, eliminating, sleeping, distress, discomfort/symptoms, depression, vitality, and sexual activity. Total 15 items.	Trial data: Norway (n = 239, 100% MM)[60]			**Floor/ceiling effects** Very small overall floor & ceiling effect.[60] **Responsiveness** responsive with SRM 0.37[60]	Change of score from 0.03 to −0.02 was important to patients.[60]
QLI[57]	Two Parts: Part 1—satisfaction with life (33 items); and Part 2—Important issues to the patients (33 items)	Trial data: USA HSCT patients (n = 20 at baseline, n = 17 post-transplant[57]		**Internal consistency** Cronbach's alpha >0.7 in all domains.[57]		Change of 3.8 score reported as clinically important difference.[57]
QoL-E[40,118]	A general well-being dimension, four general health dimension (physical, functional, social and sexual), and disease-related dimensions (fatigue and MDS-related disturbances). Total 29 Items	Trial data: MDS patients (n = 147, from 6 clinical trials)[40] Trial data: MDS patients (n = 45)[118]	**Content validity** Developed by process involving physicians and patients **Concurrent validity** Statistically significant correlation with physical well-being, emotional well-being, functional well-being, overall, and treatment outcome index scores of FACT-G.[40] **Construct validity** Factor analysis showed many domains between the two instruments formed clusters.[40]	**Internal consistency** Cronbach's alpha >0.7 in all domains.[40]	**Floor/ceiling effects** No observed floor/ceiling effects.[40] **Responsiveness** Scores improved in erythroid responder.[40,118]	
POMS[69]	Total 65 Items	Trial data: German (n = 101, 100% AML)[69]			**Responsiveness** Significant lower depression (P = 0), fatigue (P = 0) and anger) P = 0) and vigour (P = 0).[69]	

(Continues)

TABLE 4 (Continued)

Instrument name	Subscales and total Items	Sample details	Validity	Reliability	Responsiveness and floor/ceiling effects	Minimal important difference and prognostication
MyPOS[45,46]	3 Subscales (i) symptoms and function (14 items covering physical symptoms and functional impairments); (ii) emotional response (eight items describing the emotional impact of the disease); and (iii) healthcare support (five items on information needs and satisfaction with health care)[46]	Trial data: UK (n = 124, 100% Follicular lymphoma)[46] Trial data: UK (n = 380, 100% MM)[45]	**Construct validity** Higher MyPOS symptoms and function scores in participating with poorer ECOG performance status ($F = 26.17$, $P < 0.000$)[46] High total scores in newly diagnosed and relapsed or progressive disease compared to those with stable disease ($F = 11.89$, $P < 0.001$); MyPOS total score higher in those receiving chemotherapy compared to those not on treatment ($t = 3.42$, $P = 0.001$)[45] **Structural validity** Bartlett's test of sphericity ($x^2 = 1525.0$, $P < 0.001$) and the MSA (0.848) indicated good factorability. Final model falls short of demonstrating good fit; $x^2/df = 2.385$, CFI = 0.774 and RMSEA = 0.109 (90% CI: 0.097-0.121).[46] **Convergent and divergent validity** MyPOS total score negatively correlated with EORTC-QLQ-C30 ($r = -0.723$, $P < 0.1$); negative correlation with EORTC-QLQ-C30 physical function ($r = -0.791$, $P < .01$), role function($r = -0.838$, $P < 0.01$), cognitive($r = -0.584$, $O < 0.01$) and Social function($r = -0.634$, $P < 0.01$)[46] MyPOS correlated to EORTC global scale negatively ($r = -0.70$, $P < 0.001$)[45]	**Internal consistency** Cronbach's alpha ranged from 0.70 to 0.95.[46] Cronbach's alpha = 0.89. All subscales had alpha in desired range (0.7-0.9) except Healthcare support (0.64)[45]	**Responsiveness** 10/27 items had 100% response rate. 17/27 it had missing data points with highest for item for sex.[45] **Floor/ceiling effects** Floor effects for all 27 items; proportions of answer in lowest category ranged from 23.4% to 91.9%. Ceiling effects were not present for any item.[46]	

TABLE 4 (Continued)

Instrument name	Subscales and total Items	Sample details	Validity	Reliability	Responsiveness and floor/ceiling effects	Minimal important difference and prognostication
SeiQoL-DW[53,65,119,120]	5 'cues' are nominated by respondents as important to their QoL.	Trial data: UK (n = 51, 47.1% NHL, 3.9% HL, 9.8% CLL, 25.5% AML, 3.9% ALL, 9.8% CML)[119] Trial data: German (n = 64, 100% MM)[120] Trial data: German (n = 79, 58.2% MM, and 25.3% NHL)[53] Trial data: Swedish (n = 22, 4.5% HL, 18% NHL, 27% AML, 54% MM)[65]	**Construct validity** Moderate correlation between SeiQoL and HAD score (Pearson's r = −0.48; P < 0.001).[119] Moderate relation between two parameters (r = 0.522).[120] Low correlation between SEIQoL and SEIQoL-VAS (0.42) but significant (P < 0.01).[53] **Criterion validity** SEIQoL-VAS weakly correlated to EORTC-QLQ-C30 subscales (role function r = 0.31; P < 0.01; emotional and social function 0.05 level)[53]		**Responsiveness** Significant change in scores over time.[65]	
POMS-SF[65,121]	Total 37 Items	USA patients awaiting BMT (n = 428, lymphoma (35%), AML (21%), CML (19%), HL (9%), ALL (8%).[65]	The convergent validity correlations between the POMS-depression and the POMS total mood disturbance scores and the CES-D = 0.63. The negative affect scale had positive correlation at 0.44.[65]	**Internal consistency** Cronbach's alpha ranged from 0.78 to 0.91 for all the scales.[65]		

of EORTC-QLQ-CML24.[82] No responsiveness, floor and ceiling effects have been reported. The validity results showed weak correlation between "satisfaction with care and information" and "social life" scales of QLQ-C30.[82] There was only one study identified for EORTC Leu scale, which was included as part of the EORTC GIMENA AML8A and MRC AML10 clinical trial.[83] Criterion validity, construct validity and MCID were not reported. For FACT-Leu, there were two studies which enrolled the US and Japanese leukaemia patients. The one conducted with the US patients included all type of leukaemia.[39]

3.4.4 | Instruments for MDS patients

Apart from generic instruments used in haematology (EORTC-QLQ-C30 and FACT-G), only one reliable and valid instrument has been identified for MDS patients, that is QoL-E. Most of the measurement properties of QoL-E have been reported by the authors except that of MCID.

3.4.5 | Generic instruments

The SF-36, SF-12, EQ-5D, 15D, LIP, QLI, SUNS, SF-SUNS, SeiQoL-DW, POMS and POMS-SF have been used in haematology as generic instruments. The highest evidence on measurement properties in haematological malignancy patients has been found for the SF-36. One study reported correlation between the SF-26 and FACT-BMT scale.[76] Two studies identified for the SF-12 had patients only with MM; however, no detailed information for reliability and validity has been reported. Only one study reporting floor/ceiling effect, responsiveness and MCID in MM patients was identified for the 15D instrument. No information was found on reliability and validity of 15D in patients with HMs. The QLI instrument had also one study reporting internal consistency and MCID. One study identified for LIP could not be included because of unavailability of the full paper.

4 | DISCUSSION

This systematic review has identified 24 studies using inductive method to identify HRQoL issues important to patients with different HMs and 30 HRQoL instruments with reported psychometric properties to varying robustness in 57 studies. The instrument which is most commonly used, with most extensive psychometric evaluation, is EORTC-QLQ-C30, although its validation across all types of haematological malignancies could not be established. The second most widely used instrument is FACT-G for which the literature did not support validation across all types of haematological malignancies. The current literature for other disease-specific instruments or disease-specific modules of EORTC & FACT-G does provide almost complete psychometric validation of the instrument in the respective target patient population. The evidence for the generic instruments such as EQ-5D and SF-36, which are mostly used for health economic studies, does not provide complete information on psychometric properties of these instruments in patients with different

HMs. The HRQoL issues identified through the literature as reported by patients should be considered as important QoL domain in understanding the impact of HM and its treatments on patients' daily life. Because there is no predefined sample size for qualitative research, it is of paramount importance to be able to capture all the issues important to these patients. Only 3 out of 24 studies reported sampling to redundancy, which raises the question of saturation point and content validity of the instruments which have been developed using the information from such qualitative research.

The findings of this systematic review also supported previous findings that the quality-of-life issues, the impact of disease & treatment and patients' needs are different for patients with HMs and STs,[18-30] and the identified instruments do not cover specific issues important to patients with HM, for example: worrying/uncertainty about future; eating and drinking habits; being burden to others; other people judging; travelling; going on holidays; difficulty leaving the house; appearance/body image; and sleeping patterns. It is a possibility that the results are also true for patients with other conditions; however, we cannot conclusively state this because it was not the objective of this SR and has not been studied. Whether or not this is true for other patients requires further systematic review for patients with other condition.

Further, our findings are in line with that of Osborne et al,[35] that all studies, except one (ie study conducted with Japanese patients), have recruited patients from the USA and Europe for validation of the instrument. Moreover, the vast majority of these validation studies were carried out with patients enrolled in clinical trials and all such instruments have been validated to be used in clinical trial, except MyPoS which has been specifically developed for use in daily clinical practice.

As reported by Greenhalgh (2009),[84] PROs in clinical practice can be used as "screening instruments, monitoring instruments, as a method of promoting patient-centred care, as a decision aid, as a communication facilitator, and means of monitoring the quality of patient care". It is, therefore, of utmost importance that all the issues important to the patients are raised. The structure of SEIQoL-DW, which asks a patient to list the five most important issues do come close to fulfil the requirements on a PRO to be used in clinical practice, but limits the issues to five cues and also requires special training for the clinic staff, as reported by Osborne et al.[35] Except SEIQoL-DW and MyPOS, no other instrument provides a blank space for patients to enter any specific HRQoL issues important to them, which is not covered in the instrument. As PROs in clinical practice can be used on an individual level for facilitating the communication between the clinician and the patient, this information is of utmost importance.

One of the main barriers for use of a PRO in daily clinical practice is the diversity of the PRO instruments. The 30 different PROs identified in this systematic review for use in patients with HMs can make it extremely difficult for the staff to implement them in daily clinical practice. This requires staff training and acquiring additional skills to implement different PROs for different HMs, assess, interpret the outcomes and utilise the information to inform patient consultation and to aid clinical decision-making.
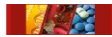
The WHO defines the primary objective of cancer diagnosis and treatment as cure, prolongation of life and improvement of quality of life.[85] Given the improved survival rate and living longer with a haematological malignancy, the use of PROs in daily clinical practice will certainly enhance the chances of addressing the HRQoL issues for such patients in the real-world situation. There is a lack of evidence in the literature for PROs validation in daily clinical practice. This systematic review has highlighted the complexity and the lack of appropriate PRO instrument for use in routine clinical practice despite the diversity of measures available. To address this, recently MyPOS has been developed for myeloma patients. This has further highlighted the need for development of a new HRQoL instrument entirely based on involvement of patients with haematological malignancies, as both research partners and study participants. Furthermore, this new instrument could be a "generic" HRQoL instrument to be used for patients with different haematological malignancies, that is "one size fits all," but this would warrant further discussion and debate involving all stakeholders.

4.1 | Recommendations for future research

The 30 HRQoL instrument identified in this systematic review and currently used in haematology are developed and validated with patients in controlled clinical trials, except MyPOS. In order to better incorporate the patient-reported outcome measures in daily clinical practice, the barrier of the lack of a standardised PRO instrument has to be overcome. The important HRQoL issues do differ for patients with different haematological malignancies; however, most domains such as physical well-being, social well-being, emotional well-being and functional well-being are common. First, there is a need of an intensive qualitative research across all haematological malignancies to understand all the issues important to HM patients with "sampling to redundancy" as one of the important criteria to meet during such research. Second, there is a need to develop a new HRQoL instrument as a composite measure. This instrument would be able to measure both impact on HRQoL and capture the signs and symptoms that HM patients are experiencing.

4.2 | Limitations

The limitations of this review include the following: focus on adult patients diagnosed with HM; and literature published in English language. The search string was developed to be as inclusive as possible. In addition, studies searched manually were also included; hence, the final list of included articles may vary slightly if carried out by a different researcher. Furthermore, the search did not include grey literature for additional studies such as letter to editors or dissertations. However, PRISMA systematic review guidelines were strictly followed at each step and should be considered as strength of this review.

AUTHOR CONTRIBUTIONS

PG was the first reviewer, designed the protocol, defined the search terms, carried out the literature search, screened the literature based on inclusion and exclusion criteria, designed the extraction table and extracted the data, made the tables and figures, performed quality scoring of the qualitative papers and wrote the first draft of the manuscript. YK was the second reviewer, defined the search terms, screened the literature on the basis of inclusion and exclusion criteria, carried out data extraction, performed quality scoring of the qualitative papers and reviewed the first draft of the manuscript. SS was the third reviewer, acted as the adjudicator to reach consensus, designed the protocol, supervised the work and reviewed the first draft of the manuscript.

CONFLICT OF INTEREST

The authors declare no competing financial interests.

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