Prognostic value of patient-reported outcomes from international randomised clinical trials on cancer

a systematic review

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Published in:
Lancet Oncology

DOI:
10.1016/S1470-2045(19)30656-4

Publication date:
2019

Document version
Peer reviewed version

An evaluation of the prognostic value of patient-reported outcomes from international cancer randomized clinical trials

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Keywords

Patient-Reported Outcomes, Prognostic Factor, Systematic Review, Randomized Controlled Trials, Statistical Methodology, Methodological Evaluation

Funding

Funding towards this work was made from a contribution from the EORTC Cancer Research Fund to support the fellowship of Justyna Mierzynska.

SUMMARY

A previous review highlighted the independent prognostic significance of baseline patient-reported outcomes (PROs) for overall survival (OS) in cancer randomized controlled trials (RCTs). In response to methodological limitations of studies included, recommendations were published in order to promote higher methodological rigour in prognostic factor studies. Our systematic review aimed to provide an update and 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 this review, more standardization and rigour were found. Most trials reported at least one PROs domain as independently prognostic. The most common factors reported were physical functioning (PF) (39%; 17/44) and global health/QoL (GHQ) (36%; 16/44). These findings highlight their value as prognostic or stratification factors in research across the majority of cancer types.

BACKGROUND

Historically, prognostic models for survival in cancer have employed well-established clinician-reported criteria, such as performance status (PS), age, and tumour stage as the main factors of interest, placing little to no emphasis on patient-reported outcomes (PROs) (1,2). A growing body of work, however, shows 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 course of the past three decades, the importance of the patient perspective has been increasingly recognized. That has led to more frequent assessment of PROs in clinical practice as well as in randomized controlled trials (RCTs) making these data more easily available for prognostic model building. There is also evidence demonstrating the growing importance of baseline PROs as independent prognostic factors for overall survival (OS). A landmark systematic review by Gotay et al. (4) including 39 publications published between 1989 and 2006 and involving 13,874 patients, found that baseline patient-reported physical functioning (PF) (28%; 11/39) and global health status/quality of life (QoL) (GHQ) (38; 15/39) independently predicted OS in the majority of cancer types (4). The additional prognostic significance of PF was supported by a meta-analysis of 10,108 patients (5).

Despite these data supporting the added prognostic value of PROs, researchers and clinicians still face challenges to complement clinical and survival based endpoints with PROs. Their use as prognostic factors in clinical practice is limited when it comes to daily assessment, detection of high risk patients and decision-making (6), undermining the systematic use of the patient perspective during the diagnostic process (7). Their integration in RCTs as stratification factors is also rare.

Hence, this review aimed to update Gotay et al.'s (4) review and focused on prognostic factor publications from 2006 to 2018. The review builds upon its results by examining the extent to which previously reported and possibly new PROs show prognostic value across different cancer types. In response to the methodological inconsistencies in studies included in Gotay et al.'s (4) review, an evaluation of prognostic factor analysis and methods was undertaken by Mauer et al. (8). This evaluation led to the creation of recommendations aimed at improving the methodological quality of future prognostic factor studies. Therefore, the second aim of our study was to assess the implementation of analysis methods and to evaluate the methodological rigour of prognostic factor analysis in recent studies.

Data collection

Search strategy and selection criteria

A systematic literature review was conducted following the general Cochrane methodology as noted in the Handbook for Systematic Reviews of Interventions (9), and adhering to PRISMA guidelines ensuring transparent and complete reporting (10,11).

MEDLINE searches were undertaken with the aim of gathering studies on cancer RCTs published in English between 2006 and 2018. The key words used were "cancer", "prognostic", and "quality of life". Other PRO related terms were also specified: "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, reference searches of selected papers were undertaken and experts in the field were consulted to help identify additional studies. All studies selected included prospective phase II, III or IV cancer RCTs; at least one PRO baseline assessment using single (e.g., pain) or multidimensional outcomes (e.g., GHQ); and at least one multivariable analysis examining the relationship between baseline PROs and OS/mortality, while controlling for cancer-related and/or sociodemographic factors. Our exclusion criteria omitted any RCTs that evaluated psychological or supplementary interventions and all publications already included in Gotay et al.'s review, to avoid redundancy (4). Supplementary treatments were defined as any other interventions that did not include anti-cancer therapy and were not purely psychological interventions (e.g., nutritional counselling). Literature reviews and conference abstracts were also excluded. Whereas Gotay et al. (4) included all types of prognostic factor studies, we restricted our review to RCTs only, recognized as the gold standard due to their increased methodological as well as statistical rigour and minimization of bias and confounding factors.

All study characteristics and results were reviewed by two independent reviewers (JM and CP, MP or FM) who also critically assessed the prognostic factor analysis of each paper. In case of disagreements, a third person was consulted to reach a consensus (CP, MP or FM).

The methodological evaluation focused on the criteria suggested by Mauer et al. (8) and included sample size, missing data, selection of predictors, model building, predictive accuracy and model validation. The fulfilment of these criteria was assessed by two independent assessors and compared to the prior review in a descriptive manner. All criteria are detailed inTables 1 and 4.

INSERT TABLE 1

Findings

Study characteristics:

The search identified 1,803 publications. Forty-four studies met all inclusion criteria for review (Figure 1).

INSERT FIGURE 1

This review includes findings from phase II or III RCTs summarizing results from 28,281 patients across 13 cancer types, including lung (20%; 9/44), head and neck (14%; 6/44), pancreatic (11%; 5/44), ovarian (11%; 5/44), colorectal (7%; 3/44), prostate (7%; 3/44), esophageal (7%; 3/44), brain (7%; 3/44), liver (4%; 2/44), breast (4%; 2/44), gastric (2%; 1/44), myeloma (2%; 1/44) and melanoma (2%; 1/44). Most studies targeted advanced or metastatic stages of the disease (75%; 33/44). Sample sizes ranged from 63 to 1,152 patients, and 23,122 cancer patients who completed PROs assessments were included in total. The main PRO tools used to assess these patients were the EORTC Quality of Life Core Questionnaire (QLQ-C30) (50%; 22/44) and the Functional Assessment of Cancer Treatment (FACT) questionnaire (37%; 16/44). The main study characteristics and prognostic factor results are summarized in Table 2 (1,12-54).

INSERT TABLE 2

Clinical factor assessment:

All the studies reported controlling for various clinical factors. PS was the most commonly used clinical factor (86%; 38/44). Treatment arm (45%; 20/44), disease stage (34%; 15/44), serum markers (32%; 14/44) and tumor size (23%; 10/44) were also used. Several studies confirmed the prognostic significance of PS (39%; 15/38) and treatment arm (50%; 10/20). Some publications (25%; 11/44) failed to report the prognostic value of any clinical factors.

Main PRO factors:

In the majority of studies (93%; 41/44), at least one PRO domain was significantly associated with OS ($p < .05$) after controlling for other clinical variables. The most commonly reported independent prognostic factors were PF (39%; 17/44) and GHQ (36%; 16/44), in nine and eight cancer types, respectively, and the most frequently reported prognostic symptom was pain (16%; 7/44). The majority of the studies that reported PF (71%; 12/17) and GHQ as prognostic factors (75%; 12/16) involved patients with advanced or metastatic stages of disease. However, the C-indices indicated only a small prognostic improvement when adding these PROs to the other clinical factors (see p. 19). The prognostic significance of PF was mainly reported using the EORTC QLQ-C30 (53%; 9/17), or FACT tools (29%; 5/17). Similarly, GHQ was found to be prognostic for OS in 31% (5/16) of the papers. All identified PRO domains found to be prognostic are listed in Table 3. Some similarities in prognostic significance were found in studies involving specific cancer types such as lung (20%; 9/44), ovarian (11%; 5/44) and prostate (7%; 3/44). In lung, PF (44%; 4/9) and GHQ (67%; 6/9) were prognostic, mainly separately. Both of these domains were also prognostic factors in ovarian cancer (60%; 3/5). All three papers including prostate cancer patients reported pain as a prognostic factor. However, such trends were not found in all studies and some presented surprising results. In one brain

study, lower social functioning (28) was associated with longer survival while in another brain study, lower emotional functioning and more communication deficits were related to longer survival (29).

Only three studies (7%; 3/44) found no relationship between PROs and OS. Of these, two involved advanced head & neck cancer patients (17,38) and one included esophageal cancer patients in stages I-IV (44).

INSERT TABLE 3

Methodological evaluation:

None of the studies followed all of the recommendations proposed by Mauer et al. (8), yet all fulfilled at least three out of 20 subcriteria. The vast majority of the studies satisfied two requirements: sample size (93%; 41/44) and model building strategy through use of Cox Proportional Hazards (PH) models (95%; 42/44). Other subcriteria such as reporting of patient characteristics with valid PRO assessment (66%; 29/44), a priori selection of PRO predictors (54%; 24/44) and univariate analyses reporting were commonly met. However, some subcriteria were not systematically reported. The description of missing data (11%; 5/44), the a priori definition of a hypothesis (11%; 5/44), the verification of assumptions in the models (20%; 9/44) and the use of external validation (4%; 2/44) were generally limited. Also, despite the importance of quantifying predictive accuracy, only 32% of papers (14/44) reported this measurement. Among these papers, 78% (11/14) reported limited improvement of the predictive accuracy. Moreover, while the use of continuous variables was recommended (8), categorical variables were regularly used (32%; 14/44), often with predefined categories (64%; 9/14). The use of interactions was discouraged by Mauer et al. (8) and most publications did not report including them in their analyses (86.4%; 38/44). Table 4 summarizes the results of the methodological evaluation of the current review (8). A list of the 44 included studies with the full methodological assessment is provided in the appendices (p. 19).

INSERT TABLE 4

DISCUSSION

The aim of this study was to update the review by Gotay et al. (4) and provide a critical analysis of the methodology reported in the papers included, based on work by Mauer et al. (8). For this purpose, we systematically appraised prognostic factor results from cancer RCTs (n= 44) published since the prior review. Prognostic factor results from cancer RCTs (n= 44) were compared and found to be similar in many regards with those reported in the review by Gotay et al. (4) (current review vs. Gotay et al.'s review): most studies were based on advanced or metastatic cancer patients (77%; 34/44 vs. 61.5%; 24/39), most frequently involving lung cancer patients (20.4%; 9/44 vs. 30.8%; 12/39). Studies were mainly phase III RCTs (75%; 33/44 vs. 74%; 29/39) and assessed PROs in most patients (n= 23,122 vs. n= 13,874) using the EORTC QLQ-C30 (50%; 22/44 vs. 56%; 22/39) (55). This instrument has been reported as one of the most widely-used tools to assess cancer patients' subjective well-being in the literature (56–59).

First, we examined the extent to which previously reported and new PROs showed prognostic value. The findings from both reviews showed that the majority of RCTs (93.2%; 41/44 vs. 92.3%; 36/39) reported at least one PRO domain which was prognostic of OS. The most commonly reported independent prognostic factors were PF (38.6%; 17/44 vs. 28.2%; 11/39) and GHQ (36.4%; 16/44 vs. 38.5%; 15/39) with, however, limited added value. These domains were prognostic mainly in advanced stages of the disease, which is consistent with the high number of studies targeting these stages only. Other PRO domains such as pain were found to be prognostic of OS in seven studies.

Additional evidence also supports the prognostic significance of specific PROs such as PF and GHQ. A relationship between PF and survival time has been shown in a number of studies (60–64) and in a meta-analysis of 10,108 cancer patients (5). GHQ has also been associated with OS in different cancer types, highlighting its prognostic value (63,65–68). These associations suggest that prognosis and, by extension, its prediction could be slightly improved by integrating PF and GHQ into prognostic models. This evidence also supports the importance of evaluating PROs when providing information regarding cancer patients' prognoses.

Despite the considerable overlap in findings between Gotay et al.'s review (1989-2006) (4) and the current results (2006-2018), there were some differences that merit discussion. Although both reviews identified three studies which did not find any prognostic PRO domains, in Gotay et al.'s review (4), all of these studies involved early breast cancer patients, which led the authors to suggest that prognostic factors might be more relevant for advanced disease stages. In the current review, the studies (17,38,44) that did not find evidence of prognostic value for PROs involved head and neck cancer patients in an advanced stage of the disease (17,38) and esophageal cancer patients in stages I-IV (44). This indicates that an advanced disease setting alone may not be a sufficient condition for finding prognostic significance of PROs. The authors of these studies hypothesized that methodological issues such as missing data could help to account for the lack of added prognostic value (38,44), suggesting that this may be better demonstrated in more rigorously designed trials. Furthermore, one of these publications assessed the prognostic value of emotional functioning only, which is a significant limitation, given little evidence to suggest that emotional functioning is a prognostic factor for OS.

A further difference between the findings in both reviews concerns the PRO domains which were found to be prognostic of OS. Although PF and GHQ remained the most common prognostic factors in both reviews, other PRO domains were less consistently reported. This may be explained by the variety of methods used to conduct the prognostic studies in terms of PRO instruments and clinical data collection. Indeed, some of these assessed multidimensional aspects of QoL while others were more focused on specific symptoms. Moreover, between these tools, the level of difference in scores may be captured using different approaches (e.g., a 10-point versus a 100-point underlying scale). These factors, combined with the different cancer types investigated, may help to account for some of the differences between both reviews. Insofar as symptoms are very trial-dependent, linked to the treatment under investigation, it is not surprising that they are less often prognostic. In contrast, PF and GHQ are relevant across a wide array of treatment modalities and disease sites. Pain was the most frequently reported prognostic symptom, which reflects its association with many different disease sites and treatments (69). In some clinical contexts, pain may be an underlying sign of more advanced disease and infiltrative growth (70), and it is possible that such patient-reported symptom information could be more sensitive during specific stages than what might be observed in a medical imaging scan, for instance. This may account for the added prognostic value of pain, in particular.

The more stringent inclusion criteria applied in the current review, which included RCTs only, may also account for differences between reviews. Since RCTs minimize potential bias and confounding factors, they provide a more robust context for the identification of prognostic significance in PROs. However, the trials nevertheless present some limitations which should be considered. For example, the low number of publications including patients in earlier disease stages makes it difficult to draw conclusions about stage-dependent prognostic significance. Moreover, although a large number of studies reported significant findings, this may reflect publication bias.

Our second aim, to undertake a methodological evaluation of the studies reviewed, showed that none of the studies followed Mauer et al.'s (8) recommendations completely and only 20.4% (9/44) implemented at least half of the criteria. However, at least three subcriteria were fulfilled per study and most of the key methodological issues were improved relative to the Mauer et al. (8) review. Several criteria, such as forced inclusion of clinical factors in the model building strategy and verification of the PH assumption, were reported less frequently in our review. Although the methodological evaluation performed in our review showed that prognostic factor analyses are improving, their implementation is still neither standardized nor systematically reported. For example, whereas most of the studies reported hazard ratios, two of them reported odds ratios. Also, some studies failed to report confidence intervals, which are needed for accurate interpretation. This inconsistent reporting complicates comparison between trials and interpretation of the prognostic findings, making it hard to draw strong conclusions and accurately assess the magnitude of effects.

This lack of rigour and standardization remains a common challenge (71) particularly insofar as clinical relevance is often not addressed. The reporting and interpretation of prognostic findings in both reviews was mainly based on statisticaly significant findings without clearly pre-defining what would be considered as clinically relevant. It is difficult to assess the magnitude of effect when so many different model-fitting techniques are used and information on model-building strategies is ommitted. The comparison of clinical versus PRO factors is further complicated by

the fact that both outcomes have different underlying measurement properties. While an increase or decrese of one point may be significant for PS, what is the equivalent level of change in patient-reported PF? These sorts of differences, combined with the different instruments used to assess PROs between studies, make it harder to draw concrete conslusions concerning the strengh of association for PROs versus clinical factors. It seems, therefore, that recommendations such as those proposed by Mauer et al. (8) are not sufficient to improve the quality of reporting. This may also be due, in part to limited visibility of Mauer et al.'s recommendations (8) combined with the fact that some of the studies included were conducted or analyzed before its publication.

Taken together, 83 studies from the past 30 years have provided evidence for prognostic significance of PROs, and specifically PF and GHQ. This suggests that these PROs should be integrated into clinical cancer research and care, given the additional prognostic information they provide. In daily practice, this information could be used when communicating with patients, to provide a more comprehensive and patient-centric description of their symptoms and functioning, and to help inform decisions regarding treatment choices (7). In terms of research, PROs could be included as stratification factors to complement other clinical factors in RCTs in which survival is a primary endpoint, PROs are included as an endpoint, and where relevant PROs have been identified as prognostic factors. Such stratification may help provide a more accurate interpretation of studies' outcomes in future clinical trials (21). In palliative research, information on the prognostic value of PROs may be especially important, given the need to minimize unwanted symptoms and side effects in an especially at-risk population.

Despite the promising findings confirming the prognostic significance of PH and GHQ, which suggests that these PROs may be the most eligible candidates for stratification, the limited statistical evidence for the increased predictive accuracy of PROs as well as the complexity surrounding the assessment of magnitude of effects, suggests that more quantitative work is required to better understand how and in which clinical settings PROs should be used for stratification. Such quantitative work would extend beyond descriptive reporting in reviews and would require patient-level data, as demonstrated in previously published meta-analyses (72). This would facilitate the creation of categories of PRO scores to promote accurate statistical and clinical interpretation. A meta-analysis generating standardized thresholds would represent a major step forward for patient risk-assessment. Moreover, a higher level of transparency and standardization in prognostic factor studies is needed, in order to more accurately compare and summarize results. Having more carefully defined clinical groups and contexts would also help to determine in which specific settings PROs are independently prognostic. Such specification could help to clarify when, for example, more specific symptoms (e.g., pain) are prognostic. Future prognostic studies should also report both statistical and clinical significance in order to better capture the magnitude of effects, which would allow for a more precise estimate of prognostic value.

The current research climate is moving towards greater standardization in all phases of PRO research, with various initiatives such as the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT-PRO) (73), CONsolidated Standards of Reporting Trials-Patient-Reported Outcomes Statement (CONSORT-PRO) (74), Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints Data (SISAQOL) Consortium (75), and the recent guidelines for systematic review and meta-analysis of prognostic factor research by Riley and colleagues (76). Having more standardized and widely disseminated

prognostic factor analysis guidelines would allow for more rigorous evaluation of the prognostic importance of PROs for OS, thereby facilitating their use in both research and practice.

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APPENDICES

INSERT TABLE A1

Contributors

JM, CP, MP, CG, CC, MM and AB conceptualized the design of the study. JM carried out the systematic literature review with CP, MP and FM as second reviewers helping with the collection of the data.JM, CP, MP, CG, FM, CC, MM, MG, KB, AE, GV and ABJM took the lead in drafting the manuscript. All authors provided critical feedback, reviewed the manuscript and approved the final draft of the manuscript.

Declaration of interests

AB and MM report being co-authors involved in two trial publications included in the systematic literature review. CC report being involved as co-authors in several publications included in the systematic literature review. EA reports personal fees from Actelion, Agenus, Bayer, Boerigher GmbH,BMS, GSK, HalioDx, IO Biotech, ISA Pharmaceuticals, MedImmune, Merck GmbH, MSD, Nektar, Novartis, Pfizer, Polynoma,Sanofi, SkylineDx, other from SkylineDx, RiverD, Theranovir, during the conduct of the study; personal fees from BMS, GSK, IO Biotech, ISA Pharmaceuticals, MedImmune, MSD, Novartis, Pfizer, Polynoma,Sanofi, SkylineDx, other from SkylineDx, RiverD, Theranovis, outside the submitted work. GV reports personal fees from Roche, personal fees from EISAI, personal fees from Genentech, personal fees from Novartis, grants from NIHR UK Government, grants from Breast Cancer NOW, grants from EORTC, outside the submitted work. The authors declared no conflicts of interest.

This study was not NIH funded.