Prognostic value of patient-reported outcomes from international randomised clinical trials on cancer: a systematic review

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A previous review published in 2008 highlighted the prognostic significance of baseline patient-reported outcomes (PROs) as independent predictors of the overall survival of patients with cancer in clinical studies. In response to the methodological limitations of studies included in the previous review, recommendations were subsequently published in the same year to promote a higher level of methodological rigour in studies of prognostic factors. Our systematic review aimed to provide an update on progress with the implementation of these recommendations and to assess whether the methodological quality of prognostic factor analyses has changed over time. Of the 44 studies published between 2006 and 2018 that were included in our review, more standardisation and rigour of the methods used for prognostic factor analysis was found compared with the previous review. 41 (93%) of the trials reported at least one PRO domain as independently prognostic. The most common significant prognostic factors reported were physical functioning (17 [39%] studies) and global health or quality of life (15 [34%] studies). These findings highlight the value of PROs as prognostic or stratification factors in research across most types of cancer.

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Introduction

Prognostic models for predicting the survival of patients with cancer typically use well established clinician-reported criteria, such as performance status, age, and tumour stage as the main factors of interest, which place little to no emphasis on patient-reported outcomes (PROs).[1,2] However, an increasing number of studies are showing that the incorporation of PROs in cancer care is crucial, as it allows for increased focus and more accurate information on issues that matter to patients.[3]

Over the last three decades, the importance of the patient perspective has been increasingly recognised. This recognition has led to more frequent assessment of PROs in clinical practice and in randomised controlled trials (RCTs) making these data more easily available for the building of prognostic models. The use of electronic-based PRO assessment methods has facilitated data collection and analysis by streamlining data management (ie, by reducing the risk of administrative error) and by minimising patient burden.[4] Computerised adaptive tests, which have higher precision than classic theory-based measures, are likely to continue to promote the use of PROs by providing more individualised results and because they require fewer patients.[5] A considerable body of evidence shows the growing importance of baseline PROs as independent prognostic factors for predicting overall survival in patients with cancer. A landmark systematic review by Gotay and colleagues,[6] which included 39 studies published between 1989 and 2006 involving 13 874 patients, found that baseline patient-reported physical functioning in 11 (28%) studies and global health status or quality of life (GHQ) in 15 (38%) studies independently predicted overall survival for most types of cancer.[6] The prognostic significance of physical functioning in addition to some clinical factors was supported by a subsequent meta-analysis of 10 108 patients.[7]

Despite previous studies supporting the added prognostic value of PROs, researchers and clinicians still face challenges in effectively combining clinical-based and survival-based endpoints with PROs. The use of PROs as prognostic factors in clinical practice is challenging when assessing patients routinely, as some clinicians might be reluctant to implement PROs due to fears of insufficient time or other operational challenges. In addition, the use of PROs as prognostic factors when identifying high-risk patients (ie, those who are at a high risk of experiencing severe symptoms and impaired functioning, or who might be at a high risk for disease progression) and selecting possible treatments[8] is also challenging. As a result, the systematic use of the patient perspective during the diagnostic and treatment process is undermined.[9] The integration of PROs in RCTs as stratification factors is also rare.

Considering the added prognostic value of PROs as predictors of overall survival in patients with cancer, and the difficulties in combining PROs with clinical factors as prognostic indicators in research and clinical settings, we aimed to provide an update on the previous review by Gotay and colleagues,[6] by reviewing and evaluating RCTs on patients with cancer published between 2006 and 2018 that assessed prognostic factors. Our review builds on the results by Gotay and colleagues[6] by examining the extent by which previously reported, and possibly new, PROs (eg, specific symptoms or multidimensional scales that have not been previously reported as prognostic) show prognostic value across different types of cancer. In response to the methodological inconsistencies in the analysis of the prognostic value of PROs between studies included in the review by Gotay and colleagues,[6] Mauer and colleagues[10] evaluated the methods used to determine the prognostic value of PROs in predicting the survival of patients with cancer. The outcomes of this evaluation led

Panel: **Methodological criteria used in the evaluation of prognostic factor analysis**

Sample size
The number of patients involved in randomised controlled trials should be sufficiently large to capture enough events and therefore provide reliable prognostic information. Given the implications for study precision and power, sample size should be explicitly reported in publications.

Missing data
Patient-reported outcomes (PROs) usually have missing data, which complicates the generalisability of PRO results to the whole trial population. Therefore, reporting which data are missing is essential. Additionally, as the type of missing data could affect PRO endpoints, the reasons why PRO data are missing should be reported. To reduce the negative effects of missing data on assessing the association between PROs and prognosis PROs, several guidelines and analysis strategies have been developed (eg, using data imputation techniques instead of deleting entire patient records).

A priori selection of PRO predictors
A priori selection of PRO predictors reduces the risk of selecting potential prognostic factors by chance, thereby reducing the risk for model overfitting and type I errors. Gaining a thorough knowledge of the subject by reviewing the medical literature, considering the preclinical data, and using clinical expertise should guide the a priori selection of predictors. The a priori selection of PRO predictors is especially important given the multidimensionality of PROs and health-related quality of life. Including a description of the PRO predictor selection process is important to ensure the reliability and generalisability of the results.

Interaction
Considering interactions between potential prognostic factors engenders additional analyses that could increase the risk of biased results and is therefore not advisable.

Type of variables
PRO scores can be categorical or continuous. Reporting of PRO scores as continuous data is preferred so that the maximum amount of information can be extracted. However, when reported PRO scores are categorical, it is advisable to define them a priori.

Prognostic model building strategy
The prognostic model chosen should aim to verify if the additional PROs facilitate more accurate prediction of the duration of overall patient survival compared with clinical factors alone. Multivariate Cox proportional hazards models are the main models used for this type of analysis. Different strategies can be used, such as selecting prognostic factors from a set of parameters with different methods (eg, forward, backward, or stepwise variable selection). Forced inclusion of clinical factors can also be used to reinforce the prognostic accuracy of the results by investigating the extent to which PRO factors add prognostic value.

Hypothesis
The formulation of a hypothesis is important to focus on a specific endpoint and minimise the risk of bias when analysing and interpreting the results.

Verification of model assumptions
Whether univariate or multivariate analyses are used, the model assumptions should be verified before formal analysis to ensure that the most appropriate method is used and the most reliable conclusions are drawn.

Quantifying predictive accuracy
Prognostic accuracy refers to the assessment of the prognostic value of PROs in addition to the clinical factors. PROs are only relevant as prognostic factors if they show a statistically and clinically significant effect on improving overall survival. Different measures are used for this assessment, including the discrimination concordance index, Schemper residuals, Nagelkerke's R^2 coefficient, the likelihood test, and partial least squares regression.

Model validation
Model validation provides a solution for model overfitting, as it helps to assess the degree to which multicollinearity might affect the analysis. Even though internal validation is often sufficient (ie, bootstrap sampling), the most accurate method for assessing model overfitting is external validation.

to the generation of recommendations aimed at improving the methodological quality of future prognostic factor research. Therefore, the second aim of our study was to assess the implementation of recommended analysis methods and to evaluate the methodological rigour of prognostic factor analysis in studies published since these recommendations were released.

Data collection

Search strategy and selection criteria

We did a systematic review of the medical literature according to the Cochrane methodology, as outlined in the Handbook for Systematic Reviews of Interventions,[11] and we adhered to PRISMA guidelines to ensure complete and transparent reporting.[12,13] We searched MEDLINE to identify RCTs involving patients with cancer published in English between Jan 1, 2006, and Dec 31, 2018. We used the search terms "cancer", "prognostic", and "quality of life"; other PRO-associated terms, "depression", "anxiety", "fatigue", "baseline pain"; and commonly used PRO instruments, "CES-D", "BDI", "QLQ-C30", "STAI", "RSCL", "PAIS", "HADS", "BPI", "MSAS", "pain assessment", "functional assessment", "FACT questionnaire", "FACT survey", "FLIC", and

"self-rated health". In addition to MEDLINE searches, we searched the references of selected papers and consulted experts in the field to help identify additional studies. All studies included in our analysis were prospective phase 2, phase 3, and phase 4 RCTs on cancer, had assessed at least one baseline PRO with single (eg, pain) or multidimensional outcomes (eg, GHQ), and had done at least one multivariate analysis to examine the association between baseline PROs and overall survival or mortality while controlling for factors associated with cancer or sociodemographic factors, or both. We excluded any RCTs that had evaluated psychological or supplementary interventions, and excluded all publications already included in the review by Gotay and colleagues[6] to avoid redundancy. Supplementary interventions were defined as any other treatment that did not include anticancer therapy and that were not purely psychological interventions (eg, nutritional counselling). Literature reviews and conference abstracts were also excluded. Although the review by Gotay and colleagues[6] included all types of prognostic factor studies, we restricted our review to include RCTs only, as these are recognised as the gold standard for clinical trials. To ensure that these high standards are met, RCTs have strong methodological and statistical rigour and use strategies to minimise bias and reduce confounding factors.

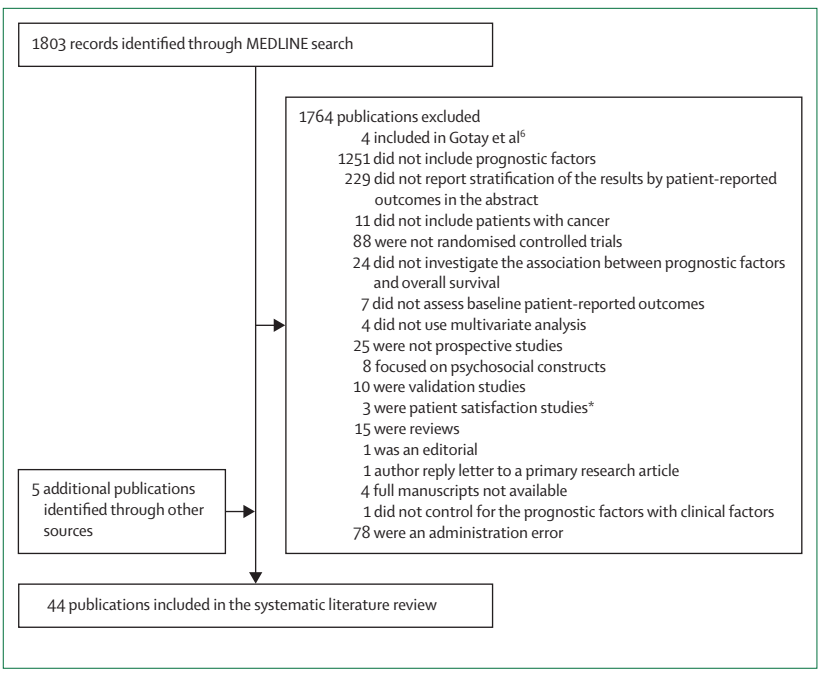

Figure: **Flowchart of studies included in the review**
*Includes studies assessing patient satisfaction to treatment and quality of care from health-care services and health-care professionals (or both).

Data extraction and quality assessment

Studies were divided into three groups. For each group, study characteristics and results were reviewed by two reviewers independently (JM and CP, MP, or FM). The same reviewers also critically assessed the methodologies used to identify prognostic factors in each article. Disagreements between reviewers were resolved through consulting a third person (CP, MP, or FM) to reach a consensus.

We evaluated the methodologies used to identify prognostic factors in included studies on the basis of the criteria outlined by Mauer and colleagues,[10] which included sample size, missing data, selection of predictors, model building, predictive accuracy, and model validation (panel). Two independent assessors (JM and CP, MP, or FM) evaluated whether included studies fulfilled these criteria, and the results were compared with the previous review[6] in a descriptive manner.

Findings

We identified 1803 publications from the systematic review of the literature, and 44 (2%) studies[1,14–56] met the criteria for inclusion in our analysis (figure).

The 44 studies included phase 2 or phase 3 RCTs summarising results from 28 281 patients across 13 different cancer types, and included nine (20%) studies on lung cancer, six (14%) on head and neck cancer, five (11%) on pancreatic cancer, five (11%) on ovarian cancer, three (7%) on colorectal cancer, three (7%) on prostate cancer, three (7%) on oesophageal cancer, three (7%) on brain cancer, two (4%) on liver cancer, two (4%) on breast cancer, one (2%) on gastric cancer, one (2%) on myeloma, and one (2%) on melanoma. 39 (89%) of 44 studies included patients with advanced or metastatic stages of disease. Sample sizes among the studies ranged from 63 patients to 1152 patients, and a total of 23 122 patients with cancer who completed PRO assessments were included in our review. The main PRO tools used to assess these patients were the European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30; 22 [50%] of 44 RCTs) and the Functional Assessment of Cancer Treatment questionnaire (13 [30%]). The main characteristics and prognostic factor results of the 44 studies included in the analysis are summarised in table 1.

Clinical factor assessment

All studies included in our review assessed various clinical factors in their analysis. Performance status was the most common clinical factor that was assessed (38 [86%] of 44 RCTs). 20 (45%) studies assessed treatment group, 15 (34%) assessed disease stage, 14 (32%) assessed serum markers, and ten (23%) assessed tumour size. 15 (39%) studies showed the prognostic significance of performance status. Of the 20 RCTs that evaluated treatment group as a prognostic factor, five (25%) showed prognostic significance. Ten (23%) of 44 RCTs did not report the prognostic significance of any clinical factors.

	Cancer type and stage (number of patients with quality of life data)	Trial phase	PRO instrument used	Controlled factors significantly associated with overall survival	Association of PROs with overall survival (HR [95% CI], p value)	Median survival (months)*
Lung cancer						
Bottomley et al (2007)[17]	Mixed stage advanced malignant pleural mesothelioma, (n=229)	3	QLQ-C30 and QLQ-LC13	Prognostic index	Pain (HR 1·177 [95% CI 1·112–1·246], p=0·01); appetite loss (HR 1·072 [95% CI 1·017–1·131], p=0·01)	10·1
Movsas et al (2009)[33]	Locally advanced, stage II, stage IIIA, and stage IIIB (n=217)	3	QLQ-C30 and QLQ-LC13	Karnofsky performance status	Physical functioning (HR 0·989 [95% CI 0·981–0·998], p=0·011); GHQ (patients with a GHQ score <66·7, HR 1·640 [95% CI 1·180–2·280], p=0·004); patients with a high baseline GHQ score of 10, HR 0·990 [95% CI 0·984–0·997], p=0·004); dyspnoea (HR 1·088 [95% CI 1·019–1·162], p=0·012)	NR
Kao et al (2013)[29]	Advanced mesothelioma (n=63)	2	LCSS	Histological subtype	Cough (HR 1·14 [95% CI 1·01–1·28], p=0·04); overall symptomatic distress (HR 1·13 [95% CI 1·00–1·27], p=0·04); interference with normal activity (physical functioning, HR 1·13 [95% CI 1·00–1·27], p=0·004); GHQ (HR 1·17 [95% CI 1·03–1·34], p=0·02); total LCSS score (HR 1·25 [95% CI 1·05–1·50], p=0·01)	9·5
Non-small-cell lung cancer						
Qi et al (2009)[55]	Advanced stage III or stage IV (n=572)	2–3	Single item Uniscale, LCSS, and FACT-Lung	Body-mass index (underweight *vs* normal)	Uniscale sample (GHQ; Uniscale sample median categorisation HR 1·63 [95% CI 1·29–2·06], p<0·0001; Uniscale clinically deficient score categorisation (HR 2·02 [95% CI 1·46–2·79], p<0·0001)	NR
Ediebah et al (2014)[50]	Advanced stage IIIB or stage IV (n=391)	3	QLQ-C30 and QLQ-LC13	Gender and WHO performance status	Physical functioning (HR 0·93 [95% CI 0·88–0·98], p=0·01); pain (HR 1·11 [95% CI 1·06–1·15], p<0·0001); dysphagia (HR 1·12 [95% CI 1·04–1·20], p=0·002)	NR
Spigel et al (2015)[41]	Stage IIIB or stage IV (n=850)	3	FACT-General, FACT-Lung, and FACT-Gynaecological oncology group-neurotoxicity	Disease stage, sex, and Eastern Cooperative Group performance status	FACT-General (GHQ, HR 0·66 [95% CI 0·56–0·77], p<0·001); FACT-Lung (HR 0·63 [95% CI 0·53–0·74], p<0·001); FACT-Lung-trial outcome index (HR 0·58 [95% CI 0·49–0·69], p<0·001); FACT-Neurotoxicity (HR 0·64 [95% CI 0·55–0·76], p<0·001); FACT-Neurotoxicity-trial outcome index (HR 0·60 [95% CI 0·51–0·70], p<0·001)	NR
Fiteni et al (2016)[25]	Advanced stage III or stage IV (n=361)	3	QLQ-C30	Treatment performance status, smoking status, histology, mini-mental state examination, and activities of daily living	GHQ (HR 0·986 [95% CI 0·980–0·992], p=0·001)	NR
Movsas et al (2016)[34]	Unresectable stage III (n=313)	3	FACT-Trial outcome index	Radiation level, planning target volume, and volume of heart receiving ≥5 Gy	FACT-Trial outcome index (GHQ, HR 0·901 [95% CI 0·813–0·998], p=0·046)	NR
Small-cell lung cancer						
Reck et al (2012)[38]	Extensive stage disease (n=NR)	3	FACT-General	NR	FACT-Physical wellbeing (physical functioning, HR 0·62 [95% CI NR], p<0·001); FACT-Functional wellbeing (HR 0·55 [95% CI NR], p<0·001); FACT-General (GHQ, HR 0·56 [95% CI NR], p<0·001)	NR
Head and neck cancer						
Coyne et al (2007)[19]	Advanced stage III or stage IV (n=1093)	3	FACT-General	Age, Karnofsky performance status, tumour classification, lymph node classification, cigarette smoking at protocol entry, income, and marital status	No significant associations	NR

(Table 1 continues on next page)

Main PRO factors

In 41 (93%) of 44 studies, at least one PRO domain was found to be significantly associated with overall survival after other clinical variables were controlled for. The most commonly reported independent prognostic factors were physical functioning (17 [39%] of 44 RCTs) in nine types of cancer, and baseline GHQ scores (15 [34%]) in eight types of cancer. The most frequently reported prognostic symptom associated with overall survival was pain (seven [16%]). Most studies reporting physical functioning (n=17) or GHQ scores (n=15) as prognostic factors involved patients with advanced or metastatic stages of disease (physical functioning, 16 [94%] of 17 RCTs; GHQ scores, 14 [93%] of 15 RCTs). However, concordance indices indicated that the addition of these PROs to other clinical factors only conferred a small

	Cancer type and stage (number of patients with quality of life data)	Trial phase	PRO instrument used	Controlled factors significantly associated with overall survival	Association of PROs with overall survival (HR [95% CI], p value)	Median survival (months)*
(Continued from previous page)						
Siddiqui et al (2008)[40]	Stage III and stage IV squamous cell carcinoma of the oral cavity, oropharynx, or supraglottic larynx, or stage II to stage IV carcinoma of the base of the tongue or hypopharynx, and stage III and IV squamous cell carcinoma of the glottic or supraglottic larynx (n=1093)	3	FACT-Head and neck cancer and FACT-General	Tumour stage, nodal stage, Karnofsky performance status, primary site, cigarette use, age, income, and marital status	No significant associations	NR
Meyer et al (2009)[53]	Stage I or stage II (n=540)	NR	QLQ-C30 and HNRQ	Cancer stage, cancer site, age as 1-year increments, smoking, alcohol, body-mass index, and trial arm assigned	Physical functioning (HR 0·87 [95% CI 0·81–0·94], p=0·00063)	NR
Urba et al (2012)[43]	Advanced recurrent or metastatic disease (n=704)	3	FACT-Head and neck cancer	Age, race, Eastern Cooperative Oncology Group performance status, and previous surgery or radiotherapy	Physical wellbeing (physical functioning, HR 0·93 [95% CI 0·88–0·98], p=0·009); subjective wellbeing (social or family wellbeing, HR 0·94 [95% CI 0·90–0·99], p=0·0014); additional concerns (head and neck cancer, HR 0·89 [95% CI 0·84–0·94], p<0·001)	8·2 in patients who scored above the median on the physical wellbeing subscale *vs* 5·2 in who did not
Truong et al (2016)[49]	Locally advanced, stage III to stage IV (n=818)	3	FACT-Head and neck cancer, perceived stress scale-head and neck cancer, and EQ-5D	NR	Palliative performance scale-head and neck cancer-diet (HR 0·875 [95% CI 0·832–0·919], p<0·001); perceived stress scale-head and neck cancer-eating (HR 0·805 [95% CI 0·705–0·919]; p=0·0013); FACT-General total (GHQ, HR 0·893 [95% CI 0·815–0·978], p=0·0152); FACT-Head and neck cancer (HR 0·892 [95% CI 0·834–0·955], p=0·0009); EQ-5D (GHQ, HR 0·875 [95% CI 0·812–0·942], p=0·0004)	NR
Xiao et al (2017)[48]	Locally advanced, stage III to stage IV (n=624–646 depending on the PRO measure)	3	Perceived stress scale-head and neck cancer, HNRQ, and SQLI	NR	Palliative performance scale-head and neck cancer-diet (HR 0·944 [95% CI 0·910–0·975], p=0·006); perceived stress scale-head and neck cancer-eating (HR 0·871 [95% CI 0·792–0·957], p=0·0041); HNRQ (HR 0·78 [95% CI 0·704–0·864], p<0·0001); SQLI (GHQ, HR 0·919 [95% CI 0·867–0·973], p=0·004); SQLI (GHQ, HR 0·919 [95% CI 0·867–0·973], p=0·004)	NR
Pancreatic cancer						
Bernhard et al (2010)[54]	Advanced (n=247)	3	LASA	Karnofsky performance status and tumour marker	Pain (HR 0·63 [95% CI 0·44–0·92], p=0·015); tiredness (HR 0·65 [95% CI 0·45–0·96], p=0·03)	NR
Romanus et al (2012)[39]	Advanced stage III, and stage IV (n=267))	3	EQ-5D	NR	EQ-5D (GHQ, HR 0·98 [95% CI 0·97–0·99], p=NR); visual analogue scale (HR 0·99 [95% CI 0·98–0·99], p=NR)	NR
Gourgou-Bourgade et al (2013)[26]	Metastatic disease (n=320)	2–3	QLQ-C30	Treatment arm, age, low serum albumin, and liver metastasis	Physical functioning (HR 0·91 [95% CI 0·84–0·99], p=0·04); dyspnea (HR 1·06 [95% CI 1·00–1·14], p=0·001); constipation (HR 1·06 [95% CI 1·01–1·11], p<0·001)	11·1 in patients who received FOLFIRINOX *vs* 6·8 in patients who received gemcitabine
Diouf et al (2016)[21]	Metastatic adenocarcinoma (n=59)	2	QLQ-C30	No significant associations	Role functioning (HR 0·980 [95% CI 0·966–0·993], p=0·0029); insomnia (HR 1·021 [95% CI 1·007–1·036], p=0·0028)	8·9

(Table 1 continues on next page)

	Cancer type and stage (number of patients with quality of life data)	Trial phase	PRO instrument used	Controlled factors significantly associated with overall survival	Association of PROs with overall survival (HR [95% CI], p value)	Median survival (months)*
(Continued from previous page)						
Vickers et al (2016)[23]	Locally advanced or metastatic disease (n=441)	3	QLQ-C30	Performance status, race, extent of disease, and treatment	Physical functioning (HR 0·86 [95% CI 0·80–0·93], p<0·0001)	NR
Ovarian cancer						
Carey et al (2008)[1]	Advanced stage IIB to stage IV (n=152)	3	QLQ-C30, and trial specific checklist	Performance status and treatment	Cognitive functioning (HR 0·89 [95% CI 0·81–0·98], p=0·01); GHQ (HR 0·92 [95% CI 0·86–0·99], p=0·03)	NR
Chase et al (2012)[45]	Advanced stage IVB, recurrent, or persistant cervical cancer with adenosquamous or adenocarcinoma histology (n=938)	3	FACT-Cervix and BPI-SF	NR	Physical wellbeing (physical functioning, HR 0·963 [95% CI 0·951–0·975], p<0·001)	NR
von Gruenigen et al (2012)[56]	Stage III (n=399)	3	FACT-General	NR	Physical wellbeing (physical functioning HR 0·80 [95% CI 0·68–0·93], p=0·005)	NR
Roncolato et al (2017)[47]	Platinum-resistant (n=462)	3	QLQ-C30 and QLQ-OV28	NR	Physical functioning (HR 0·98 [95% CI 0·98–0·99], p<0·001); abdominal or gastrointestinal symptoms (HR 1·01 [95% CI 1·01–1·02], p<0·001)	NR
Phippen et al (2017)[37]	Advanced epithelial stage III or stage IV (n=1152)	3	FACT-Ovarian trial outcome index	Increasing age, Gynecological Oncology Group performance status 2, and residual disease of >1 cm	FACT-Trial outcome index (GHQ, HR 0·963 [95% CI 0·939–0·987], p=0·003)	NR
Colorectal cancer						
Efficace et al (2008)[24]	Metastatic disease (n=443)	3	QLQ-C30	White blood cell, alkaline phosphatase, number of metastatic sites	Social funtioning (HR 0·940 [95% CI 0·905–0·976], p=0·001)	19·5
Diouf et al (2014)[20]	Metastatic disease (n=249)	3	EQ-5D	Performance status, number of metastatic sites, serum lactate dehydrogenase	Mobility (physical functioning, HR 1·66 [95% CI 1·12–2·48], p=0·0117)	18·6
Mol et al (2016)[32]	Advanced disease (n=1254)	3	QLQ-C30	Normal *vs* elevated serum lactate dehydrogenase levels, number of metastatic sites, and resection primary tumour	Good *vs* poor physical functioning, study 1 (HR 0·57 [95% CI 0·46–0·72], p<0·0001), and study 2 (HR 0·68 [95% CI 0·55–0·84], p=0·046)	NR
Prostate cancer						
Halabi et al (2008)[27]	Metastatic, castration-refractory, stage II (n=599)	3	BPI	Performance status (2 *vs* 0), Gleason sum presence of visceral disease, previous radiotherapy treatment, opioid analgesic use, age, alkaline phosphatase levels, number of years since diagnosis, prostate-specific antigen levels, and lactate dehydrogenase levels	Pain interference (HR 1·43 [95% CI 1·17–1·74], p<0·001)	NR
Bahl et al (2013)[14]	Metastatic, castration-resistant (n=342)	3	McGill-Melzack pain questionnaire and analgesic scoring method	Rising prostate specific antigen at baseline, treatment, time from previous docetaxel dose to randomisation in the trial, time (years) from first hormone treatment to enrolment in the trial, and baseline alkaline phosphatase levels	Pain (OR 0·482 [95% CI 0·268–0·867], p=0·0149)	13·7
Beer et al (2017; trial 1)[52]	Metastatic castration-resistant (n=NR)	3	FACT-Prostate	NR	FACT-Prostate total (HR 0·88 [95% CI 0·84–0·93], p=NR); FACT-General total (GHQ, HR 0·90 [95% CI 0·87–0·95], p=NR); FAPSI (HR 0·94 [95% CI 0·90–0·97], p=NR); trial outcome index (HR 0·83, [95% CI 0·78–0·88], p=NR); functional wellbeing (HR 0·90 [95% CI 0·84–0·96], p=NR); social wellbeing (social or family wellbeing, HR 1·11 [95% CI 1·05–1·19], p=NR)	NR

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	Cancer type and stage (number of patients with quality of life data)	Trial phase	PRO instrument used	Controlled factors significantly associated with overall survival	Association of PROs with overall survival (HR [95% CI], p value)	Median survival (months)*
(Continued from previous page)						
Beer et al (2017; trial 2)[52]	Metastatic castration-resistant (n=NR)	3	FACT-Prostate	NR	Physical wellbeing (physical functioning, HR 0·85 [95% CI 0·77–0·93], p=NR); emotional wellbeing (emotional functioning, HR 1·17 [95% CI 1·08–1·26], p=NR); prostate cancer subscale score (HR 0·89 [95% CI 0·84–0·94], p=NR); prostate cancer subscale pain-related (pain, HR 0·88 [95% CI 0·83–0·94], p=NR); FAPSI (HR 0·88 [95% CI 0·84–0·91], p=NR); FACT-Prostate trial outcome index (HR 0·82 [95% CI 0·72–0·79], p=NR); FACT-General total (HR 0·94 [95% CI 0·89–0·98], p=NR); FACT-Prostate total (HR 0·90 [95% CI 0·86–0·95], p=NR)	NR
Oesophageal cancer						
Bergquist et al (2007)[15]	Advanced disease (n=96)	NR	QLQ-C30 and QLQ-OES18	Metastatic stage	Fatigue (HR 1·10 [95% CI 1·02–1·19], p=0·016); reflux (HR 1·10 [95% CI 1·00–1·22], p=0·04)	91 days
van Heijl et al (2010)[28]	Potentially curable (n=187)	NR	MOS SF-20 and an adapted version of RSCL	Tumour length and tumour stage	Physical symptoms (HR 0·668 [95% CI 0·470–0·942], p=0·021)	NR
Bascoul-Mollevi et al (2017)[46]	Inoperable, stage I to stage IVA (n=239)	2–3	QLQ-C30 and QLQ-OES18	Tumour stage at diagnosis	No significant associations	NR
Liver cancer						
Bonnetain et al (2008)[16]	Advanced hepatocellular carcinoma (n=489)	3	SQLI	Jaundice, hepatomegaly, hepatalgia, ascites, portal vein thrombosis, total bilirubin, α-fetoprotein, albumin, and small hepatocellular carcinoma	SQLI (HR 0·84 [95% CI 0·79–0·90], p=0·0001)	5·3
Diouf et al (2013)[22]	Palliative (n=215)	3	QLQ-C30	α-fetoprotein, total bilirubin, albumin, vein thrombosis, distant metastasis, hepatomegaly, oedema, and ascites	Physical functioning (HR 2·00 [95% CI 1·32–3·04], p=0·0012); role functioning (HR NR [95% CI NR], p=NR)	6·8
Brain cancer						
Mauer et al (2007)[30]	Newly diagnosed, histologically confirmed anaplastic oligodendroglioma (n=247)	3	QLQ-C30 and QLQ-BN20	Age, performance status (0 *vs* 2), tumour location, and necrosis	Emotional functioning (HR 1·217 [95% CI 1·077–1·374], p=0·0016); communication deficit (HR 0·92 [95% CI 0·855–0·990], p=0·0261); future uncertainty (HR 1·110 [95% CI 1·001–1·232], p=0·048); weakness of legs (HR 1·137 [95% CI 1·064–1·215], p=0·0001)	40·3 in patients receiving radiation therapy plus procarbazine, lomustine, and vincristine *vs* 30·6 in patients receiving radiotherapy alone
Mauer et al (2007)[31]	Newly diagnosed glioblastoma (n=490)	3	QLQ-C30 and QLQ-BN20	Age, tumour resection (biopsy *vs* total), mini-mental state examination, and corticosteroids at entry to the trial	Cognitive functioning (HR 0·918 [95% CI 0·878–0·959], p=0·0001); social functioning (HR 1·090 [95% CI 1·046–1·137], p<0·0001); GHQ (HR 0·929 [95% CI 0·882–0·979], p=0·0055)	NR
Paquette et al (2016)[51]	Unresectable glioblastoma, stage IV (n=102)	2	QLQ-C30 and QLQ-BN20	Sensitivity deficit	Future uncertainty (HR 1·011 [95% CI 1·004–1·019], p=0·004)	NR
Breast cancer						
Smyth et al (2016)[35]	Advanced disease (RSCL, n=336; BPI, n=286)	3	BPI-SF and RSCL	NR	Worst pain (HR 1·05 [95% CI 1·00–1·10, p=0·0342); activity level (physical functioning, HR 0·89 [95% CI 0·83–0·95], p=0·0004)	NR
Svensson et al (2012)[42]	Locally advanced or distant metastatic disease (n=252)	3	QLQ-C30	NR	Fatigue (HR 1·09 [95% CI 1·01–1·18], p=0·003)	NR

(Table 1 continues on next page)

	Cancer type and stage (number of patients with quality of life data)	Trial phase	PRO instrument used	Controlled factors significantly associated with overall survival	Association of PROs with overall survival (HR [95% CI], p value)	Median survival (months)*
(Continued from previous page)						
Multiple myeloma						
Viala et al (2007)[44]	Relapsed, refractory (n=NR)	2	QLQ-C30, QLQ-MY24, FACIT-Fatigue scale, and FACT-Gynecologic Oncology Group-neurotoxicity scale	Karnofsky performance status and platelet count	Physical functioning (OR 1·06 [95% CI NR], p=0·0042); fatigue (OR 0·981 [95% CI NR], p=0·0394)	17·0
Gastric cancer						
Park et al (2008)[36]	Advanced disease (n=164)	2	QLQ-C30	Bone metastasis, haemoglobin level, and age	Social functioning (HR 0·36 [95% CI 0·21–0·62], p<0·001)	9·5
Melanoma						
Brandberg et al (2013)[18]	High-risk, stage III (n=785)	3	QLQ-C30	Age, tumour stage, and node stage	Role functioning (HR 0·94 [95% CI 0·90–0·99], p=0·001)	NR

PRO=patient-reported outcome. HR=hazard ratio. QLQ-C30=Quality of Life Core Questionnaire. QLQ-LC13=Quality of Life Questionnaire-Lung cancer module. QLQ-OV28=Quality of Life Questionnaire-Ovarian cancer module. GHQ=Global health status or quality-of-life score. NR=not reported. LCSS=Lung Cancer System Score. FACT=Functional Assessment of Cancer Treatment. EQ-5D=EuroQol-5 dimensions. HNRQ=Head and Neck Radiotherapy Questionnaire. SQLI=Spitzer Quality of Life Index. LASA=Linear Analog Scale Assessment. BPI-SF=Brief Pain Inventory-short form. FAPSI=FACT Advanced Prostate Symptom Index. QLQ-OES18=Quality of Life Questionnaire-Oesophageal cancer module. MOS SF-20=Medical Outcomes Study-Short Form General Health Survey. RSCL=Rotterdam Symptom Checklist. QLQ-BN20=Quality of Life Questionnaire-Brain cancer module. QLQ-MY24=Quality of Life Questionnaire-Myeloma module. FACIT=Functional Assessment of Chronic Illness Therapy. OR=odds ratio. *Unless otherwise stated.

Table 1: **Study characteristics, measures, and results for the prognostic significance of included studies**

	Number of studies (randomised controlled trials) included in the present review (n=44)	Number of studies included in Gotay et al[6] (n=39)	Number of randomised controlled trials included in Gotay et al[6] (n=29)
Physical functioning	17 (39%)	11 (28%)	8 (28%)
Global health status or quality of life	15 (34%)	15 (38%)	13 (45%)
Pain	7 (16%)	7 (18%)	6 (21%)
Social functioning	5 (11%)	4 (10%)	3 (10%)
Fatigue	4 (9%)	6 (15%)	1 (3%)
Role functioning	3 (7%)	6 (15%)	5 (17%)
Emotional functioning	2 (5%)	5 (13%)	2 (7%)
Cognitive functioning	2 (5%)	1 (3%)	1 (3%)
Dyspnoea	2 (5%)	1 (3%)	1 (3%)
Appetite loss	1 (2%)	10 (26%)	7 (24%)
Constipation	1 (2%)	2 (5%)	2 (7%)
Dysphagia	1 (2%)	1 (3%)	1 (3%)
Insomnia	1 (2%)	1 (3%)	1 (3%)

Only overlapping patient-reported outcomes identified in the current review and the review by Gotay et al[6] are reported.

Table 2: **Prognostic patient-reported outcome domains identified in the present review and in the review by Gotay et al[6]**

See Online for appendix

improvement in prognostic power for predicting overall survival in patients (appendix pp 1–3). The prognostic significance of physical functioning was mainly reported by use of the EORTC QLQ-C30 (nine [53%] of 17 RCTs) or Functional Assessment of Cancer Treatment questionnaire (five [29%] of 17 RCTs) tools. All PRO domains identified as prognostic factors for overall survival are listed in table 2. Similarities in terms of which PROs were identified as prognostic were found in studies involving patients with specific types of cancer, such as lung cancer (nine [20%] of 44 RCTs), ovarian cancer (five [11%]), and prostate cancer (three [7%]). In patients with lung cancer, physical functioning and GHQ scores were identified as separate prognostic factors (ie, either physical functioning or GHQ scores were found to be prognostic in studies of lung cancer; physical functioning, four [44%] of nine RCTs; GHQ scores, seven [78%] of nine RCTs). Physical functioning was found to be a prognostic factor in three (60%) of five studies involving patients with ovarian cancer, and GHQ scores were prognostic in two (40%) of five studies on patients with ovarian cancer. All three RCTs involving patients with prostate cancer reported pain as a prognostic factor. However, even though similar prognostic PROs were identified for specific cancer types, the same PROs were not always found to be prognostic in all studies of the same cancer type, and some studies showed unexpected results. In one study involving patients with brain cancer,[30] reduced social functioning was significantly associated with longer overall survival, whereas lower emotional functioning and more communication deficits were significantly associated to longer survival in another study on patients with brain cancer.[31]

Only three (7%) of 44 studies did not identify an association between PROs and overall survival. Of these, two studies[19,40] included patients with advanced head and neck cancer, and one study[46] involved patients with stage I–IV oesophageal cancer.

Methodological evaluation

None of the 44 studies included in our analysis followed all the recommendations proposed by Mauer and colleagues;[10] however, all studies fulfilled at least three

of the 20 subcriteria (table 3). Most studies satisfied sample size requirements (41 [93%] of 44 studies) and model building strategy requirements (42 [95%]) by use of Cox proportional hazards models. Other subcriteria, such as reporting of patient characteristics using a valid PRO assessment method (29 [66%]), a priori selection of PRO predictors (24 [54%]), and univariate analysis reporting (30 [70%]) were commonly met. However, some subcriteria were not systematically reported. Descriptions of missing data were not reported in five (11%) studies, the a priori definition of a hypothesis was not reported in five (11%) studies, the verification of assumptions in the prognostic models was not reported in nine (20%) studies, and the use of external validation was not reported in two (4%) studies. Also, despite the importance of quantifying the predictive accuracy of the prognostic factor results, only 14 (32%) studies reported results for this measurement. Among these 14 studies, 11 (78%) reported some improvements in the predictive accuracy of PROs in addition to clinical factors (appendix pp 1–3). Moreover, although reporting of continuous variables has been recommended,[10] categorical variables were reported in 14 (32%) of 44 studies, and nine (64%) studies used predefined categories (appendix pp 1–3). Assessing interactions between potential prognostic factors was discouraged by Mauer and colleagues.[10] Consistent with this recommendation, most studies (38 [86%]) included in our analysis did not report assessing interactions between potential prognostic factors. Table 3 compares the number of studies in our review that fulfilled the recommendations and subcriteria outlined by Mauer and colleagues.[10] A list of the 44 studies included in our analysis with full details of the methodological assessments is shown in the appendix (pp 1–3).

	Number of studies in the present review (n=44)	Number of studies in the Mauer et al[10] review (n=49)
Sample size		
Included number of patients who reported baseline PROs	41 (93%)	NR
Missing data		
Reported reasons for missing PRO assessments at baseline	5 (11%)	5 (10%)
Included information on baseline characteristics for patients with PROs	29 (66%)	27 (55%)
Included information on the survival of patients with PROs	13 (30%)	9 (18%)
Reported the exact numbers of available data for each separate PRO score	15 (34%)	14 (29%)
A priori selection of predicted prognostic PROs		
Selected potential prognostic PROs a priori guided by knowledge of the subject matter*	24 (55%)	22 (45%)
Interaction		
Reported absence of interactions between potential prognostic factors in the final model	38 (86%)	46 (94%)
Type of variables		
Dichotomised PRO scores at a cutoff point (median included)	14 (32%)	27 (55%)
Selected the cutoff point a priori (median included)	9 (20%)	NR
Provided continuous summary statistics on PRO scores	37 (84%)	27 (55%)
Model building strategy		
Used Cox proportional hazards model for multivariate analysis	42 (95%)	43 (88%)
Used univariate screening to preselect PRO scores or clinical factors (or both) for consideration in the final multivariate model	31 (70%)	16 (33%)
Forced inclusion of preselected clinical factors to enter the multivariate model	12 (27%)	21 (43%)
Hypothesis		
Specified an a priori hypothesis	5 (11%)	NR
Verification of model assumptions		
Used an appropriate method to check the assumption in a Cox proportional hazards model†	9 (20%)	16 (33%)
Quantifying predictive accuracy of PROs on prognosis		
Used suitable methods to determine the predictive accuracy of PROs in univariate or multivariate analyses‡	14 (32%)	7 (14%)
Assessed improvements in the predictive accuracy as a result of adding PROs as potential prognostic factors in the model	11 (25%)	NR
Model validation		
Did internal model validation (eg, bootstrap resampling)	16 (36%)	9 (18%)
Did external model validation	1 (2%)	NR
Validated the model in an external study	1 (2%)	NR

Data are n (%). PRO=patient-reported outcome. NR=not reported. *Subject matter refers to literature reviews and clinical expertise. †Appropriate methods include the Schoenfeld residuals or log–log transformation to the survival function. ‡Suitable methods include Harrell's C discrimination index, Schemper-Henderson Predictive Measure, Nagelkerke R^2, the likelihood-ratio test, and partial least squares regression.

Table 3: **Randomised controlled trials that fulfilled specific methodological and statistical criteria for assessment of PROs**

Discussion

The aim of our review was to provide an update on the review by Gotay and colleagues,[6] in terms of which PROs are prognostic and whether new prognostic PROs have been identified, and to critically review the methodological approaches used to assess the prognostic significance of PROs in RCTs largely published since the recommendations by Mauer and colleagues[10] were released. To achieve these aims, we systematically appraised the prognostic factor results from 44 RCTs on patients with cancer that were published since the review by Gotay and colleagues.[6] The prognostic factor results of the studies analysed in our review were similar in many regards to those reported in the review by Gotay and colleagues.[6] First, the majority of studies showing an association between PROs and overall survival in patients with cancer included in both reviews involved patients with cancer at an advanced stage or patients with metastatic disease (39 [89%] of 44 RCTs in our review *vs* 24 [62%] of 39 clinical trials in Gotay and colleagues[6]). Second, several studies included in both reviews involved patients with lung cancer (nine [20%] of 44 RCTs *vs* 12 [31%] of 39 clinical studies). Third, the majority of studies included in both reviews were phase 3 RCTs (33 [75%] of 44 RCTs *vs* 29 [74%] of 39 clinical studies). Finally, the EORTC QLQ-C30[57] was used to assess PROs in a similar proportion of patients in both studies (22 [50%] of 44 RCTs *vs* 22 [56%] of 39 clinical studies). This questionnaire is one of the most common tools

used for assessing the subjective wellbeing of patients with cancer in the medical literature.[58–61]

In our review, we first examined the extent to which previously reported PROs and new PROs showed prognostic value in patients with cancer. Most of the RCTs included in our review and in Gotay and colleagues[6] reported at least one PRO domain as a predictor of overall survival (41 [93%] of 44 RCTs in our review *vs* 36 [92%] of 39 clinical studies in the previous review[6]). The most commonly reported independent prognostic PRO factors were physical functioning (17 [39%] of 44 RCTs in our review *vs* 11 [28%] of 39 clinical studies in the previous review[6]) and GHQ scores (16 [36%] of 44 RCTs *vs* 15 [39%] of 39 clinical studies). However, when considering the prognostic value of clinical factors, these PROs had limited added prognostic value. Physical functioning and GHQ scores were prognostic factors mainly in patients with advanced stage cancer, which is consistent with the high number of studies included in our review that targeted these stages only. Other PRO domains (eg, pain) were prognostic of overall survival in seven (16%) of 44 RCTs included in our review.

Additional evidence also supports the prognostic significance of specific PROs in predicting overall survival of patients with cancer, such as physical functioning and GHQ scores. Previous studies[62–66] and a meta-analysis[7] of 10 108 cancer patients have shown a significant association between physical functioning and patient survival. Additionally, previous studies[65,67–70] have shown that global quality of life is also significantly associated with the overall survival of patients with different types of cancer, which highlights the prognostic value of this PRO domain. These results suggest that prognosis and, by extension, the prediction of prognosis, could be slightly improved by integrating physical functioning and global quality of life into prognostic models of patients with cancer. These findings also highlight the importance of evaluating PROs when providing information about the prognosis of patients with cancer in both clinical and research settings.

Despite the considerable overlap in the results between the review by Gotay and colleagues, which analysed clinical studies published between 1989 and 2006, and our review, which included RCTs published between 2006 and 2018, there were some key differences. Although both reviews identified three studies that did not identify any significant prognostic PRO domains, all of these studies in the previous review[6] involved patients with early-stage breast cancer. As such, the authors suggested that PROs might only be significant prognostic factors for patients with advanced disease stages.[6] The three studies that did not find evidence for the prognostic value of PROs analysed in our review included patients with advanced stages of head and neck cancer[19,40] and patients with stage I–IV oesophageal cancer.[46] This observation indicates that an advanced stage of disease might not be the only factor that affects the prognostic significance of PROs. The authors of these studies[40,46] hypothesised that methodological issues, such as missing data, might account for the lack of added prognostic value of PROs, and they suggested that more rigorously designed trials might clarify this issue. Furthermore, one of these studies[19] assessed the prognostic significance of emotional functioning only, which is a substantial limitation given that there is little evidence to suggest that emotional functioning is a prognostic factor for predicting overall survival in patients with cancer.

Another difference between our review and the review by Gotay and colleagues[6] is the PRO domains that were identified as prognostic factors for overall survival in patients with cancer. Although physical functioning and global quality of life were identified as prognostic factors in both reviews, other PRO domains were less consistently reported between the two reviews. This could be explained by differences in the methods used to identify prognostic factors between different studies, in terms of the PRO instruments used and the type of clinical data collected. Indeed, some of the studies assessed multidimensional aspects of patient quality of life, whereas others had a greater focus on specific symptoms. Additionally, differences in scoring methods for the same tools across different studies might exist (eg, a ten-point underlying scale *vs* a 100-point underlying scale). These factors, combined with the different types of cancer investigated, could account for some of the differences between our review and the previous review.[6] The type of symptoms reported in studies on cancer are trial-dependent and linked to the treatment under investigation; therefore, it is not surprising that they are less often prognostic. By contrast, physical functioning and general quality of life are relevant across a wide array of treatment modalities and disease sites. Pain was found to be the most frequently reported prognostic symptom across the studies included in our review, which reflects the association of this symptom with many different disease sites and treatments.[71] In some clinical contexts, pain might be a symptom of advanced disease and infiltrative tumour growth.[72] It is also possible that patient-reported symptoms, such as pain, could be more sensitive during specific disease stages than medical imaging results (ie, pain could be indicative of disease progression even before such growth could be detected by medical imaging). This might account for the added prognostic value of pain in specific circumstances.

More stringent inclusion criteria were applied in our review than the review by Gotay and colleagues,[6] which might also account for the observed differences between the reviews. For example, only RCTs were included in our review. Since RCTs minimise potential bias and confounding factors, this type of clinical study provides a more robust context for evaluating the prognostic significance in PROs. Nevertheless, RCTs present some

limitations that should be considered. For instance, the low number of publications included in our review that involved patients with early-stage disease, means that it is difficult to draw conclusions about the stage-dependent prognostic significance of PROs. Additionally, many studies reported a significant association between PROs and overall survival, which could reflect publication bias.

The second aim of our review was to evaluate the methodologies used to assess the prognostic value of PROs in the studies included in our analysis. The results showed that none of the studies followed all of the recommendations by Mauer and colleagues,[10] and only nine (20%) of 44 studies implemented over half of the criteria. However, at least three of the recommended subcriteria were fulfilled in all studies, and most of the key methodological issues were improved relative to the review by Mauer and colleagues.[10] Several criteria, such as forced inclusion of clinical factors in the model building strategy and verification of the Cox proportional hazards assumption, were reported less frequently by the studies included in our review. Although assessment of the methodologies used in the 44 studies included in our review showed that the evaluation of potential prognostic factors among studies is improving compared with the study by Mauer and colleagues,[10] the implementation of methodologies is still not standardised or systematically reported. For instance, 42 (95%) of the 44 studies reported hazard ratios whereas, two (5%) studies reported odds ratios. Additionally, two (5%) studies did not report confidence intervals, which are needed for accurate interpretation of the results. This inconsistent reporting complicates comparisons between trials and the interpretation of the prognostic findings, which means that it is difficult to draw strong conclusions and accurately assess the magnitude of effects.

The absence of rigour and standardisation remains a common challenge in PRO studies in cancer trials,[73] particularly as clinical relevance is often not addressed. The reporting and interpretation of prognostic findings in our review and the review by Gotay and colleagues[6] were mainly based on statistically significant findings without clearly predefining what would be considered as clinically relevant. It is difficult to assess the magnitude of an effect when several different model-fitting techniques are used, and information on model-building strategies is omitted. Comparison of clinical and PRO factors is further complicated by the fact that both outcomes have different underlying measurement properties. Although an increase or decrease of one point could be significant when scoring performance status, what effect the equivalent degree of change in patient-reported physical functioning is not clear. Differences such as these, combined with the different instruments used to assess PROs between studies, mean that it is difficult to draw strong conclusions about how the strength of association between PROs and overall survival compares with that of clinical factors. Therefore, it appears that recommendations, such as those proposed by Mauer and colleagues,[10] might not be sufficient to improve the quality of reporting. However, it is important to note that some of the studies included in our review were done or analysed before the recommendations were published. In addition, it is possible that some of the authors of studies published since the recommendations were released might not have been aware of their existence.

Taking the results of our review and the review by Gotay and colleagues[6] into account, 83 studies published within the last 30 years have provided evidence for the prognostic significance of PROs, particularly physical functioning and global quality of life. These findings suggest that physical functioning and global quality of life should be integrated into clinical cancer research and care, given that they could provide additional prognostic information. In daily clinical practice, this information could be used when communicating with patients, by allowing them to provide a more comprehensive and personal description of their symptoms and functioning. This information could also help inform decisions regarding treatment choices.[9] In a research setting, PROs could be used as stratification factors to complement other clinical factors in RCTs for which survival is a primary endpoint. Such stratification could help to provide a more accurate interpretation of study outcomes in future clinical trials.[23] In addition, prognostic PROs could be included as an endpoint in RCTs, particularly those PROs that have been identified as prognostic factors. In palliative research, information on the prognostic value of PROs could be especially important, given the need to minimise unwanted symptoms and side-effects in patient populations who are particularly at risk.

The results showing the prognostic significance of physical functioning and global quality of life are promising and suggest that these PROs could be eligible candidates for stratification factors in future clinical studies. However, the statistical evidence for the increased predictive accuracy of PROs is scarce, and assessing the magnitude of effects remains complex. Therefore, more quantitative work is required to better understand how and in which clinical settings PROs should be used as stratification factors. Such quantitative work would extend beyond descriptive reporting in reviews and would require patient-level data, as shown in a previously published meta-analysis.[74] This would facilitate the creation of categories of PRO scores to promote accurate statistical and clinical interpretation. A meta-analysis generating standardised thresholds would represent a major step forward for patient risk assessments. In addition, a higher degree of transparency and standardisation in prognostic factor studies is needed, to more accurately compare the results between studies and summarise the key findings. Having more carefully defined clinical groups and contexts would also help to establish in which specific settings (ie, in which types of

cancer and treatment settings) PROs are independent prognostic factors. Such specification could also help to clarify when more specific symptoms (eg, pain) are prognostic. Future prognostic studies should also report both the statistical and clinical significance of PROs to better capture the magnitude of effects, which would allow for a more precise estimate of the prognostic value of PROs than reporting either the statistical or clinical significance of PROs alone.

Conclusion

The current research climate is moving towards greater standardisation of the reporting and analysis methods of PROs in all phases of research, with various initiatives such as the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT-PRO),[75] Consolidated Standards of Reporting Trials -Patient-Reported Outcomes Statement (CONSORT-PRO)[76] Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints Data (SISAQOL) Consortium,[77] and the guidelines for systematic review and meta-analysis of prognostic factor research by Riley and colleagues[78] in 2019. Having more standardised and widely disseminated prognostic factor analysis guidelines will allow for more rigorous evaluation of the prognostic importance of PROs for the overall survival of patients with cancer, thereby facilitating their use in both research and clinical practice.

Contributors

JM, CP, MP, CG, CC, MM, and AB conceptualised the design of the study. JM did the systematic literature review, with CP, MP, and FM as second reviewers who helped with data collection. JM, CP, and MP took the lead in drafting the manuscript. CG, FM, CC, MM, MG, KB, AE, GV, and AB assisted with data interpretation and writing. JR contributed to the writing of the manuscript. All authors provided detailed feedback, reviewed the manuscript, and approved the final draft of the manuscript.

Declaration of interests

AB and MM were coauthors involved in two trial publications included in the current systematic literature review. CC was a coauthor of several publications included in the current systematic literature review. AE reports personal fees from Actelion, Agenus, Bayer, Boerigher, Bristol-Myers Squibb, GlaxoSmithKline, HalioDx, IO Biotech, ISA Pharmaceuticals, MedImmune, Merck, Merck Sharp & Dohme, Nektar, Novartis, Pfizer, Polynoma, Sanofi, SkylineDx, and equity from SkylineDx, RiverD, and Theranovir during the conduct of the study; AE also reports personal fees from Bristol-Myers Squibb, GlaxoSmithKline, IO Biotech, ISA Pharmaceuticals, MedImmune, Merck Sharp & Dohme, Novartis, Pfizer, Polynoma, Sanofi, SkylineDx, and equity from SkylineDx, RiverD, and Theranovis outside of the submitted work. GV reports personal fees from Roche, Eisai, Genentech, and Novartis, and reports grants from the National Institute for Health Research (UK), Breast Cancer NOW, and the European Organization for Research and Treatment of Cancer, all outside of the submitted work. The remaining authors have no competing interests to declare.

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