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Complete List of Authors:	Riva, Silvia; St Mary's University; University Hospital of Milan Arenare, Laura Di Maio, Massimo; Università degli Studi di Torino, Dipartimento di Oncologia, AO Ordine Mauriziano Efficace, Fabio; Italian Group for Adult Hematologic Diseases (GIMEMA) Montesarchio, Vincenzo; AORN Ospedali dei Colli, Oncologia Frontini, Luciano; Federation of Italian Cooperative Oncology Groups (FICOG) Giannarelli, Diana; Istituto Nazionale per lo Studio e la Cura dei Tumori Regina Elena, IRCCS, Unità di Biostatistica Bryce, Jane; Istituto Nazionale Tumori IRCCS Fondazione Pascale, Unità Sperimentazioni Cliniche Del Campo, Laura; Federazione italiana delle Associazioni di Volontariato in Oncologia (FAVO) De Lorenzo, Francesco; Associazione Italiana Malati di Cancro (AIMAC); European Cancer Patient Coalition (ECPC) Iannelli, Elisabetta; F.A.V.O. Italian Federation of Volunteer-Based Cancer Organizations Traclò, Francesca; Associazione Italiana Malati di Cancro (AIMAC) Gitto, Lara; Università degli Studi di Messina, Dipartimento di Economia Jommi, Claudio; Università Bocconi Vaccaro, Concetta Maria; Censis - Centro Studi Investimenti Sociali, Area Welfare e Salute Barberio, Daniela; Istituto Nazionale Tumori IRCCS Fondazione Pascale, Struttura Semplice Dipartimentale di Psiconcologia Clinica Cinieri, Saverio; Ospedale Perrino, Oncologia Porta, Camillo; Fondazione IRCCS Policlinico San Matteo Del Mastro, Lucia; Ospedale Policlinico San Martino Istituto di Ricovero e Cura a Carattere Scientifico per l'Oncologia, Dipartimento di Medicina Interna e Medicina Specialistica; Università di Genova, Dipartimento di Medicina Interna e Medicina Specialistica Zagonel, Vittorina; Istituto Oncologico Veneto Istituto di Ricovero e Cura a Carattere Scientifico Cogoni, Alessio Aligi; AOU di Sassari, Unità operativa complessa di Oncologia Medica Bordonaro, Roberto; Azienda Ospedaliera di Rilievo Nazionale e di Alta Specializzazione Garibaldi Ospedale Garibaldi-Nesima, Oncologia Gimigliano, Anna; Istituto Nazionale Tumori IRCCS Fondazione Pascale, Clinical Trials Unit

	Piccirillo, Maria Carmela; Istituto Nazionale Tumori IRCCS Fondazione Pascale, Clinical Trials Unit Guizzaro, Lorenzo; Università degli Studi della Campania Luigi Vanvitelli Gallo, Ciro; Università degli Studi della Campania Luigi Vanvitelli, Statistica Medica Perrone, Francesco; Istituto Nazionale Tumori IRCCS Fondazione Pascale, Clinical Trials Unit
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Development of PROFFIT, a patient-reported instrument for measuring financial toxicity of cancer within a public healthcare system

Silvia Riva[1,2], Laura Arenare[3], Massimo Di Maio[4], Fabio Efficace[5], Vincenzo Montesarchio[6], Luciano Frontini[7], Diana Giannarelli[8], Jane Bryce[3,9,10], Laura Del Campo[11], Francesco De Lorenzo[12], Elisabetta Iannelli[13], Francesca Traclò[13], Lara Gitto[14], Claudio Jommi[15], Concetta Maria Vaccaro[16], Daniela Barberio[17], Saverio Cinieri[18], Camillo Porta[19a], Lucia Del Mastro[20,21], Vittorina Zagonel[22], Alessio Aligi Cogoni[23], Roberto Bordonaro[24], Anna Gimigliano[3], Maria Carmela Piccirillo[3], Lorenzo Guizzaro[25], Ciro Gallo[25*], Francesco Perrone[3*]

[1] St Mary's University, Twickenham, London, UK
[2] Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, University Hospital of Milan, Italy
[3] Unità Sperimentazioni Cliniche, Istituto Nazionale per lo Studio e la Cura dei Tumori, IRCCS, Fondazione G.Pascale, Napoli, Italy
[4] Dipartimento di Oncologia, Università di Torino, AO Ordine Mauriziano, Torino, Italy
[5] Gruppo Italiano per le Malattie Ematologiche dell'Adulto (GIMEMA) Health Outcomes Research Unit, Roma, Italy
[6] Azienda Ospedaliera Specialistica dei Colli, Napoli, Italy
[7] Federation of Italian Cooperative Oncology Groups (FICOG), Milano, Italy
[8] Unità di Biostatistica, Istituto Nazionale per lo Studio e la Cura dei Tumori Regina Elena, IRCCS, Roma, Italy
[9] Dipartimento di Biomedicina e Prevenzione, Università degli Studi di Roma "Tor Vergata", Roma, Italy
[10] Ascension St. John Clinical Research Institute, Tulsa, USA
[11] Federazione italiana delle Associazioni di Volontariato in Oncologia (FAVO), Rome, Italy
[12] European Cancer Patient Coalition (ECPC), Brussels, Belgium
[13] Associazione Italiana Malati di Cancro (AIMAC), Roma, Italy
[14] Dipartimento di Economia, Università degli Studi di Messina, Italy
[15] CERGAS (Centre for Health and Social Care Management), SDA Bocconi School of Management, Milano, Italy
[16] Area Welfare e Salute, Centro Studi Investimenti Sociali (CENSIS), Roma, Italy
[17] Struttura Semplice Dipartimentale di Psiconcologia Clinica, Istituto Nazionale per lo Studio e la Cura dei Tumori, IRCCS, Fondazione G.Pascale, Napoli, Italy
[18] Unità Operativa Complessa di Oncologia Medica, Ospedale Perrino, Brindisi, Italy
[19] Struttura Complessa di Oncologia Medica, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy
[20] UO Breast Unit, IRCCS Ospedale Policlinico San Martino, Genova, Italy
[21] Dipartimento di Medicina Interna e Medicina Specialistica (DIMI), Università di Genova, Italy
[22] U.O.C. Oncologia 1, Istituto Oncologico Veneto, IOV, IRCCS Padova, Italy
[23] Unità operativa complessa di Oncologia Medica - AOU di Sassari, Italy
[24] Struttura Complessa di Oncologia Medica, ARNAS Garibaldi-Nesima, Catania, Italy
[25] Statistica Medica, Università degli Studi della Campania "Luigi Vanvitelli", Napoli, Italy.

* co-last authors
[a] present address: Dipartimento di Scienze Biomediche ed Oncologia Umana, Università degli Studi di Bari 'A. Moro' e Azienda Ospedaliero-Universitaria Consorziale Policlinico di Bari, Bari, Italy.

Corresponding author
Dr. Francesco Perrone
Unità Sperimentazioni Cliniche
Istituto Nazionale per lo Studio e la Cura dei Tumori,
IRCCS Fondazione Pascale, Napoli
Via Mariano Semmola
80131 Napoli, Italy
f.perrone@istitutotumori.na.it
fax +390817702938
phone +390815903571

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Abstract (290 words)

Objectives: To measure and explain financial toxicity (FT) of cancer in Italy, where a public healthcare system exists and cancer patients are not expected (or only marginally) to pay out-of-pocket for health care.

Setting: Ten clinical oncological centres, distributed across Italian macroregions (North, Centre, South and Islands), including hospitals, university hospitals and national research institutes.

Participants: From Oct 8th, 2019 to Dec 11th, 2019, 184 patients, aged 18 or more, who were receiving or had received within the previous three months active anticancer treatment were enrolled, 108 (59%) females and 76 (41%) males.

Intervention: A 30-item pre-final questionnaire, previously developed within the qualitative tasks of the project, was administered, either electronically (n=115) or by papersheet (n=69).

Primary and secondary outcome measures: According to the protocol and the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) methodology, the final questionnaire was developed by mean of explanatory factor analysis and tested for reliability, internal consistency (Cronbach's α test and item-total correlation) and stability of measurements over time (test–retest reliability by intra-class correlation coefficient and weighted Cohen's Kappa coefficient).

Results: After exploratory factor analysis, a scale measuring FT (FT-scale) was identified, made by 7 items dealing with outcomes of FT. The Cronbach alpha coefficient for the FT-scale was 0.87 and the item-total correlation coefficients ranged from 0.53 to 0.74. Further, 9 single items representing possible determinants of FT were also retained in the final instrument. Test-retest analysis revealed a good internal validity of the 16 items retained in the final questionnaire.

Conclusions: The PROFFIT (Patient Reported Outcome for Fighting FInancial Toxicity) instrument consists of 16 items and is the first reported instrument to assess FT of cancer developed in a country with a fully public healthcare system.

Trial registration: clinicaltrials.gov NCT 03473379.

ARTICLE SUMMARY

Strengths and limitations of this study

- Previous research data, using a generic quality of life instrument, supported that financial problems do affect the outcome of cancer patients in Italy, notwithstanding the Italian healthcare system is based on universal coverage and patients do not pay to access cancer treatment.
- No tool for measuring and understanding financial toxicity of cancer had been ever produced in the context of a public healthcare system with universal coverage.
- The development of PROFFIT was done according to a widely accepted methodology for the production of patient reported outcome measures.
- Correlation of PROFFIT with known anchors (quality of life tools, performance status) and the responsiveness of the instrument over the course of the disease are being studied.
- PROFFIT might be of interest for other countries where a public healthcare system exists; however, cross-cultural adaptation and linguistic validation should be performed before it be used outside Italy.

INTRODUCTION

Financial toxicity (FT) following cancer diagnosis and treatment is an increasingly recognized problem worldwide. While initial reports came from the United States, recent data suggest its importance in many other countries with different healthcare systems, like for example Japan, Nepal, Canada and Italy. [1-7] In 2016, we reported financial difficulties among Italian cancer patients enrolled in clinical trials, and their association with worse quality of life and overall survival. [5] Using individual data from 16 randomized trials, we found that patients reporting some degree of financial burden at baseline had a higher chance of worsening global quality of life (QoL) response after treatment, and that patients, who developed financial toxicity during treatment, had a statistically significant shorter survival. [5]

Therefore, in 2018, we started the multicentre PROFFIT (Patient Reported Outcome for Fighting FInancial Toxicity of cancer) project to develop a tool for measuring and understanding financial toxicity of cancer that would be sensitive to dimensions of a universal healthcare system. The PROFFIT protocol and the early qualitative findings of the project were reported elsewhere. [8, 9] We herein report the quantitative analysis of the 30 items resulting from the early phases of the project and the final questionnaire.

METHODS

The study protocol was approved by the independent ethical review board of the institutions enrolling patients and is registered on clinicaltrials.gov NCT03473379. Overall, the project was performed according to International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guidelines. [10, 11]

Patient sample and data acquisition

To be included patients had to fulfil the following enrolment criteria: i) adult patients (>18 years), ii) histologically or cytologically confirmed diagnosis of any type of solid cancer or haematological malignancy, iii) medical treatment (chemotherapy, target agents, immunotherapy, hormonal treatment, radiotherapy or combinations of such therapies) ongoing or terminated within the previous three months. The questionnaires could be administered either as paper document or as a tablet digital version, according to centre choice. Written informed consent was required. The minimum sample size was calculated to assess the test-retest reliability. With an acceptable level of intraclass correlation coefficient (ICC) equal to 0.70 and an expected ICC of 0.80, a one-sided alfa 0.05, 80% power, at least 118 patients had to be enrolled.

Instrument

The first two tasks of the PROFFIT project, concept elicitation and item generation, have been previously described. [9] Briefly, as for concept elicitation, an extensive list of topics related to FT was derived from literature review, expert survey and focus groups. Ten FT domains (medical care, domestic economy, emotion, family, job, health workers, welfare

state, free time and transportation) were described by 156 topics, that reduced to 55 items after correction for redundancy, and to 30 items after importance analysis. These items were tested as for comprehensibility, recall, judgement and response in 45 cognitive interviews and represented the pre-final instrument.

Two groups of items were identified by the study steering committee: (1) *outcome* items (n=10), i.e. indicators, that reflect the level of the supposed latent FT and that do not alter or influence the latent construct they measure, and (2) *determinant* items (n= 20), i.e. causal indicators, that are considered to affect FT and that may change the latent variable. [12] Separate analyses were performed in the outcome and determinant groups.

Statistical analysis

To reduce possible redundancy, the between-item correlation matrix was preliminarily estimated by pairwise Spearman rank correlation coefficients (r_s), because of the ordinal nature of items; cut-off was set equal to 0.65, and for each pair of items with r_s >0.65 the item with the greater score in the previously published importance analysis was retained. [9] Exploratory factor analysis (EFA) was used to discover the presence of multi-item scales and the distribution of the items consistent with the theoretical framework of FT. [13] To extract factors we used the Principal Axis Factor (PAF) analysis with Varimax rotation and Kaiser normalization. To determine the number of scale factors, we relied on the Kaiser criterion to select factors with eigenvalue >1, the Scree test to depict the percentage of total variance explained by the factors extracted, and the interpretability of the factor solution. PAF assumptions were assessed by Bartlett sphericity test and Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy. [14]

No missing data imputation was initially planned, but we found 37% of information was missing for the five items related to job, from patients who declared themselves retired or jobless (i.e. househusbands, housewives or individuals in search of employment).

Consistently we performed the analyses involving job-related items both in the sample of patients with complete valid information (hereby defined as “restricted sample”), and in the whole sample (hereby defined as “full sample”), by imputing, for each subject, the missing values with the average score of the items answered.

The face validity of the resulting scale was examined, both in terms of the scale global meaning and in terms of the appropriateness of each individual item to that scale. Internal consistency, i.e. within-scale between-items correlations, was assessed by Cronbach’s alpha correlation coefficient, assuming as acceptable a value >0.70. Relationships between each individual item x_i and the total score of the scale to which they were assumed to belong were assessed by Spearman rank correlation coefficient with correction for overlap, i.e. by omitting x_i from the total score. To evaluate stability of measurements over time, the questionnaire was to be administered again after one week and the test–retest reliability was assessed by intra-class correlation coefficient (ICC) and weighted Cohen’s Kappa coefficient. We considered a minimally acceptable level of reliability equal to 0.70 and an expected ICC of 0.80.

Descriptive statistics were used to characterize the study sample and their mean scores answers. The data met all the necessary assumptions for this factor analysis. Statistical analyses were performed with SPSS version 25.0 (SPSS; Chicago, IL, USA) and with Stata 14 (Stata, College Station, TX, USA)

English translation

To allow international comprehension of the final PROFFIT questionnaire, an English translation was done according to methodology proposed by Wild et al.[15] First, a translation committee was established including five members of the Steering Committee (FP, SR, CG, MDM, FE), two English mother-tongue translators and two Italian mother-tongue translators. Second, the two English translators independently translated the tool

into English producing two forward translations (T1 and T2) that were collected and subsequently discussed in a meeting where the agreement on the English version was achieved. Third, the two Italian translators (unaware of the original Italian version) independently back-translated the English version into Italian; their translations were collected and discussed in a meeting including the whole translation committee. During such meeting the final English translation was generated and approved by the Steering Committee. It is important to underline that the English translation has to be considered just to allow comprehension by non-Italian readers because it has not been cross-culturally adapted and validated within a population of English native patients.

RESULTS

From Oct 8th, 2019 to Dec 11th, 2019, 185 patients were enrolled at 10 participating centres; one patient was excluded because the baseline questionnaire was missing due to a technical problem with web connection of the tablet application. Questionnaires were administered as paper document in 4 centres (69 patients) and as digital tablet application in 6 centres (115 patients). Job-related items had a 37% rate of missing responses; all the remaining items were answered in 100% of the cases, leading to the full sample of 184 patients and the restricted sample of 116 patients.

Demographic and clinical characteristics of the 184 patients are shown in **Table 1**. Median age was 59 years (range 29-83) and participants were predominantly female. More than half of the patients had a high level of schooling (high school or degree), and around 70% were married. In terms of clinical characteristics, the great majority of patients had a previous surgery for cancer, and the most common treatment was chemotherapy. As expected, in the restricted sample, patients were younger, with a higher level of education and more frequently actively working.

At the preliminary between-item correlation analysis in the restricted sample without missing imputation for job items (116 patients), six items were excluded because r_s was greater than 0.65, leading to 9 outcome and 15 determinant items for subsequent analyses.

PAF assumptions on the 9 outcome items were met with very good parameters (KMO = 0.82 and Bartlett's test of sphericity, p-value <.001), and two items were excluded because of low communality. Thus, final PAF was performed on 7 outcome items. In the restricted sample, two initial eigenvalues >1 explained 66% of the total variance: both were expression of financial burden, but the second one was mostly related to job. All items had factor loadings greater than 0.40. In the full sample (KMO = 0.87 and Bartlett's test of sphericity, p-value <.001), with missing imputation for the job-related item, all the 7 items were related to one factor explaining 57% of the total variance; factor loadings and communalities are

reported in **Table S1**, for both the restricted and the full sample. Thus, the PROFFIT FT-scale includes 7 outcome items. The Cronbach alpha coefficient for the PROFFIT FT-scale was 0.85 in the restricted sample and 0.87 in the full sample, indicating that the correlation between the items and the score is consistently reliable. Correlations between each single item of the FT-scale and the total score (after removal of the single item), ranged from 0.37 to 0.73 in the restricted sample, and from 0.53 to 0.74 in the full sample (**Table S2**).

Similarly, assumptions on the 15 determinants items were met with satisfactory parameters (KMO = 0.68 and Bartlett's test of sphericity, p-value <0.001). PAF on the determinant items eliminated 6 items because of low communality and showed that the other 9 items were only mildly related, without a clear definition of any factor, hence they were retained as single items.

Therefore, the final PROFFIT instrument includes the FT-scale (consisting of 7 items) and 9 single items assessing possible determinants of FT. In **Table 2**, both the Italian items and the English translation are reported. The postulated causal structure for PROFFIT is reported in Figure 1.

Due to cyclic structure of ongoing anticancer treatment, most retest questionnaires were actually administered later than the planned one-week interval from the first assessment. In principle, such deviation might reduce Therefore, we excluded from the test-retest analysis all questionnaires administered more than 35 days (n=52) after the first ones because of the possibility that more than one cycle of treatment could had been given during the interval. Within 132 cases of the full sample, median time between test and retest was 21 days; all ICCs and Cohen's weighted K coefficients were good, ranging from 0.52 and 0.79; ICC and weighted K were 0.79 and 0.81, respectively, for the job-related item, retested in 80 patients (**Table S3)**.

DISCUSSION

Financial toxicity has been initially described in the United States as a factor negatively affecting cancer patients during their journey, in several ways.[7] Particularly, both QoL and survival have been reported to be worse among patients facing with financial hardships and bankruptcy. [16, 17] This might be not surprising given that the US health system prevalently requires out of pocket co-payment of medical expenses, and that the cost of cancer treatment has been steadily increasing. [18]

On the contrary, we were surprised when we earlier observed that financial problems (measured by the EORTC QLQ-C30 questionnaire) were associated with worse QoL and shorter survival also among Italian cancer patients, who actually live in a country with a public healthcare system where no co-payment is required for healthcare costs.[5] However, the extreme simplicity of the single-item question (item #28) of the EORTC QLQ-C30 questionnaire did not allow further understanding of the determinants of the phenomenon. Therefore, we decided to develop an instrument to more thoroughly describe financial toxicity and to explore potential determinants, within the Italian public health system, where the dynamics should be different as compared with a prevalently private health system like the US one. [19, 20] Here we report this instrument, PROFFIT, that, to the best of our knowledge, is the first one fully published from an European country, and that is candidate to be cross-culturally adapted and validated in other countries with health systems similar to the Italian public health system.

The need to have a specific instrument to measure financial toxicity has been previously addressed in the United States by the Investigators who produced and validated the Comprehensive Score for Financial Toxicity (COST) instrument. [21, 22]

The methodology applied to develop PROFFIT is similar to that applied for the COST development, as both followed the ISPOR guidelines. [10, 11] Nevertheless, the content of the two instruments differ, according to the three domains (psychological response, material

conditions and coping behaviours) proposed by Altice et al. to describe financial hardship. [23] Indeed, while 8 of the 11 items of the COST version 1 questionnaire fall into the "affect" theme and the psychological response domain, 11 out of the 16 PROFFIT items pertain to the material conditions domain. This marked difference supports that the sociocultural context and the health and social care systems may significantly affect the causes and the consequences of financial problems of cancer patients. [19, 20] Therefore, specific instruments should be used within different contexts, and an analysis of differences between social and health systems should be done before choosing which instrument might be more appropriate for measuring financial toxicity. An instrument like PROFFIT, including several items related to determinants of financial toxicity, may be helpful to identify potential targets for action; and such targets, indeed, might be not immediately identified within a public health system that should cover all the needs of cancer patients. Namely, items related to transportation costs, to medical expenses not adequately covered by the public health system and the items pertaining to the quality of medical and non-medical staff and the communication among them clearly indicate some roadmaps of intervention that should be addressed within projects of education, organisation and financial support of various compartments of the welfare system.

While developing PROFFIT, a complex matter derived from management of items related to job activities. Indeed, around one third of patients did not respond to these items. For this reason, we approached the analysis using both (1) a restricted sample, the subgroup including only subjects answering all items, and (2) the full sample, involving all subjects, where missing responses were imputed based on responses to the other valid items. The restricted sample might be most sensitive to financial distress deriving from job loss or reduction but would not be representative of the real-world cancer patient population due to the selective exclusion of older patients, and generalizability would be reduced. On the contrary, the full sample, that is representative of the general cancer patient population might

be less sensitive to relevance of job problems. We will investigate this topic more deeply in the near future within further validation studies.

Notwithstanding a longer than planned interval between test and retest questionnaire administration, that might in principle reduce reproducibility, a good reliability was observed with all the items.

We decided not to define a fixed temporal frame to which refer the response, differently from what is frequently done in patient reported outcomes. The decision was prompted by the consideration that in the final PROFFIT questionnaires, some of the items represent patient-reported experiences, rather than pure outcomes, and might derive from the accumulation of problems over the time. This should make the instrument more sensitive for cross-sectional studies, where it is not strictly important to define whether responses refer to a precise time window. Of course, when PROFFIT will be used as a tool within prospective trials comparing different treatment strategies, a fixed time window should be indicated in order to capture the period of interest.

We are performing further prospective analysis testing the correlation of PROFFIT with known anchors (quality of life tools, performance status) and the responsiveness of the instrument over the course of the disease. In the meanwhile, the questionnaire is available for Italian investigators wishing to use it and for international Investigators wishing to cross-validate it into different languages and countries. No fee will be required for using the questionnaire for purely academic studies, but registration of the protocols will be required and written agreements with the National Cancer Institute of Naples, Italy, will be requested.

In conclusion, financial toxicity is a major problem in oncology also within an universal healthcare system, hence the availability of specific and validated instruments is crucial to better understand its causes and its relationship with different aspects of cancer disease. Ultimately, data generated via this newly developed tool will provide insights on how to

collaborate in the fight against financial toxicity, and hopefully improve the outcomes of cancer patients.

Table 1. Characteristics of participating patients

	Full sample N = 184	Restricted sample N = 116
Gender, n (%)		
Female	108 (58,7%)	63 (54,3%)
Male	76 (41,3%)	53 (45,7%)
Age, median (range)	59 (29-82)	55 (29-74)
Age category, n (%)		
<=60	94 (51,1%)	72 (62,1%)
>60	90 (48,9%)	44 (37,9%)
Region of the participating institution, n (%)		
North	71 (38,6%)	46 (39,7%)
Center	15 (8,2%)	9 (7,8%)
South	71 (38,6%)	43 (37,1%)
Islands	27 (14,7%)	18 (15,5%)
Education level, n (%)		
Elementary school	23 (12,5%)	8 (6,9%)
Middle school	57 (31,0%)	33 (28,4%)
High school/degree	104 (56,5%)	75 (64,7%)
Marital status, n (%)		
Married	132 (71,7%)	82 (70,7%)
Other	52 (28,3%)	34 (29,3%)
With dependent family members, n (%)		
No	107 (58,2%)	60 (51,7%)
Yes	77 (41,8%)	56 (48,3%)
Family members with cancer or chronic disease, n (%)		
No	82 (44,6%)	52 (44,8%)
Yes	102 (55,4%)	64 (55,2%)
Working status, n (%)		
Working	84 (45,7%)	82 (70,7%)
Not working	100 (54,3%)	34 (29,3%)
Distance (km) from the hospital, median (range)	20 (1-430)	25 (1-286)
Previous treatment		
Surgery	129 (70,1%)	81 (69,8%)
Chemotherapy	157 (85,3%)	94 (81,0%)
Target-based agents	55 (29,9%)	37 (31,9%)
Immunotherapy	38 (20,7%)	28 (24,1%)
Hormonal therapy	31 (16,8%)	18 (15,5%)
Radiotherapy	43 (23,4%)	28 (24,1%)
Last/ongoing treatment		
Chemotherapy	135 (73,4%)	79 (68,1%)
Target-based agents	18 (9,8%)	13 (11,2%)
Immunotherapy	25 (13,6%)	19 (16,4%)
Hormonal therapy	5 (2,7%)	4 (3,4%)
Radiotherapy	1 (0,5%)	1 (0,9%)
Primary tumour site		
Breast	59 (32,1%)	36 (31,0%)
Lower_GI	51 (27,7%)	24 (20,7%)
Genito-urinary	34 (18,5%)	27 (23,3%)
Thoracic	18 (9,8%)	13 (11,2%)
Upper_GI	13 (7,1%)	10 (8,6%)
Other	9 (4,9%)	6 (5,2%)

Table 2. Final PROFFIT instrument

Item type and number	Italian version	**English translation** (for comprehension only)
Outcome items (FT-scale)		
1.	Sono in grado di sostenere le mie spese mensili senza difficoltà (ad esempio per affitto, elettricità, telefono…)	I can afford my monthly expenses without difficulty (for example rent, electricity, phone…)
2.	La mia malattia ha ridotto le mie disponibilità economiche	My illness has reduced my financial resources
3.	Sono preoccupato dei problemi economici che potrei avere in futuro a causa della malattia	I am concerned by the economic problems I may have in the future due to my illness
4.	La mia condizione economica incide sulle mie possibilità di curarmi	My economic situation affects the possibility of receiving medical care
5.	Ho ridotto le spese per attività ricreative come vacanze, ristoranti o spettacoli per affrontare le spese della mia malattia	I have reduced my spending on leisure activities such as holidays, restaurants or entertainment in order to cope with expenses related to my illness
6.	Ho ridotto le spese per acquisti essenziali (ad esempio il cibo) per affrontare le spese per la mia malattia	I have reduced spending on essential goods (for example food) in order to cope with expenses related to my illness
7.	Sono preoccupata/o di non riuscire a lavorare a causa della mia malattia	I am worried that I will not be able to work due to my illness
Determinant items (single items)		
8.	Il Servizio Sanitario Nazionale copre tutti i costi sanitari associati alla mia malattia	The National Health Service covers all health costs related to my illness
9.	Ho sostenuto spese per una o più visite private per la mia malattia	I have paid for one or more private medical examinations for my illness
10.	Ho sostenuto spese per farmaci supplementari o integratori per la mia malattia	I have paid for additional medicines or supplements related to my illness
11.	Devo sostenere spese per cure integrative a mio carico (es. fisioterapia, psicoterapia, cure odontoiatriche)	I have to pay for additional treatment myself (for example physiotherapy, psychotherapy, dental care)
12.	Il centro di cura è lontano dalla mia abitazione	The treatment centre is a long way from where I live
13.	Ho dovuto sostenere rilevanti costi di trasporto per curarmi	I have spent a considerable amount of money on travel for treatment
14.	Il personale sanitario (cioè medici, infermieri, etc.) ha agevolato il percorso di cura	Medical staff (that is doctors, nurses etc.) have been helpful throughout my medical care
15.	Il personale ospedaliero amministrativo (cioè centro di prenotazione, segreterie, etc.) ha agevolato il percorso di cura	Staff in hospital administration (that is for booking appointments, secretaries, etc.) have been helpful throughout my medical care
16.	C'è stata comunicazione tra i medici e le strutture sanitarie che mi seguono	Medical staff and medical facilities I attended communicated with each other

Legend of figure

Figure 1. Postulated causal structure for PROFFIT tool

Acknowledgments

See appendix.

Authors contribution

FP obtained funding. SR, JB, CG and FP drafted the protocol. MDM, FE, VM, LF, DG, LDC, FDL, EI, FT, LG, CJ, CMV, and MCP contributed to protocol writing. MDM, VM, DG, DB, SC, CP, LDM, VZ, AAC, RB and FP contributed to patients' enrolment. SR, LA, LG, CG and FP performed statistical analysis and drafted the manuscript. All Authors contributed to the manuscript and approved the final version.

Data

Data will be made available upon request to the corresponding author.

Patient and public involvment

The project was informed by patients' thanks to the involvement of patients and representatives of patients' associations in the Steering Committee that oversaw all the phases of the project, including protocol definition, qualitative analysis (previously reported elsewhere) producing the pre-final questionnaire, and final analyses producing the final questionnaire (reported here); they are co-author of this manuscript and of the previous manuscripts dealing with this project (LDC, FDL, EI, FT). They will also contribute in dissemination of the results of the project.

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CJ has received personal fees from Amgen, Astra Zeneca, Biogen, Boehringer Ingelheim, Celgene, Gilead, GSK, Ipsen, Janssen-Cilag, Takeda and Sanofi.

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CP acted as a Speaker and/or Consultant for MSD, BMS, AstraZeneca, Ipsen, Pfizer, Eisai, EUSA, Novartis, Merck, General Electrics and Angelini; furthermore, was an Expert Testimony for Pfizer and EUSA.

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The other Authors have no conflict to disclose.

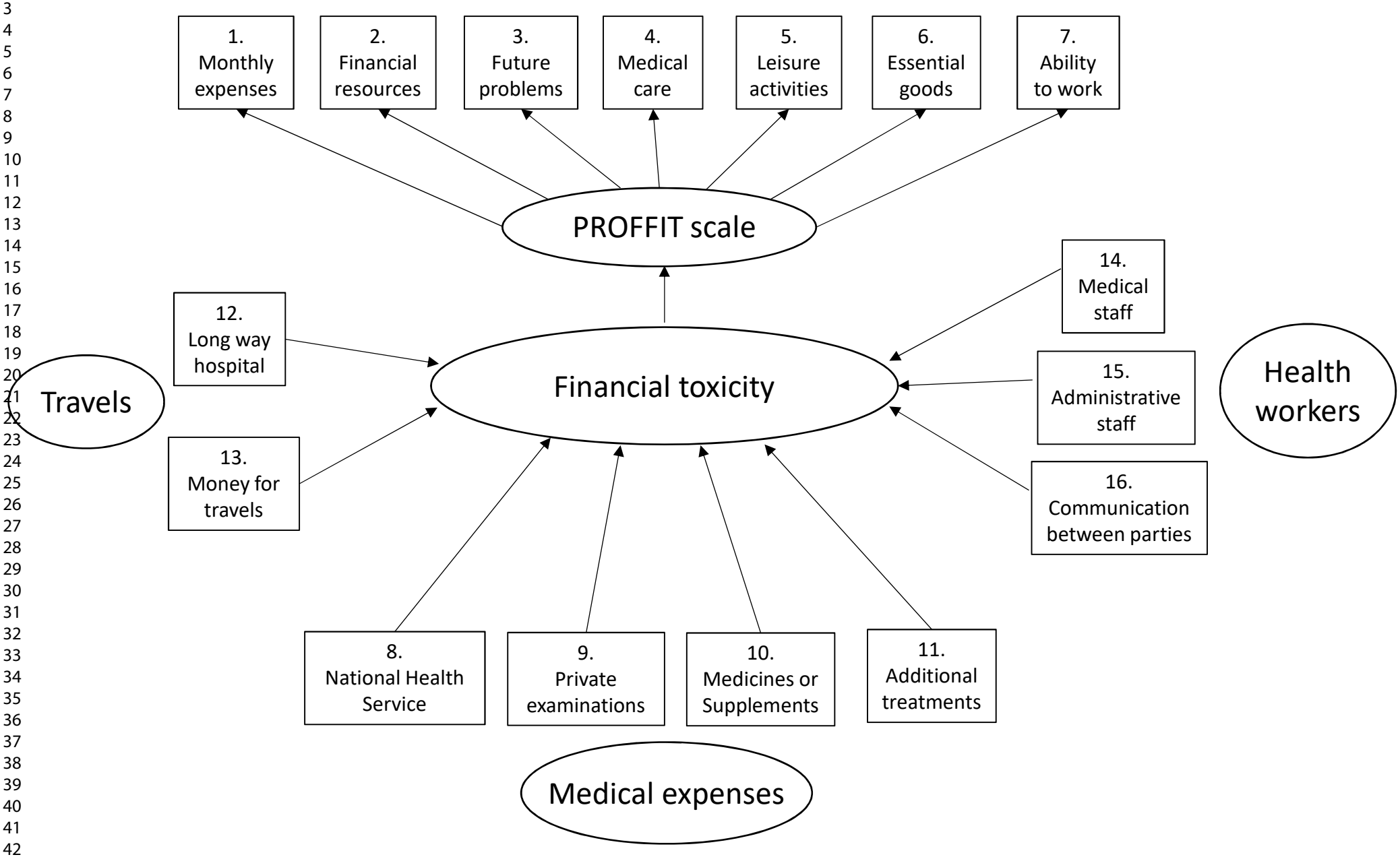
1. Monthly expenses
2. Financial resources
3. Future problems
4. Medical care
5. Leisure activities
6. Essential goods
7. Ability to work
PROFFIT scale
12. Long way hospital
13. Money for travels
Travels
Financial toxicity
14. Medical staff
15. Administrative staff
16. Communication between parties
Health workers
8. National Health Service
9. Private examinations
10. Medicines or Supplements
11. Additional treatments
Medical expenses

Figure 1.

Development of PROFFIT, a patient-reported instrument for measuring financial toxicity of cancer within a public healthcare system

Appendix

The PROFFIT Steering Committee includes: Francesco Perrone, Jane Bryce, Ciro Gallo, Silvia Riva, Fabio Efficace, Francesco De Lorenzo, Elisabetta Iannelli, Laura Del Campo, Francesca Traclò, Massimo Di Maio (also as representative of AIOM – Associazione Italiana di Oncologia Medica), Luciano Frontini, Vincenzo Montesarchio (also as representative of CIPOMO – Collegio Italiano dei Primari di Oncologia Medica Ospedalieri), Diana Giannarelli, Lara Gitto, Claudio Jommi, Concetta Maria Vaccaro.

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- U.O.C. Oncologia Medica - Ospedale Senatore Antonio Perrino, Brindisi (Saverio Cinieri, Manuela Caloro, Laura Orlando, Dario Loparco)

- Oncologia Medica 2 - IRCCS AOU San Martino - IST, Genova (Lucia Del Mastro)
- AO Ordine Mauriziano - S.C.D.U Oncologia Medica, Torino (Massimo Di Maio)
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PROFFIT

PATIENT REPORTED OUTCOME FOR FIGHTING FINANCIAL TOXICITY OF CANCER

Scoring procedure

Four categories of agreement with the statement of each item are allowed, scoring from 1 to 4: 1 - I do not agree at all, 2 - I agree partially, 3 - I agree substantially, 4 - I very much agree. Missing responses must be described but must not be used for scores calculation.

PROFFIT raw scores are to be normalised to 0-100%, where 100 indicates the highest toxicity.

For calculation of the FT-score, including items #1 to #7, the following steps should be followed:

- Reverse the score for Item 1 according to the following formula

$$X_{1-reverese} = 5 - X_1$$

where X_1 is the response given to item 1.

- Calculate the FT-score according to the following formula

$$\frac{X_{1-reverse} + X_2 + X_3 + X_4 + X_5 + X_6 + X_7 - Y}{3 \times Y} \times 100$$

where X is the response given for each item and Y is the number of items with valid response.

For calculation of the score for items #8, #12, #14, #15 and #16 use the following formula

$$\frac{4 - X_j}{3} \times 100$$

where X is the response given and *j* is the item (8, 12, 15, or 16).

For calculation of the score for items #9, #10, #11, #13 use the following formula

$$\frac{X_j - 1}{3} \times 100$$

where X is the response given and *j* is the item (9, 10, 11 or 13).

Table S1. EFA on the seven outcome items remaining in the final questionnaire

Item number	Full sample (N=184)		Restricted sample (N=116)				
	Unrotated factor loading	Communality	Unrotated factor loading		Rotated factor loading		Communality
	Factor 1		Factor 1	Factor 2	Factor 1	Factor 2	
1	-0.558	0.312	-0.456	0.246	-0.498	-0.146	0.269
2	0.803	0.644	0.823	0.246	0.412	0.754	0.737
3	0.787	0.619	0.793	0.138	0.467	0.656	0.648
4	0.738	0.545	0.698	-0.315	0.718	0.267	0.588
5	0.735	0.541	0.700	0.143	0.397	0.594	0.510
6	0.697	0.488	0.635	-0.406	0.737	0.158	0.566
7	0.587	0.345	0.428	0.415	0.013	0.596	0.356

Table S2. Spearman correlation coefficients between each item and total score*

Item number	Full sample (N=184)	Restricted sample (N=116)
1	0.5325	0.5243
2	0.7360	0.7267
3	0.7251	0.7158
4	0.6646	0.6559
5	0.6887	0.6765
6	0.6712	0.6626
7	0.5537	0.3684

*calculated removing each item from the sum

Table S3. Test-retest results

Item number	ICC	Weighted K	Agreement %
Outcome items			
1.	0.70	0.70	95.7
2.	0.68	0.68	93.7
3.	0.56	0.56	90.7
4.	0.64	0.64	93.2
5.	0.65	0.65	91.0
6.	0.65	0.65	93.9
7.	0.79	0.81	94.4
Determinant items			
8.	0.61	0.61	94.4
9.	0.72	0.72	94.2
10.	0.65	0.65	93.0
11.	0.61	0.62	92.4
12.	0.79	0.79	96.6
13.	0.78	0.78	92.2
14.	0.53	0.52	96.5
15.	0.59	0.58	95.0
16.	0.61	0.61	93.9

Reporting checklist for cross sectional study.

Based on the STROBE cross sectional guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	4

Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	#3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	#4	Present key elements of study design early in the paper	6
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	10
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants.	6
	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	6
Bias	#9	Describe any efforts to address potential sources of bias	7-8

Study size	#10	Explain how the study size was arrived at	6
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	7
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	7-8
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	7-8
Statistical methods	#12c	Explain how missing data were addressed	8
Statistical methods	#12d	If applicable, describe analytical methods taking account of sampling strategy	8
Statistical methods	#12e	Describe any sensitivity analyses	7-8
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	10
Participants	#13b	Give reasons for non-participation at each stage	10

Participants	#13c	Consider use of a flow diagram	Considered but deemed useless
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	10 (Table 1)
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	10
Outcome data	#15	Report numbers of outcome events or summary measures. Give information separately for exposed and unexposed groups if applicable.	Not applicable
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Not applicable
Main results	#16b	Report category boundaries when continuous variables were categorized	Not applicable
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable

Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	10-11
Discussion			
Key results	#18	Summarise key results with reference to study objectives	13-14
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	13-14
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	14-15
Generalisability	#21	Discuss the generalisability (external validity) of the study results	14
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

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A cross-sectional study to develop and describe psychometric characteristics of a patient-reported instrument (PROFFIT) for measuring financial toxicity of cancer within a public healthcare system

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A cross-sectional study to develop and describe psychometric characteristics of a patient-reported instrument (PROFFIT) for measuring financial toxicity of cancer within a public healthcare system

Silvia Riva[1,2], Laura Arenare[3], Massimo Di Maio[4], Fabio Efficace[5], Vincenzo Montesarchio[6], Luciano Frontini[7], Diana Giannarelli[8], Jane Bryce[3,9,10], Laura Del Campo[11], Francesco De Lorenzo[12], Elisabetta Iannelli[13], Francesca Traclò[13], Lara Gitto[14], Claudio Jommi[15], Concetta Maria Vaccaro[16], Daniela Barberio[17], Saverio Cinieri[18], Camillo Porta[19a], Lucia Del Mastro[20,21], Vittorina Zagonel[22], Alessio Aligi Cogoni[23], Roberto Bordonaro[24], Anna Gimigliano[3], Maria Carmela Piccirillo[3], Lorenzo Guizzaro[25], Ciro Gallo[25*], Francesco Perrone[3*]

[1] St Mary's University, Twickenham, London, UK
[2] Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, University Hospital of Milan, Italy
[3] Unità Sperimentazioni Cliniche, Istituto Nazionale per lo Studio e la Cura dei Tumori, IRCCS, Fondazione G.Pascale, Napoli, Italy
[4] Dipartimento di Oncologia, Università di Torino, AO Ordine Mauriziano, Torino, Italy
[5] Gruppo Italiano per le Malattie Ematologiche dell'Adulto (GIMEMA) Health Outcomes Research Unit, Roma, Italy
[6] Azienda Ospedaliera Specialistica dei Colli, Napoli, Italy
[7] Federation of Italian Cooperative Oncology Groups (FICOG), Milano, Italy
[8] Unità di Biostatistica, Istituto Nazionale per lo Studio e la Cura dei Tumori Regina Elena, IRCCS, Roma, Italy
[9] Dipartimento di Biomedicina e Prevenzione, Università degli Studi di Roma "Tor Vergata", Roma, Italy
[10] Ascension St. John Clinical Research Institute, Tulsa, USA
[11] Federazione italiana delle Associazioni di Volontariato in Oncologia (FAVO), Rome, Italy
[12] European Cancer Patient Coalition (ECPC), Brussels, Belgium
[13] Associazione Italiana Malati di Cancro (AIMAC), Roma, Italy
[14] Dipartimento di Economia, Università degli Studi di Messina, Italy
[15] CERGAS (Centre for Health and Social Care Management), SDA Bocconi School of Management, Milano, Italy
[16] Area Welfare e Salute, Centro Studi Investimenti Sociali (CENSIS), Roma, Italy
[17] Struttura Semplice Dipartimentale di Psiconcologia Clinica, Istituto Nazionale per lo Studio e la Cura dei Tumori, IRCCS, Fondazione G.Pascale, Napoli, Italy
[18] Unità Operativa Complessa di Oncologia Medica, Ospedale Perrino, Brindisi, Italy
[19] Struttura Complessa di Oncologia Medica, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy
[20] UO Breast Unit, IRCCS Ospedale Policlinico San Martino, Genova, Italy
[21] Dipartimento di Medicina Interna e Medicina Specialistica (DIMI), Università di Genova, Italy
[22] U.O.C. Oncologia 1, Istituto Oncologico Veneto, IOV, IRCCS Padova, Italy
[23] Unità operativa complessa di Oncologia Medica - AOU di Sassari, Italy
[24] Struttura Complessa di Oncologia Medica, ARNAS Garibaldi-Nesima, Catania, Italy
[25] Statistica Medica, Università degli Studi della Campania "Luigi Vanvitelli", Napoli, Italy.

* co-last authors
[a] present address: Dipartimento di Scienze Biomediche ed Oncologia Umana, Università degli Studi di Bari 'A. Moro' e Azienda Ospedaliero-Universitaria Consorziale Policlinico di Bari, Bari, Italy.

Corresponding author
Dr. Francesco Perrone
Unità Sperimentazioni Cliniche
Istituto Nazionale per lo Studio e la Cura dei Tumori,
IRCCS Fondazione Pascale, Napoli
Via Mariano Semmola
80131 Napoli, Italy
f.perrone@istitutotumori.na.it
fax +390817702938
phone +390815903571

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Abstract

Objectives: To measure and explain financial toxicity (FT) of cancer in Italy, where a public healthcare system exists and cancer patients are not expected (or only marginally) to pay out-of-pocket for health care.

Setting: Ten clinical oncological centres, distributed across Italian macro-regions (North, Centre, South and Islands), including hospitals, university hospitals and national research institutes.

Participants: From Oct 8th, 2019 to Dec 11th, 2019, 184 patients, aged 18 or more, who were receiving or had received within the previous three months active anticancer treatment were enrolled, 108 (59%) females and 76 (41%) males.

Intervention: A 30-item pre-final questionnaire, previously developed within the qualitative tasks of the project, was administered, either electronically (n=115) or by paper sheet (n=69).

Primary and secondary outcome measures: According to the protocol and the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) methodology, the final questionnaire was developed by mean of explanatory factor analysis and tested for reliability, internal consistency (Cronbach's α test and item-total correlation) and stability of measurements over time (test–retest reliability by intra-class correlation coefficient and weighted Cohen's Kappa coefficient).

Results: After exploratory factor analysis, a score measuring FT (FT-score) was identified, made by 7 items dealing with outcomes of FT. The Cronbach alpha coefficient for the FT-score was 0.87 and the item-total correlation coefficients ranged from 0.53 to 0.74. Further, 9 single items representing possible determinants of FT were also retained in the final

instrument. Test-retest analysis revealed a good internal validity of the FT-score and the 16 items retained in the final questionnaire.

Conclusions: The PROFFIT (Patient Reported Outcome for Fighting FInancial Toxicity) instrument consists of 16 items and is the first reported instrument to assess FT of cancer developed in a country with a fully public healthcare system.

Trial registration: clinicaltrials.gov NCT 03473379.

ARTICLE SUMMARY

Strengths and limitations of this study

- PROFFIT was developed as a reaction to the finding that financial problems affect the outcome of cancer patients in Italy, notwithstanding the Italian healthcare system is based on universal coverage and patients do not pay to access cancer treatment.
- No tool for measuring and understanding financial toxicity of cancer had been ever produced in the context of a public healthcare system with universal coverage.
- The development of PROFFIT was done according to a widely accepted methodology to produce patient reported outcome measures.
- Correlation of PROFFIT with known anchors (quality of life tools, performance status) and the responsiveness of the instrument over the course of the disease are being studied.
- PROFFIT might be of interest for other countries where a public healthcare system exists.

INTRODUCTION

Financial toxicity (FT) following cancer diagnosis and treatment is an increasingly recognized problem worldwide. While initial reports came from the United States, recent data suggest its importance in many other countries with different healthcare systems, like for example Japan, Nepal, Canada and Italy. [1-7] In 2016, we reported financial difficulties among Italian cancer patients enrolled in clinical trials, and their association with worse quality of life and overall survival. [5] Using individual data from 16 randomized trials, we found that patients reporting some degree of financial burden at baseline had a higher chance of worsening global quality of life (QoL) response after treatment, and that patients, who developed financial toxicity during treatment, had a statistically significant shorter survival. [5]

Therefore, in 2018, we started the multicentre PROFFIT (Patient Reported Outcome for Fighting FInancial Toxicity of cancer) project to develop a tool for measuring and understanding financial toxicity of cancer that would be sensitive to dimensions of a universal healthcare system. The PROFFIT protocol and the early qualitative findings of the project were reported elsewhere. [8, 9] We herein report the quantitative analysis of the 30 items resulting from the early phases of the project and the final questionnaire.

METHODS

The study protocol was approved by the independent ethical review board of the institutions enrolling patients and is registered on clinicaltrials.gov NCT03473379. Overall, the project was performed according to International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guidelines. [10, 11]

Patient sample and data acquisition

To be included patients had to fulfil the following enrolment criteria: i) adult patients (>18 years), ii) histologically or cytologically confirmed diagnosis of any type of solid cancer or haematological malignancy, iii) medical treatment (chemotherapy, target agents, immunotherapy, hormonal treatment, radiotherapy or combinations of such therapies) ongoing or terminated within the previous three months. The questionnaires could be administered either as paper document or as a tablet digital version, according to centre choice. Written informed consent was required. The minimum sample size was calculated to assess the test-retest reliability. With an acceptable level of intraclass correlation coefficient (ICC) equal to 0.70 and an expected ICC of 0.80, a one-sided alfa 0.05, 80% power, at least 118 patients had to be enrolled.

Instrument

The first two tasks of the PROFFIT project, concept elicitation and item generation, have been previously described. [9] Briefly, as for concept elicitation, an extensive list of topics related to FT was derived from literature review, expert survey and focus groups. Ten FT

domains (medical care, domestic economy, emotion, family, job, health workers, welfare state, free time and transportation) were described by 156 topics, that reduced to 55 items after correction for redundancy, and to 30 items after importance analysis. These 30 items were proposed to further 45 patients within cognitive interviews testing comprehensibility, recall, judgement and response; the 30 items refined after cognitive interviews represented the pre-final instrument **(Table S1)**.

Two groups of items were identified by the study steering committee: (1) *outcome* items (n=10), i.e. indicators, that reflect the level of the supposed latent FT and that do not alter or influence the latent construct they measure, and (2) *determinant* items (n= 20), i.e. causal indicators, that are considered to affect FT and that may change the latent variable. [12] Separate analyses were performed in the outcome and determinant groups.

Statistical analysis

To reduce possible redundancy, the between-item correlation matrix was preliminarily estimated by pairwise Spearman rank correlation coefficients (r_s), because of the ordinal nature of items; cut-off was set equal to 0.65, and for each pair of items with r_s >0.65 the item with the greater score in the previously published importance analysis was retained. [9] Because information was missing for the five items related to job in 68/184 (37%) patients, who declared themselves retired or jobless (i.e. househusbands, housewives or individuals in search of employment), correlation coefficients were estimated separately for job items (excluding patients with missing data on job items) and for all the other items (within the full population).

Exploratory factor analysis (EFA) was used to discover the presence of multi-item scales and the distribution of the items consistent with the theoretical framework of FT. [13] To

extract factors we used the Principal Axis Factoring (PAF) analysis with Varimax rotation and Kaiser normalization. To determine the number of scale factors, we relied on the Kaiser criterion to select factors with eigenvalue >1, the Scree test to depict the percentage of total variance explained by the factors extracted, and the interpretability of the factor solution. PAF assumptions were assessed by Bartlett sphericity test and Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy. [14]

Due to missing data in job items, EFA was performed both in the sample of patients with complete valid information (hereby defined as "restricted sample"), and in the whole sample (hereby defined as "full sample"), by imputing, for each subject, the missing values with the average score of the other answered items. A more detailed description of the analysis is reported in the Appendix.

The face validity of the resulting scale was examined, both in terms of the scale global meaning and in terms of the appropriateness of each individual item to that scale. Internal consistency, i.e. within-scale between-items correlations, was assessed by Cronbach's alpha correlation coefficient, assuming as acceptable a value >0.70. Relationships between each individual item x_i and the total score of the scale to which they were assumed to belong were assessed by Spearman rank correlation coefficient with correction for overlap, i.e. by omitting x_i from the total score. To evaluate stability of measurements over time, the questionnaire was to be administered again after one week and the test–retest reliability was assessed by intra-class correlation coefficient (ICC) and weighted Cohen's Kappa coefficient. We considered a minimally acceptable level of reliability equal to 0.70 and an expected ICC of 0.80.

Descriptive statistics were used to characterize the study sample and their mean scores answers. The data met all the necessary assumptions for this factor analysis. Statistical

analyses were performed with SPSS version 25.0 (SPSS; Chicago, IL, USA) and with Stata 14 (Stata, College Station, TX, USA)

English translation

To allow international comprehension of the final PROFFIT questionnaire, an English translation was done according to methodology proposed by Wild et al.[15] First, a translation committee was established including five members of the Steering Committee (FP, SR, CG, MDM, FE), two English mother-tongue translators and two Italian mother-tongue translators. Second, the two English translators independently translated the tool into English producing two forward translations (T1 and T2) that were collected and subsequently discussed in a meeting where the agreement on the English version was achieved. Third, the two Italian translators (unaware of the original Italian version) independently back-translated the English version into Italian; their translations were collected and discussed in a meeting including the whole translation committee. During such meeting the final English translation was generated and approved by the Steering Committee. It is important to underline that the English translation has to be considered just to allow comprehension by non-Italian readers because it has not been cross-culturally adapted and validated within a population of English native patients.

Patient and public involvement

The project was informed by patients' thanks to the involvement of patients and representatives of patients' associations in the Steering Committee that oversaw all the phases of the project, including protocol definition, qualitative analysis (previously reported elsewhere) producing the pre-final questionnaire, and final analyses producing the final

questionnaire (reported here); they are co-author of this manuscript and of the previous manuscripts dealing with this project (LDC, FDL, EI, FT). They will also contribute in dissemination of the results of the project.

RESULTS

From Oct 8th, 2019 to Dec 11th, 2019, 185 patients were enrolled at 10 participating centres; one patient was excluded because the baseline questionnaire was missing due to a technical problem with web connection of the tablet application. Questionnaires were administered as paper document in 4 centres (69 patients) and as digital tablet application in 6 centres (115 patients). Job-related items had a 37% rate of missing responses; all the remaining items were answered in 100% of the cases, leading to the full sample of 184 patients and the restricted sample of 116 patients.

Demographic and clinical characteristics of both samples are shown in **Table 1**. In the full sample, median age was 59 years (range 29-83) and participants were predominantly female. More than half of the patients had a high level of schooling (high school or degree), and around 70% were married. In terms of clinical characteristics, the great majority of patients had a previous surgery for cancer, and the most common treatment was chemotherapy. As expected, in the restricted sample, patients were younger, with a higher level of education and more frequently actively working.

At the preliminary between-item correlation analysis, six items were excluded (three job-related) because r_s was greater than 0.65, leading to 9 outcome and 15 determinant items for subsequent analyses (**Table S2a and S2b**).

EFA on the 9-outcome correlation matrix was first performed in the restricted sample of 116 subjects with complete information, because of the presence of the job item Q99. PAF assumptions on the 9 outcome items were met with very good parameters (KMO = 0.82 and Bartlett's test of sphericity, p-value <.001). Two items were excluded because of low communality (see appendix for details). With 7 outcome items, two initial eigenvalues were >1 and explained 66% of the total variance; both could be interpreted as expression of financial burden, the first one being more correlated with items mirroring an actual burden

while the second one appeared more correlated with worries about the future. This interpretation is reinforced when oblique Promax rotation was applied (see appendix).

In the full sample (KMO = 0.87 and Bartlett's test of sphericity, p-value <.001), with missing imputation for the job-related item, similar findings were observed. Seven items were retained with only one factor >1 explaining 57% of the total variance; factor loadings and communalities are reported in the appendix (EFA on outcome paragraph).

Thus, the PROFFIT FT-score includes 7 outcome items. The Cronbach alpha coefficient for the PROFFIT FT-score was 0.85 in the restricted sample and 0.87 in the full sample, indicating that the correlation between the items and the score is consistently reliable. Correlations between each single item of the FT-score and the total score (after removal of the single item), ranged from 0.37 to 0.73 in the restricted sample, and from 0.53 to 0.74 in the full sample (**Table S3**).

Similarly, assumptions on the 15 determinants items were met with satisfactory parameters (KMO = 0.68 and Bartlett's test of sphericity, p-value <0.001). PAF on the determinant items eliminated 6 items because of low communality and showed that the other 9 items were only mildly related, without a clear definition of any factor, hence they were retained as single items (see appendix – EFA on determinants paragraph - for more details).

Therefore, the final PROFFIT instrument includes the FT-score (consisting of 7 items) and 9 single items assessing possible determinants of FT. In **Table 2**, both the Italian items and the English translation are reported. The postulated causal structure for PROFFIT is reported in **Figure 1**.

We excluded from the test-retest analysis all questionnaires administered more than 35 days (n=52) after the first ones because of the possibility that more than one cycle of treatment could had been given during the interval. However, due to cyclic structure of ongoing

anticancer treatment, most retest questionnaires were actually administered later than the planned one-week interval from the first assessment. Within 132 cases of the full sample, median time between test and retest was 21 days; ICC and Cohen's weighted K coefficients of the FT-score were excellent, being equal to 0.81 and 0.82, respectively. Considering each singular item, all ICCs and K coefficients were good, ranging from 0.52 and 0.79 (**Table S4).**

Associations of FT-score with baseline characteristics of patients are reported in **Table S5**. Significant and relevant differences were found in accordance with Italian macro-region, age, education level and family disease burden.

DISCUSSION

Financial toxicity has been initially described in the United States as a factor negatively affecting cancer patients during their journey, in several ways.[7] Particularly, both QoL and survival have been reported to be worse among patients facing with financial hardships and bankruptcy. [16, 17] This might be not surprising given that the US health system prevalently requires out of pocket co-payment of medical expenses, and that the cost of cancer treatment has been steadily increasing. [18]

On the contrary, we were surprised when we earlier observed that financial problems (measured by the EORTC QLQ-C30 questionnaire) were associated with worse QoL and shorter survival also among Italian cancer patients, who actually live in a country with a 74% public coverage of healthcare system. [5, 19] However, the extreme simplicity of the single-item #28 of the EORTC QLQ-C30 questionnaire did not allow further understanding of the determinants of the phenomenon. Therefore, we decided to develop an instrument to describe financial toxicity more thoroughly and to explore potential determinants, within the Italian public health system, where the dynamics should be different as compared with a prevalently private health system like the US one. [20, 21].

The Italian health care system was shaped, since 1978, as a National Health Service (NHS) model, where the State is the most important financer, via general tax levies. [22] The NHS model prevails in Northern and Southern European Countries, whereas Central Europe is mostly characterized by social insurance-based model, funded by payroll taxes. Regardless the model, the European health care systems are characterized by a high proportion of healthcare expenditure covered by compulsory public programs, ranging from 66% in Spain to 78% in UK, compared to 49% in the USA. [19] The Italian NHS is decentralised, since regions are responsible for healthcare budget. [22] In Europe decentralisation does not depend on the healthcare system model: both NHS-shaped models (e.g. UK vs Spain) and

social-Insurance models (e.g. France vs Germany) are centralised vs decentralised respectively. Italy shows a lower intermediation of private expenditure than the other major European countries: in 2018 out-of-pocket expenditure accounted for 89% of private expenditure in Italy, compared to 40%, 55% and 75% in Germany, France and UK/Spain respectively. [23] The mean yearly amount of out-of-pocket expenses for cancer patients was estimated in the same year to be 1841 euros within a survey conducted by the Federazione italiana delle Associazioni di Volontariato in Oncologia – FAVO. [24]

Here we report the PROFFIT questionnaire that, to the best of our knowledge, is the first instrument fully published from a European country, and that is candidate to be cross-culturally adapted and validated in other countries with health systems similar to the Italian public health system. The PROFFIT questionnaire includes the FT-score (consisting of 7 items) and 9 single items assessing possible determinants of FT. In principle, the 7-item FT-score could be immediately generalizable to every system, once validity has been confirmed, while the 9 single-item determinants are strictly dependent on the healthcare system. The latter ones, that are lacking in other tools like COST, were acknowledged by patients in the cognitive interviews and should be the variable part of the questionnaire to be assessed in the various frameworks. In terms of construct validity, the PROFFIT score appears to be sensitive to patients' differences (e.g. Italian macro-regions, age, education level and family burden of disease), while, on the contrary, the time from cancer diagnosis has no impact on that score. However, together with other clinical questions, differences will be further validated in a larger independent sample in the ongoing step 4 of the project by using confirmatory analysis.

The need to have a specific instrument to measure financial toxicity has been previously addressed in the United States by the Investigators who produced and validated the Comprehensive Score for Financial Toxicity (COST) instrument. [25, 26]

The methodology applied to develop PROFFIT is similar to that applied for the COST development, as both followed the ISPOR guidelines. [10, 11] Nevertheless, the content of the two instruments differ, according to the three domains (psychological response, material conditions and coping behaviours) proposed by Altice et al. to describe financial hardship. [27] Indeed, while 8 of the 11 items of the COST version 1 questionnaire fall into the "affect" theme and the psychological response domain, 11 out of the 16 PROFFIT items pertain to the material conditions domain. This marked difference supports that the sociocultural context and the health and social care systems may significantly affect the causes and the consequences of financial problems of cancer patients. [20, 21] Therefore, specific instruments should be used within different contexts, and an analysis of differences between social and health systems should be done before choosing which instrument might be more appropriate for measuring financial toxicity. An instrument like PROFFIT, including several items related to determinants of financial toxicity, may be helpful to identify potential targets for action; and such targets, indeed, might be not immediately identified within a public health system that should cover all the needs of cancer patients. Namely, items related to transportation costs, to medical expenses not adequately covered by the public health system and the items pertaining to the quality of medical and non-medical staff and the communication among them clearly indicate some roadmaps of intervention that should be addressed within projects of education, organisation and financial support of various compartments of the welfare system.

Around one third of patients did not respond to items related to job activities. For this reason, we performed correlation analysis separately for job-related items and for all the other items,

and approached EFA using both a restricted sample, including only subjects answering all items, and the full sample, involving all subjects, where missing responses were imputed based on responses to the other valid items. We did that, according to the protocol, for both increasing the power of the analysis and as a sensitivity analysis of findings in the restricted sample. We chose to input the average score rather than the minimum score because the latter could be true for retired people (at least in the Italian population), but not for younger people without job. Further, this choice is consistent with the calculus of the score, where the missing items are not considered in the denominator. Accordingly, the restricted sample might be most sensitive to financial distress deriving from job loss or reduction but would not be representative of the real-world cancer patient population due to the selective exclusion of older patients, and generalizability would be reduced. On the contrary, the full sample, that is representative of the general cancer patient population might be less sensitive to relevance of job problems. We will further investigate the impact of job conditions in larger multicentre clinical studies through a more detailed definition of job categories, including all the types of unemployment that led to missing responses.

Notwithstanding a longer than planned interval between test and retest questionnaire administration, that might in principle reduce reproducibility, a good reliability was observed with all the items.

While usually a fixed time window is indicated in patient reported outcomes to define the period of interest, we decided not to use a fixed temporal frame to which refer the response. The decision was prompted by the consideration that in the final PROFFIT questionnaires, some of the items represent patient-reported experiences, rather than pure outcomes, and might derive from the accumulation of problems over the time. This should make the instrument more sensitive for cross-sectional studies, where it is not strictly important to define whether responses refer to a precise time window. Of course, when PROFFIT will be

used as a tool within prospective trials comparing different treatment strategies, a fixed time might be indicated.

According to the protocol, larger studies are planned to confirm criterion and construct validity of the PROFFIT instrument, and to assess the responsiveness of the tool [12] over the course of the disease. In the meanwhile, the questionnaire is available for all Investigators wishing to cross-validate it into different languages and countries. No fee will be required for using the questionnaire for purely academic studies, but registration of the protocols will be required and written agreements with the National Cancer Institute of Naples, Italy, will be requested.

In conclusion, financial toxicity is a major problem in oncology also within a universal healthcare system, hence the availability of specific and validated instruments is crucial to better understand its causes and its relationship with different aspects of cancer disease. Ultimately, data generated via this newly developed tool will provide insights on how to collaborate in the fight against financial toxicity, and hopefully improve the outcomes of cancer patients.

Table 1. Characteristics of participating patients

	Full sample N = 184	Restricted sample N = 116
Gender, n (%)		
Female	108 (58,7)	63 (54,3)
Male	76 (41,3)	53 (45,7)
Age, median (range)	59 (29-82)	55 (29-74)
Age category, n (%)		
<=60	94 (51,1)	72 (62,1)
>60	90 (48,9)	44 (37,9)
Macro-region of the participating institution, n (%)		
North	71 (38,6)	46 (39,7)
Center	15 (8,2)	9 (7,8)
South	71 (38,6)	43 (37,1)
Islands	27 (14,7)	18 (15,5)
Education level, n (%)		
Elementary school	23 (12,5)	8 (6,9)
Middle school	57 (31,0)	33 (28,4)
High school/degree	104 (56,5)	75 (64,7)
Marital status, n (%)		
Married	132 (71,7)	82 (70,7)
Other	52 (28,3)	34 (29,3)
With dependent family members, n (%)		
No	107 (58,2)	60 (51,7)
Yes	77 (41,8)	56 (48,3)
Family members with cancer or chronic disease, n (%)		
No	82 (44,6)	52 (44,8)
Yes	102 (55,4)	64 (55,2)
Working status, n (%)		
Working	84 (45,7)	82 (70,7)
Not working	100 (54,3)	34 (29,3)
Distance (km) from the hospital, median (range)	20 (1-430)	25 (1-286)
Time (years) from initial diagnosis, n (%)		
≤1	80 (43,5)	54 (46,6)
1-5	65 (35,3)	38 (32,8)
≥5	39 (21,2)	24 (20,7)

Table 1. Characteristics of participating patients

	Full sample N = 184	Restricted sample N = 116
Previous treatment, n (%)		
Surgery	129 (70,1)	81 (69,8)
Chemotherapy	157 (85,3)	94 (81,0)
Target-based agents	55 (29,9)	37 (31,9)
Immunotherapy	38 (20,7)	28 (24,1)
Hormonal therapy	31 (16,8)	18 (15,5)
Radiotherapy	43 (23,4)	28 (24,1)
Last/ongoing treatment, n (%)		
Chemotherapy	135 (73,4)	79 (68,1)
Target-based agents	18 (9,8)	13 (11,2)
Immunotherapy	25 (13,6)	19 (16,4)
Hormonal therapy	5 (2,7)	4 (3,4)
Radiotherapy	1 (0,5)	1 (0,9)
Primary tumour site, n (%)		
Breast	59 (32,1)	36 (31,0)
Lower_gastrointestinal tract	51 (27,7)	24 (20,7)
Genito-urinary	34 (18,5)	27 (23,3)
Thoracic	18 (9,8)	13 (11,2)
Upper_gastrointestinal tract	13 (7,1)	10 (8,6)
Other	9 (4,9)	6 (5,2)

Table 2. Final PROFFIT instrument

Item type and number	Italian version	**English translation** (for comprehension only)
Outcome items (FT-score)		
1.	Sono in grado di sostenere le mie spese mensili senza difficoltà (ad esempio per affitto, elettricità, telefono…)	I can afford my monthly expenses without difficulty (for example rent, electricity, phone…)
2.	La mia malattia ha ridotto le mie disponibilità economiche	My illness has reduced my financial resources
3.	Sono preoccupato dei problemi economici che potrei avere in futuro a causa della malattia	I am concerned by the economic problems I may have in the future due to my illness
4.	La mia condizione economica incide sulle mie possibilità di curarmi	My economic situation affects the possibility of receiving medical care
5.	Ho ridotto le spese per attività ricreative come vacanze, ristoranti o spettacoli per affrontare le spese della mia malattia	I have reduced my spending on leisure activities such as holidays, restaurants or entertainment in order to cope with expenses related to my illness
6.	Ho ridotto le spese per acquisti essenziali (ad esempio il cibo) per affrontare le spese per la mia malattia	I have reduced spending on essential goods (for example food) in order to cope with expenses related to my illness
7.	Sono preoccupata/o di non riuscire a lavorare a causa della mia malattia	I am worried that I will not be able to work due to my illness
Determinant items (single items)		
8.	Il Servizio Sanitario Nazionale copre tutti i costi sanitari associati alla mia malattia	The National Health Service covers all health costs related to my illness
9.	Ho sostenuto spese per una o più visite private per la mia malattia	I have paid for one or more private medical examinations for my illness
10.	Ho sostenuto spese per farmaci supplementari o integratori per la mia malattia	I have paid for additional medicines or supplements related to my illness
11.	Devo sostenere spese per cure integrative a mio carico (es. fisioterapia, psicoterapia, cure odontoiatriche)	I have to pay for additional treatment myself (for example physiotherapy, psychotherapy, dental care)
12.	Il centro di cura è lontano dalla mia abitazione	The treatment centre is a long way from where I live
13.	Ho dovuto sostenere rilevanti costi di trasporto per curarmi	I have spent a considerable amount of money on travel for treatment
14.	Il personale sanitario (cioè medici, infermieri, etc.) ha agevolato il percorso di cura	Medical staff (that is doctors, nurses etc.) have been helpful throughout my medical care
15.	Il personale ospedaliero amministrativo (cioè centro di prenotazione, segreterie, etc.) ha agevolato il percorso di cura	Staff in hospital administration (that is for booking appointments, secretaries, etc.) have been helpful throughout my medical care
16.	C'è stata comunicazione tra i medici e le strutture sanitarie che mi seguono	Medical staff and medical facilities I attended communicated with each other

Legend of figure

Figure 1. Postulated causal structure for PROFFIT tool

Acknowledgments

See appendix.

Authors contribution

FP obtained funding. SR, JB, CG and FP drafted the manuscript. MDM, FE, VM, LF, DG, LDC, FDL, EI, FT, LG, CJ, CMV, and MCP contributed to manuscript writing. MDM, VM, DG, DB, SC, CP, LDM, VZ, AAC, RB, AG and FP contributed to patients' enrolment. SR, LA, LG, CG and FP performed statistical analysis and drafted the manuscript. All Authors contributed to the manuscript and approved the final version.

Data

Data will be made available upon request to the corresponding author.

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Ethical approval statement

The study protocol was initially approved by the Ethics Committee of the National Cancer Institute of Naples, that acted as coordinating Ethics Committe. Date of first approval is October 18, 2017 and code of approval is 18/17oss. Thereafter, the protocol was approved by Ethics Committee at each participating centre.

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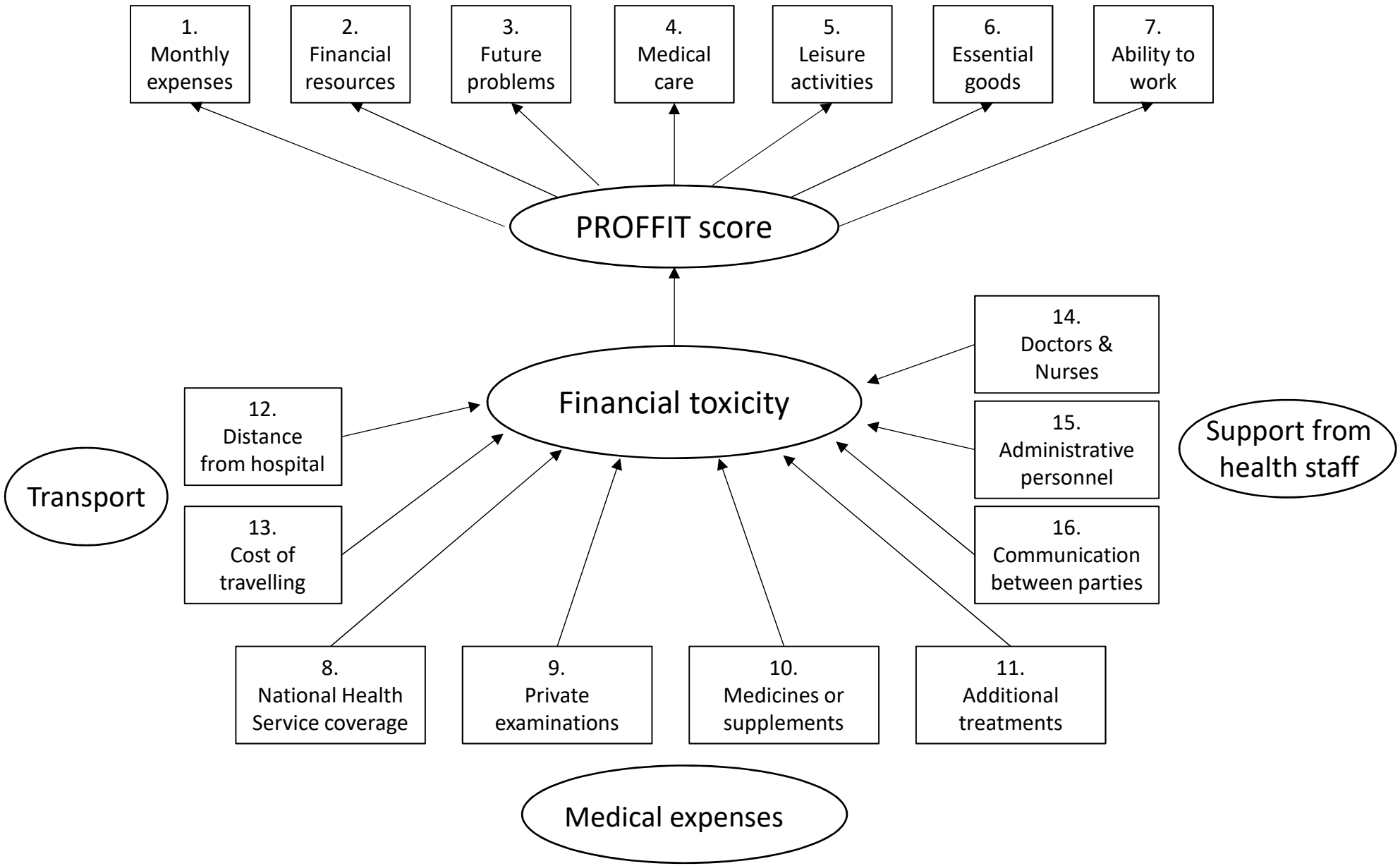
1. Monthly expenses
2. Financial resources
3. Future problems
4. Medical care
5. Leisure activities
6. Essential goods
7. Ability to work
PROFFIT score
Financial toxicity
14. Doctors & Nurses
15. Administrative personnel
16. Communication between parties
Support from health staff
12. Distance from hospital
13. Cost of travelling
Transport
8. National Health Service coverage
9. Private examinations
10. Medicines or supplements
11. Additional treatments
Medical expenses

Figure 1.

A cross-sectional study to develop and describe psychometric characteristics of a patient-reported instrument (PROFFIT) for measuring financial toxicity of cancer within a public healthcare system

Appendix

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Steering Committee and participating Investigators

The PROFFIT Steering Committee includes: Francesco Perrone, Jane Bryce, Ciro Gallo, Silvia Riva, Fabio Efficace, Francesco De Lorenzo, Elisabetta Iannelli, Laura Del Campo, Francesca Traclò, Massimo Di Maio (also as representative of AIOM – Associazione Italiana di Oncologia Medica), Luciano Frontini, Vincenzo Montesarchio (also as representative of CIPOMO – Collegio Italiano dei Primari di Oncologia Medica Ospedalieri), Diana Giannarelli, Lara Gitto, Claudio Jommi, Concetta Maria Vaccaro.

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Scoring procedure

Responses to PROFFIT items are coded in four categories of agreement with the statement of each item, scoring from 1 to 4:
1 - I do not agree at all, 2 - I agree partially, 3 - I agree substantially, 4 - I very much agree.

PROFFIT results are reported as a FT-score (including items #1 to #7) and nine separate items for FT determinants. All the scores are normalised to 0-100%, where 100 indicates the highest toxicity.

For **calculation of the FT-score**, including items #1 to #7, the following steps should be followed:

- Reverse the score for Item #1 according to the following formula

$$X_{1-reverse} = 5 - X_1$$

where X_1 is the response given to item #1.

- Calculate the FT-score according to the following formula

$$\frac{X_{1-reverse} + X_2 + X_3 + X_4 + X_5 + X_6 + X_7 - Y}{3 \times Y} \times 100$$

where X is the response given for each item and Y is the number of items with valid response; if Y is 3 or less the score should be considered missing. At least 4 valid responses are needed to calculate the FT-score.

Examples of calculation of FT score

Item: response	Intermediate	Final FT score
Example 1		
#1: I very much agree (4) #2: I agree partially (2) #3: I agree substantially (3) #4: I do not agree at all (1) #5: I agree partially (2) #6: I agree substantially (3) #7: I do not agree at all (1)	$X_{1-reverse} = 5 - 4 = 1$	$\frac{1+2+3+1+2+3+1-7}{3\times 7}\times 100 = 38$
Example 2.		
#1: I do not agree at all (1) #2: I very much agree (4) #3: I agree substantially (3) #4: I agree substantially (3) #5: I do not agree at all (1) #6: I agree partially (2) #7: MISSING	$X_{1-reverse} = 5 - 1 = 4$	$\frac{4+4+3+3+1+2-6}{3\times 6}\times 100 = 61$

For calculation of the score for items #8, #12, #14, #15 and #16 use the following formula

$$\frac{4 - X_j}{3} \times 100$$

where X is the response given and *j* is the item (8, 12, 15, or 16).

For calculation of the score for items #9, #10, #11, #13 use the following formula

$$\frac{X_j - 1}{3} \times 100$$

where X is the response given and *j* is the item (9, 10, 11 or 13).

Examples of calculation of single determinants scores

Item: response	Final single score
Example 3.	
#8: I do not agree at all (1) #14: I agree substantially (3)	$\frac{4-1}{3} \times 100 = 100$ $\frac{4-3}{3} \times 100 = 33$
Example 4.	
#9: I very much agree (4) #13: I agree partially (2)	$\frac{4-1}{3} \times 100 = 100$ $\frac{2-1}{3} \times 100 = 33$

Table S1. List of items in the pre-final instrument

Item ID in the pre-final instrument	*Item ID in the final instrument*	*Item*
Q1		Ho rapidamente trovato la struttura dove curarmi
Q2		Il tempo necessario per la diagnosi è stato breve
Q5		Ho sentito molto il peso della burocrazia (ad esempio per prenotare visite o per usufruire di benefici assistenziali, previdenziali e lavorativi)
Q26	10	Ho sostenuto spese per farmaci supplementari o integratori per la mia malattia
Q27	9	Ho sostenuto spese per una o più visite private per la mia malattia
Q28	11	Devo sostenere spese per cure integrative a mio carico (es. fisioterapia, psicoterapia, cure odontoiatriche)
Q49	8	Il Servizio Sanitario Nazionale copre tutti i costi sanitari associati alla mia malattia
Q68	1	Sono in grado di sostenere le mie spese mensili senza difficoltà (ad esempio per affitto, elettricità, telefono…)
Q76	3	Sono preoccupata/o dei problemi economici che potrei avere in futuro a causa della malattia
Q85	2	La mia malattia ha ridotto le mie disponibilità economiche
Q86	4	La mia condizione economica incide sulle mie possibilità di curarmi
Q90		I miei problemi economici mi preoccupano
Q95		La mia famiglia ha dovuto sostenere i costi di trasporto, vitto e alloggio per curarmi in una città diversa da quella in cui vivo
Q99	7	Sono preoccupata/o di non riuscire a lavorare a causa della malattia
Q102		Ho perso molti giorni lavorativi a causa della mia malattia
Q103		Non riesco a guadagnare come prima per via della mia malattia
Q106		Ho dovuto smettere di lavorare a causa della mia malattia
Q107		Ho ridotto le ore al lavoro a causa della mia malattia
Q111	14	Il personale sanitario (cioè medici, infermieri, etc.) ha agevolato il percorso di cura
Q112	15	Il personale ospedaliero amministrativo (cioè centro di prenotazione, segreterie, etc.) ha agevolato il percorso di cura
Q113	16	C'è stata comunicazione tra i medici e le strutture sanitarie che mi seguono
Q114		Il medico di famiglia ha agevolato il percorso di cura
Q121	5	Ho ridotto le spese per attività ricreative come vacanze, ristoranti o spettacoli per affrontare le spese della mia malattia
Q122	6	Ho ridotto le spese per acquisti essenziali (ad esempio il cibo) per affrontare le spese per la mia malattia
Q138		I servizi di trasporto per raggiungere l'ospedale (mezzi pubblici, parcheggi) sono scarsi
Q139		Ho dovuto sostenere i costi di trasporto, vitto e alloggio per curarmi in una città diversa da quella in cui vivo
Q140	13	Ho dovuto sostenere rilevanti costi di trasporto per curarmi
Q141	12	Il centro di cura è lontano dalla mia abitazione
Q151		È stato facile ottenere le agevolazioni economiche a cui ho diritto (ad esempio esenzione dal ticket, assegni o pensioni di invalidità)
Q156		So che la mia malattia mi dà diritto ad agevolazioni economiche (ad esempio esenzione dal ticket, assegni o pensioni di invalidità)

Questionnaire development

The first step of the analysis was estimating the between-item correlation matrix. Because of the ordinal nature of the items the pairwise Spearman rank correlation coefficients (r_s) were used.

We ascertained that there were about a third (68/184, 37%) of missing responses for the five job items from patients, who declared themselves retired or jobless (i.e. househusbands, housewives or individuals in search of employment); thus we decided to estimate two separate bivariate correlation matrices, one limited to job items, where only the 116 cases without missing information were used (**Table S2a below**), and one for all the other items, where the complete sample of 184 cases was used (**Table S2b below**).

For every pair, whose r_s >0.65, the item with the greater score in the previously published importance analysis was retained.

At the end of this preliminary analysis, six items (Q103, Q106, Q107, Q90, Q95, Q139) were excluded, because r_s was greater than 0.65, leading to 9 outcome and 15 determinant items for subsequent analyses. Out of the five job items, two were retained, one outcome (Q99) and one determinant (Q102).

Table S2. Spearman correlation coefficients between items

Table S2a. Job items

	Q99	Q102	Q103	Q106	Q107
Q99	1				
Q102	0,63	1			
Q103	0,72	0,66	1		
Q106	0,55	0,50	0,60	1	
Q107	0,56	0,67	0,67	0,78	1

Table S2b. All other items

	Q1	Q2	Q5	Q26	Q27	Q28	Q49	Q68	Q76	Q85	Q86	Q90	Q95	Q111	Q112	Q113	Q114	Q121	Q122	Q138	Q139	Q140	Q141	Q151	Q156
Q1	1																								
Q2	0,29	1																							
Q5	-0,08	-0,05	1																						
Q26	-0,18	-0,13	0,22	1																					
Q27	-0,16	-0,04	0,33	0,30	1																				
Q28	-0,07	-0,03	0,40	0,36	0,40	1																			
Q49	0,18	0,15	-0,23	-0,46	-0,27	-0,41	1																		
Q68	0,09	0,15	-0,03	-0,25	-0,09	-0,13	0,34	1																	
Q76	-0,22	-0,10	0,21	0,41	0,29	0,29	-0,32	-0,45	1																
Q85	-0,18	-0,04	0,27	0,46	0,31	0,37	-0,41	-0,41	0,65	1															
Q86	-0,24	-0,11	0,27	0,40	0,39	0,34	-0,46	-0,44	0,56	0,57	1														
Q90	-0,21	-0,15	0,16	0,34	0,22	0,26	-0,29	-0,53	0,71	0,67	0,70	1													
Q95	-0,23	-0,10	0,19	0,25	0,29	0,30	-0,23	-0,12	0,20	0,33	0,28	0,21	1												
Q111	0,35	0,25	-0,26	-0,26	-0,30	-0,29	0,38	0,14	-0,11	-0,17	-0,31	-0,13	-0,17	1											
Q112	0,25	0,10	-0,12	-0,20	-0,15	-0,16	0,41	0,10	-0,17	-0,18	-0,31	-0,14	-0,10	0,53	1										
Q113	0,21	0,13	-0,20	-0,05	-0,45	-0,22	0,22	0,00	-0,11	-0,07	-0,22	-0,15	-0,11	0,43	0,33	1									
Q114	0,15	0,09	-0,23	-0,10	-0,17	-0,24	0,12	0,25	-0,24	-0,12	-0,24	-0,24	0,02	0,37	0,38	0,28	1								
Q121	-0,21	-0,15	0,12	0,31	0,36	0,28	-0,21	-0,41	0,57	0,59	0,48	0,62	0,28	-0,06	-0,09	-0,17	-0,10	1							
Q122	-0,08	-0,09	0,09	0,36	0,25	0,31	-0,37	-0,47	0,48	0,49	0,64	0,66	0,33	-0,15	-0,17	-0,15	-0,10	0,57	1						
Q138	-0,08	-0,05	0,28	0,25	0,22	0,27	-0,30	-0,17	0,24	0,34	0,31	0,31	0,08	-0,24	-0,23	-0,03	-0,15	0,18	0,34	1					
Q139	-0,23	-0,02	0,18	0,28	0,33	0,36	-0,25	-0,19	0,26	0,36	0,34	0,23	0,69	-0,14	-0,10	-0,07	-0,02	0,30	0,42	0,15	1				
Q140	-0,17	-0,04	0,27	0,30	0,33	0,29	-0,27	-0,21	0,28	0,41	0,33	0,31	0,59	-0,20	-0,10	-0,02	-0,04	0,38	0,45	0,27	0,66	1			
Q141	-0,14	0,02	0,16	0,09	0,11	0,10	-0,02	-0,08	0,11	0,18	0,12	0,12	0,34	-0,04	0,04	0,05	-0,13	0,10	0,18	0,11	0,45	0,55	1		
Q151	0,10	0,11	-0,15	-0,21	-0,15	-0,11	0,27	0,24	-0,20	-0,29	-0,29	-0,24	-0,09	0,18	0,20	0,17	0,20	-0,22	-0,21	-0,10	-0,18	-0,18	-0,07	1	
Q156	0,15	0,27	-0,02	-0,14	-0,03	-0,07	0,33	0,39	-0,18	-0,22	-0,32	-0,25	-0,07	0,22	0,23	0,20	0,18	-0,15	-0,32	-0,22	-0,13	-0,08	0,01	0,35	1

Exploratory Factor Analysis (EFA)

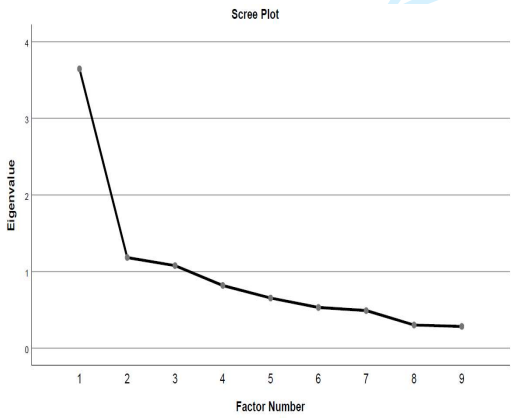
EFA on Outcome

EFA on the 9-outcome correlation matrix was performed by Principal Axis Factor (PAF) extraction option of SPSS, with VARIMAX rotation, in the sample of 116 subjects with complete information, because of the presence of the job item Q99.

The items considered at the start were Q5, Q68, Q76, Q85, Q86, Q99, Q121, Q122, Q151.

In the initial factor solution, three factors met the Kaiser criterion of eigenvalue >1 and accounted for 66% of the variance, the first axis alone explaining 41% of the total variance (see Table and scree plot below).

Factor	Total	% of variance	Cumulative %
1	3.645	40.501	40.501
2	1.185	13.163	53.665
3	1.079	11.986	65.651
4	0.819	9.105	74.756
5	0.656	7.286	82.042
6	0.533	5.927	87.969
7	0.492	5.470	93.439
8	0.304	3.383	96.821
9	0.286	3.179	100.000



Communalities and unrotated factor loadings are reported in the table below.

	Communalities			Factor		
	Initial	Extraction		1	2	3
Q5	0.133	0.31		0.261	0.203	-0.448
Q68	0.233	0.266		-0.452	0.248	-0.020
Q76	0.574	0.653		0.793	0.152	-0.027
Q85	0.605	0.729		0.819	0.238	0.034
Q86	0.510	0.677		0.723	-0.305	-0.248
Q99	0.248	0.344		0.424	0.387	0.119
Q121	0.471	0.593		0.704	0.118	0.290
Q122	0.437	0.623		0.630	-0.458	0.131
Q151	0.089	0.116		-0.265	-0.018	0.214

The item Q151 shows communality <0.20, Child 2006), and factor loadings <0.3 (Field, 2013) with all three factors, and was removed from further analyses.

Analogously at the next step the item Q5 was removed (communality = 0.072).

Eventually, seven items were retained with two factors meeting the Kaiser criterion of eigenvalue >1.

Communalities and factor loadings after Varimax rotation in the reduced sample of 116 patients are reported below. Many items cross loaded on both axes, that seemed both expression of financial burden: after rotation, the first one was more correlated with items mirroring an actual severe burden (Q86, Q122), while the second one appeared more correlated with worries about the future.

	Communalities			Factor	
	Initial	Extraction		1	2
Q68	0.222	0.269		-0.498	-0.145
Q76	0.570	0.648		0.468	0.655
Q85	0.600	0.737		0.413	0.753
Q86	0.491	0.588		0.719	0.266
Q99	0.247	0.356		0.012	0.596
Q121	0.470	0.510		0.397	0.594
Q122	0.426	0.566		0.735	0.159

The previous interpretation might imply that some correlation between axes would be expected. Thus, the oblique Promax rotation was applied. The same seven-item final solution was found with two factors meeting the Kaiser criterion of eigenvalue >1, and findings were reinforced. The factor loadings with Promax rotation are reported below.

	Factor	
	1	2
Q68	-0.549	0.047
Q76	0.248	0.616
Q85	0.129	0.766
Q86	0.764	0.004
Q99	-0.292	0.753
Q121	0.191	0.571
Q122	0.839	-0.140

The same analysis was repeated in the whole sample, replacing the missing information on the Q99 job in the 68 cases with the average score of the other items. We did that, according to the protocol, for both increasing the power of the analysis and as a sensitivity analysis of findings in the restricted sample. We chose to input the average score rather than the minimum score (that would sound *I am not worried at all that I will not be able to work due to my illness*) because it could be true for retired people (at least in the Italian population), but not for younger people without job. We think, indeed, that imputing the minimum score would definitely bias the score toward the null, while imputing the average could possibly only slightly overestimate the financial issues. Further, this choice is consistent with the calculus of the score, where the missing items are not considered in the denominator. This question will be further dealt with in the next validation steps.
In the full sample similar and stronger results were found: items Q151 and Q5 were removed because of low communalities (both <0.10). With the eventual 7-item analysis only the first axis met the Kaiser criterion of eigenvalue >1. Communalities and factor loadings in the complete sample are reported below. With one factor extracted no rotation was needed.

	Communalities			Factor
	Initial	Extraction		1
Q68	0.309	0.309		-0.556
Q76	0.555	0.622		0.788
Q85	0.582	0.647		0.805
Q86	0.534	0.547		0.739
Q99	0.318	0.273		0.522
Q121	0.494	0.537		0.733
Q122	0.506	0.485		0.697

Therefore, the PROFFIT FT-score includes 7 outcome items.

EFA on Determinants

EFA on the 15-outcome correlation matrix was performed by Principal Axis Factor (PAF) extraction option of SPSS, with VARIMAX rotation, in the sample of 116 subjects with complete information, because of the presence of the job item Q102.

The items considered at the start were Q1, Q2, Q26, Q27, Q28, Q49, Q102, Q111, Q112, Q113, Q114, Q138, Q140, Q141, Q156. In principle, the 15 determinants could be expression of three categories: (i) direct medical expenses (Q26, Q27, Q28, Q49), (ii) indirect costs due to travelling needs for medical care (Q138, Q140, Q141), (iii) indirect costs due to bureaucracy (Q1, Q2, Q111, Q112, Q113, Q114, Q156), plus a single job item (Q102).

In the initial factor solution, five factors met the Kaiser criterion of eigenvalue >1 and accounted for 62% of the variance (Table below), but the first axis explained only the 26% of the total variance.

Factor	Total	% of variance	Cumulative %
1	3.869	25.793	25.793
2	1.851	12.341	38.133
3	1.403	9.356	47.490
4	1.135	7.567	55.057
5	1.041	6.943	62.000
6	0.975	6.502	68.503
7	0.825	5.501	74.004
8	0.766	5.104	79.107
9	0.664	4.425	83.532
10	0.583	3.885	87.417
11	0.554	3.696	91.113
12	0.416	2.774	93.887
13	0.364	2.426	96.313
14	0.326	2.171	98.484
15	0.227	1.516	100.000

The job item Q102 had the smallest communality (0.183) and was removed. All the other items had complete responses, thus it seemed meaningless to continue in the restricted sample, and the subsequent analysis was only performed in the complete sample, where all of the responses were available.

The initial factor solution with 14 items in the full sample is reported below. Almost nothing changed: five factors met the Kaiser criterion of eigenvalue >1 and accounted for 63% of the variance, and the first axis explained only the 26% of the total variance.

Factor	Total	% of variance	Cumulative %
1	3.571	25.508	25.508
2	1.712	12.232	37.740
3	1.290	9.211	46.951
4	1.223	8.733	55.684
5	1.078	7.703	63.387
6	0.869	6.207	69.594
7	0.776	5.543	75.136
8	0.735	5.253	80.389
9	0.649	4.635	85.023
10	0.554	3.954	88.978
11	0.451	3.219	92.197
12	0.413	2.949	95.146
13	0.373	2.662	97.808
14	0.307	2.192	100.000

At the next steps items Q1, Q2, Q156, Q138 and Q114 were removed in turn because of small communalities, leading to the final solution with nine items and four factors retained. Communalities and factor loadings in the complete sample are reported below.

	Communalities			Factor		
	Initial	**Extraction**	**1**	**2**	**3**	**4**
Q26	0.305	0.425	0.628	-0.113	0.124	0.050
Q27	0.374	0.597	0.350	0.010	0.183	0.664
Q28	0.335	0.453	0.604	-0.048	0.137	0.259
Q49	0.393	0.576	-0.660	0.372	-0.012	-0.045
Q111	0.369	0.487	-0.210	0.592	-0.081	-0.294
Q112	0.333	0.610	-0.144	0.765	0.039	-0.049
Q113	0.319	0.556	0.001	0.332	0.059	-0.665
Q140	0.426	0.741	0.283	-0.069	0.803	0.105
Q141	0.316	0.449	0.009	0.033	0.669	0.005

Seemingly the first axis is related to direct medical expenses, the second axis to health bureaucracy items and the third axis to travelling costs, but some cross load on the factors is present.

Therefore we decided to retain the nine determinant items as single items in the final questionnaire.

Convergent validity

We said above that the PROFFIT FT-score includes 7 outcome items. In the table below correlation between each item and the total score of the scale, removing that item from the sum (convergent validity), is reported. Correlations are quite good, all r_s being greater than 0.5 in the full sample.

Table S3. Spearman correlation coefficients between each item and total score*

Item number	Full sample (N=184)	Restricted sample (N=116)
1	0.5325	0.5243
2	0.7360	0.7267
3	0.7251	0.7158
4	0.6646	0.6559
5	0.6887	0.6765
6	0.6712	0.6626
7	0.5537	0.3684

*calculated removing each item from the sum

Repeatability

Agreement between repeated measurements was assessed by intra-class correlation coefficient (ICC) and weighted Cohen's Kappa coefficient. Scores were stable enough over time, with ICCs ranging from 0.56 and 0.79. ICC was equal to 0.81 for the FT-score.

Table S4. Test-retest results

	ICC	Weighted K	Agreement %
Outcome items			
Item 1	0.70	0.70	95.7
Item 2	0.68	0.68	93.7
Item 3	0.56	0.56	90.7
Item 4	0.64	0.64	93.2
Item 5	0.65	0.65	91.0
Item 6	0.65	0.65	93.9
Item 7	0.79	0.81	94.4
FT-score	*0.81*	*0.82*	*97.4*
Determinant items			
Item 8	0.61	0.61	94.4
Item 9	0.72	0.72	94.2
Item 10	0.65	0.65	93.0
Item 11	0.61	0.62	92.4
Item 12	0.79	0.79	96.6
Item 13	0.78	0.78	92.2
Item 14	0.53	0.52	96.5
Item 15	0.59	0.58	95.0
Item 16	0.61	0.61	93.9

Table S5. Association of FT score with baseline characteristics of patients

	Median	(IQR)	P (Mann-Whitney)
All patients	38.1	(23.8-57.1)	
Region of the hospital			**0.005**
North	**28.6**	**(14.3-47.6)**	
Center	**33.3**	**(23.8-61.9)**	
South	**42.9**	**(23.8-57.1)**	
Islands	**52.4**	**(33.3-57.1)**	
Gender			0.932
Female	38.1	(23.8-57.1)	
Male	33.3	(23.8-52.4)	
Age category			**0.005**
<=65	**42.9**	**(23.8-57.1)**	
>65	**26.2**	**(14.3-47.6)**	
Education level			**0.018**
Elementary/Middle school	**42.9**	**(23.8-57.1)**	
High school/degree	**33.3**	**(19.0-50.0)**	
Cohabitant/Married			0.298
No	33.3	(23.8-52.4)	
Yes	38.1	(23.8-57.1)	
With dependent family members			0.060
No	33.3	(19.0-52.4)	
Yes	42.9	(28.6-57.1)	
Family members with cancer or chronic disease			**0.017**
No	**31.0**	**(19.0-52.4)**	
Yes	**42.9**	**(23.8-57.1)**	
Working status			0.531
Not working	33.3	(19.0-52.4)	
Working	38.1	(23.8-57.1)	
Site of treatment			0.134
Within the region of residency	38.1	(23.8-57.1)	
Outside the region of residency	28.6	(19.0-42.9)	
Time (years) from initial diagnosis			0.920
≤1	38.1	(23.8-57.1)	
1-5	33.3	(23.8-52.4)	
≥5	33.3	(19.0-61.9)	
Previous surgery			0.175
No	42.9	(23.8-61.9)	
Yes	33.3	(23.8-52.4)	
Last/ongoing anticancer treatment at registration			0.546
Chemotherapy	38.1	(23.8-57.1)	
Target-based agents	40.5	(23.8-52.4)	
Immunotherapy	28.6	(9.5-47.6)	
Hormonal therapy	38.1	(33.3-42.9)	
Radiotherapy	28.6	(28.6-28.6)	

Reporting checklist for cross sectional study.

Based on the STROBE cross sectional guidelines.

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Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	3-4

Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	#3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	#4	Present key elements of study design early in the paper	6
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	11
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants.	6
	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	6
Bias	#9	Describe any efforts to address potential sources of bias	7-8

Study size	#10	Explain how the study size was arrived at	6
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	7
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	7-8
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	7-8
Statistical methods	#12c	Explain how missing data were addressed	8
Statistical methods	#12d	If applicable, describe analytical methods taking account of sampling strategy	8
Statistical methods	#12e	Describe any sensitivity analyses	7-8
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	11
Participants	#13b	Give reasons for non-participation at each stage	11

Participants	#13c	Consider use of a flow diagram	Considered but deemed useless
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	11 (Table 1)
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	11
Outcome data	#15	Report numbers of outcome events or summary measures. Give information separately for exposed and unexposed groups if applicable.	Not applicable
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Not applicable
Main results	#16b	Report category boundaries when continuous variables were categorized	Not applicable
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable

Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	11-13
Discussion			
Key results	#18	Summarise key results with reference to study objectives	15
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	16-17
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	15-16
Generalisability	#21	Discuss the generalisability (external validity) of the study results	18
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	22

BMJ Open

A cross-sectional study to develop and describe psychometric characteristics of a patient-reported instrument (PROFFIT) for measuring financial toxicity of cancer within a public healthcare system

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Complete List of Authors:	Riva, Silvia; St Mary's University; University Hospital of Milan Arenare, Laura Di Maio, Massimo; Università degli Studi di Torino, Dipartimento di Oncologia, AO Ordine Mauriziano Efficace, Fabio; Italian Group for Adult Hematologic Diseases (GIMEMA) Montesarchio, Vincenzo; AORN Ospedali dei Colli, Oncologia Frontini, Luciano; Federation of Italian Cooperative Oncology Groups (FICOG) Giannarelli, Diana; Istituto Nazionale per lo Studio e la Cura dei Tumori Regina Elena, IRCCS, Unità di Biostatistica Bryce, Jane; Istituto Nazionale Tumori IRCCS Fondazione Pascale, Unità Sperimentazioni Cliniche Del Campo, Laura; Federazione italiana delle Associazioni di Volontariato in Oncologia (FAVO) De Lorenzo, Francesco; Associazione Italiana Malati di Cancro (AIMAC); European Cancer Patient Coalition (ECPC) Iannelli, Elisabetta; F.A.V.O. Italian Federation of Volunteer-Based Cancer Organizations Traclò, Francesca; Associazione Italiana Malati di Cancro (AIMAC) Gitto, Lara; Università degli Studi di Messina, Dipartimento di Economia Jommi, Claudio; Università Bocconi Vaccaro, Concetta Maria; Censis - Centro Studi Investimenti Sociali, Area Welfare e Salute Barberio, Daniela; Istituto Nazionale Tumori IRCCS Fondazione Pascale, Struttura Semplice Dipartimentale di Psiconcologia Clinica Cinieri, Saverio; Ospedale Perrino, Oncologia Porta, Camillo; Fondazione IRCCS Policlinico San Matteo Del Mastro, Lucia; Ospedale Policlinico San Martino Istituto di Ricovero e Cura a Carattere Scientifico per l'Oncologia, Dipartimento di Medicina Interna e Medicina Specialistica; Università di Genova, Dipartimento di Medicina Interna e Medicina Specialistica Zagonel, Vittorina; Istituto Oncologico Veneto Istituto di Ricovero e Cura a Carattere Scientifico Cogoni, Alessio Aligi; AOU di Sassari, Unità operativa complessa di Oncologia Medica Bordonaro, Roberto; Azienda Ospedaliera di Rilievo Nazionale e di Alta Specializzazione Garibaldi Ospedale Garibaldi-Nesima, Oncologia Gimigliano, Anna; Istituto Nazionale Tumori IRCCS Fondazione Pascale,

	Clinical Trials Unit Piccirillo, Maria Carmela; Istituto Nazionale Tumori IRCCS Fondazione Pascale, Clinical Trials Unit Guizzaro, Lorenzo; Università degli Studi della Campania Luigi Vanvitelli Gallo, Ciro; Università degli Studi della Campania Luigi Vanvitelli, Statistica Medica Perrone, Francesco; Istituto Nazionale Tumori IRCCS Fondazione Pascale, Clinical Trials Unit
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A cross-sectional study to develop and describe psychometric characteristics of a patient-reported instrument (PROFFIT) for measuring financial toxicity of cancer within a public healthcare system

Silvia Riva[1,2], Laura Arenare[3], Massimo Di Maio[4], Fabio Efficace[5], Vincenzo Montesarchio[6], Luciano Frontini[7], Diana Giannarelli[8], Jane Bryce[3,9,10], Laura Del Campo[11], Francesco De Lorenzo[12], Elisabetta Iannelli[13], Francesca Traclò[13], Lara Gitto[14], Claudio Jommi[15], Concetta Maria Vaccaro[16], Daniela Barberio[17], Saverio Cinieri[18], Camillo Porta[19a], Lucia Del Mastro[20,21], Vittorina Zagonel[22], Alessio Aligi Cogoni[23], Roberto Bordonaro[24], Anna Gimigliano[3], Maria Carmela Piccirillo[3], Lorenzo Guizzaro[25], Ciro Gallo[25*], Francesco Perrone[3*]

[1] St Mary's University, Twickenham, London, UK
[2] Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, University Hospital of Milan, Italy
[3] Unità Sperimentazioni Cliniche, Istituto Nazionale per lo Studio e la Cura dei Tumori, IRCCS, Fondazione G.Pascale, Napoli, Italy
[4] Dipartimento di Oncologia, Università di Torino, AO Ordine Mauriziano, Torino, Italy
[5] Gruppo Italiano per le Malattie Ematologiche dell'Adulto (GIMEMA) Health Outcomes Research Unit, Roma, Italy
[6] Azienda Ospedaliera Specialistica dei Colli, Napoli, Italy
[7] Federation of Italian Cooperative Oncology Groups (FICOG), Milano, Italy
[8] Unità di Biostatistica, Istituto Nazionale per lo Studio e la Cura dei Tumori Regina Elena, IRCCS, Roma, Italy
[9] Dipartimento di Biomedicina e Prevenzione, Università degli Studi di Roma "Tor Vergata", Roma, Italy
[10] Ascension St. John Clinical Research Institute, Tulsa, USA
[11] Federazione italiana delle Associazioni di Volontariato in Oncologia (FAVO), Rome, Italy
[12] European Cancer Patient Coalition (ECPC), Brussels, Belgium
[13] Associazione Italiana Malati di Cancro (AIMAC), Roma, Italy
[14] Dipartimento di Economia, Università degli Studi di Messina, Italy
[15] CERGAS (Centre for Health and Social Care Management), SDA Bocconi School of Management, Milano, Italy
[16] Area Welfare e Salute, Centro Studi Investimenti Sociali (CENSIS), Roma, Italy
[17] Struttura Semplice Dipartimentale di Psiconcologia Clinica, Istituto Nazionale per lo Studio e la Cura dei Tumori, IRCCS, Fondazione G.Pascale, Napoli, Italy
[18] Unità Operativa Complessa di Oncologia Medica, Ospedale Perrino, Brindisi, Italy
[19] Struttura Complessa di Oncologia Medica, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy
[20] UO Breast Unit, IRCCS Ospedale Policlinico San Martino, Genova, Italy
[21] Dipartimento di Medicina Interna e Medicina Specialistica (DIMI), Università di Genova, Italy
[22] U.O.C. Oncologia 1, Istituto Oncologico Veneto, IOV, IRCCS Padova, Italy
[23] Unità operativa complessa di Oncologia Medica - AOU di Sassari, Italy
[24] Struttura Complessa di Oncologia Medica, ARNAS Garibaldi-Nesima, Catania, Italy
[25] Statistica Medica, Università degli Studi della Campania "Luigi Vanvitelli", Napoli, Italy.

* co-last authors
[a] present address: Dipartimento di Scienze Biomediche ed Oncologia Umana, Università degli Studi di Bari 'A. Moro' e Azienda Ospedaliero-Universitaria Consorziale Policlinico di Bari, Bari, Italy.

Corresponding author
Dr. Francesco Perrone
Unità Sperimentazioni Cliniche
Istituto Nazionale per lo Studio e la Cura dei Tumori,
IRCCS Fondazione Pascale, Napoli
Via Mariano Semmola
80131 Napoli, Italy
f.perrone@istitutotumori.na.it
fax +390817702938
phone +390815903571

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Abstract

Objectives: To measure and explain financial toxicity (FT) of cancer in Italy, where a public healthcare system exists and cancer patients are not expected (or only marginally) to pay out-of-pocket for health care.

Setting: Ten clinical oncological centres, distributed across Italian macro-regions (North, Centre, South and Islands), including hospitals, university hospitals and national research institutes.

Participants: From Oct 8th, 2019 to Dec 11th, 2019, 184 patients, aged 18 or more, who were receiving or had received within the previous three months active anticancer treatment were enrolled, 108 (59%) females and 76 (41%) males.

Intervention: A 30-item pre-final questionnaire, previously developed within the qualitative tasks of the project, was administered, either electronically (n=115) or by paper sheet (n=69).

Primary and secondary outcome measures: According to the protocol and the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) methodology, the final questionnaire was developed by mean of explanatory factor analysis and tested for reliability, internal consistency (Cronbach's α test and item-total correlation) and stability of measurements over time (test–retest reliability by intra-class correlation coefficient and weighted Cohen's Kappa coefficient).

Results: After exploratory factor analysis, a score measuring FT (FT-score) was identified, made by 7 items dealing with outcomes of FT. The Cronbach alpha coefficient for the FT-score was 0.87 and the item-total correlation coefficients ranged from 0.53 to 0.74. Further, 9 single items representing possible determinants of FT were also retained in the final

instrument. Test-retest analysis revealed a good internal validity of the FT-score and the 16 items retained in the final questionnaire.

Conclusions: The PROFFIT (Patient Reported Outcome for Fighting FInancial Toxicity) instrument consists of 16 items and is the first reported instrument to assess FT of cancer developed in a country with a fully public healthcare system.

Trial registration: clinicaltrials.gov NCT 03473379.

ARTICLE SUMMARY

Strengths and limitations of this study

- PROFFIT was developed as a reaction to the finding that financial problems affect the outcome of cancer patients in Italy, notwithstanding the Italian healthcare system is based on universal coverage and patients do not pay to access cancer treatment.
- No tool for measuring and understanding financial toxicity of cancer had been ever produced in the context of a public healthcare system with universal coverage.
- The development of PROFFIT was done according to a widely accepted methodology to produce patient reported outcome measures.
- Correlation of PROFFIT with known anchors (quality of life tools, performance status) and the responsiveness of the instrument over the course of the disease are being studied.
- PROFFIT might be of interest for other countries where a public healthcare system exists.

INTRODUCTION

Financial toxicity (FT) following cancer diagnosis and treatment is an increasingly recognized problem worldwide. While initial reports came from the United States (US), recent data suggest its importance in many other countries with different healthcare systems, like for example Japan, Nepal, Canada and Italy. [1-7] In 2016, we reported financial difficulties among Italian cancer patients enrolled in clinical trials, and their association with worse quality of life and overall survival. [5] Using individual data from 16 randomized trials, we found that patients reporting some degree of financial burden at baseline had a higher chance of worsening global quality of life (QoL) response after treatment, and that patients, who developed financial toxicity during treatment, had a statistically significant shorter survival. [5]

Therefore, in 2018, we started the multicentre PROFFIT (Patient Reported Outcome for Fighting FInancial Toxicity of cancer) project to develop a tool for measuring and understanding financial toxicity of cancer that would be sensitive to dimensions of a universal healthcare system. The PROFFIT protocol and the early qualitative findings of the project were reported elsewhere. [8 9] We herein report the quantitative analysis of the 30 items resulting from the early phases of the project and the final questionnaire.

METHODS

The study protocol was approved by the independent ethical review board of the institutions enrolling patients and is registered on clinicaltrials.gov NCT03473379. Overall, the project was performed according to International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guidelines. [10 11]

Patient sample and data acquisition

To be included patients had to fulfil the following enrolment criteria: i) adult patients (>18 years), ii) histologically or cytologically confirmed diagnosis of any type of solid cancer or haematological malignancy, iii) medical treatment (chemotherapy, target agents, immunotherapy, hormonal treatment, radiotherapy or combinations of such therapies) ongoing or terminated within the previous three months. The questionnaires could be administered either as paper document or as a tablet digital version, according to centre choice. Written informed consent was required. The minimum sample size was calculated to assess the test-retest reliability. With an acceptable level of intraclass correlation coefficient (ICC) equal to 0.70 and an expected ICC of 0.80, a one-sided alfa 0.05, 80% power, at least 118 patients had to be enrolled.

Instrument

The first two tasks of the PROFFIT project, concept elicitation and item generation, have been previously described. [9] Briefly, as for concept elicitation, an extensive list of topics related to FT was derived from literature review, expert survey and focus groups. Ten FT

domains (medical care, domestic economy, emotion, family, job, health workers, welfare state, free time and transportation) were described by 156 topics, that reduced to 55 items after correction for redundancy, and to 30 items after importance analysis. These 30 items were proposed to further 45 patients within cognitive interviews testing comprehensibility, recall, judgement and response; the 30 items refined after cognitive interviews represented the pre-final instrument **(Table S1)**.

Two groups of items were identified by the study steering committee: (1) *outcome* items (n=10), i.e. indicators, that reflect the level of the supposed latent FT and that do not alter or influence the latent construct they measure, and (2) *determinant* items (n= 20), i.e. causal indicators, that are considered to affect FT and that may change the latent variable. [12] Separate analyses were performed in the outcome and determinant groups.

Statistical analysis

To reduce possible redundancy, the between-item correlation matrix was preliminarily estimated by pairwise Spearman rank correlation coefficients (r_s), because of the ordinal nature of items; cut-off was set equal to 0.65, and for each pair of items with r_s >0.65 the item with the greater score in the previously published importance analysis was retained. [9] Because information was missing for the five items related to job in 68/184 (37%) patients, who declared themselves retired or jobless (i.e. househusbands, housewives or individuals in search of employment), correlation coefficients were estimated separately for job items (excluding patients with missing data on job items) and for all the other items (within the full population).

Exploratory factor analysis (EFA) was used to discover the presence of multi-item scales and the distribution of the items consistent with the theoretical framework of FT. [13] To extract

factors we used the Principal Axis Factoring (PAF) analysis with Varimax and Promax rotation, and Kaiser normalization. To determine the number of scale factors, we relied on the Kaiser criterion to select factors with eigenvalue >1, the Scree test to depict the percentage of total variance explained by the factors extracted, and the interpretability of the factor solution. PAF assumptions were assessed by Bartlett sphericity test and Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy. [14]

Due to missing data in job items, EFA was performed both in the sample of patients with complete valid information (hereby defined as "restricted sample"), and in the whole sample (hereby defined as "full sample"), by imputing, for each subject, the missing values with the average score of the other answered items. A more detailed description of the whole analysis path is reported in the Appendix.

The face validity of the resulting scale was examined, both in terms of the scale global meaning and in terms of the appropriateness of each individual item to that scale. Internal consistency, i.e. within-scale between-items correlations, was assessed by Cronbach's alpha correlation coefficient, assuming as acceptable a value >0.70. Relationships between each individual item x_i and the total score of the scale to which they were assumed to belong were assessed by Spearman rank correlation coefficient with correction for overlap, i.e. by omitting x_i from the total score. To evaluate stability of measurements over time, the questionnaire was to be administered again after one week and the test–retest reliability was assessed by intra-class correlation coefficient (ICC) and weighted Cohen's Kappa coefficient. We considered a minimally acceptable level of reliability equal to 0.70 and an expected ICC of 0.80.

A preliminary construct validity analysis, as requested from Reviewers, was performed evaluating the association of the FT with baseline demographic and clinical variables;

however, findings are only suggestive, and need to be independently validated in a larger independent sample, whose recruitment is ongoing, as stated in the protocol.[8]

Descriptive statistics were used to characterize the study sample and their mean scores answers. The data met all the necessary assumptions for this factor analysis. Statistical analyses were performed with SPSS version 25.0 (SPSS; Chicago, IL, USA) and with Stata 14 (Stata, College Station, TX, USA)

English translation

To allow international comprehension of the final PROFFIT questionnaire, an English translation was done according to methodology proposed by Wild et al.[15] First, a translation committee was established including five members of the Steering Committee (FP, SR, CG, MDM, FE), two English mother-tongue translators and two Italian mother-tongue translators. Second, the two English translators independently translated the tool into English producing two forward translations (T1 and T2) that were collected and subsequently discussed in a meeting where the agreement on the English version was achieved. Third, the two Italian translators (unaware of the original Italian version) independently back-translated the English version into Italian; their translations were collected and discussed in a meeting including the whole translation committee. During such meeting the final English translation was generated and approved by the Steering Committee. It is important to underline that the English translation has to be considered just to allow comprehension by non-Italian readers because it has not been cross-culturally adapted and validated within a population of English native patients.

Patient and public involvement

The project was informed by patients' thanks to the involvement of patients and representatives of patients' associations in the Steering Committee that oversaw all the phases of the project, including protocol definition, qualitative analysis (previously reported elsewhere) producing the pre-final questionnaire, and final analyses producing the final questionnaire (reported here); they are co-author of this manuscript and of the previous manuscripts dealing with this project (LDC, FDL, EI, FT). They will also contribute in dissemination of the results of the project.

RESULTS

From Oct 8th, 2019 to Dec 11th, 2019, 185 patients were enrolled at 10 participating centres; one patient was excluded because the baseline questionnaire was missing due to a technical problem with web connection of the tablet application. Questionnaires were administered as paper document in 4 centres (69 patients) and as digital tablet application in 6 centres (115 patients). Job-related items had a 37% rate of missing responses; all the remaining items were answered in 100% of the cases, leading to the full sample of 184 patients and the restricted sample of 116 patients.

Demographic and clinical characteristics of both samples are shown in **Table 1**. In the full sample, median age was 59 years (range 29-83) and participants were predominantly female. More than half of the patients had a high level of schooling (high school or degree), and around 70% were married. In terms of clinical characteristics, the great majority of patients had a previous surgery for cancer, and the most common treatment was chemotherapy. As expected, in the restricted sample, patients were younger, with a higher level of education and more frequently actively working.

At the preliminary between-item correlation analysis, six items were excluded (three job-related) because r_s was greater than 0.65, leading to 9 outcome and 15 determinant items for subsequent analyses (**Table S2a and S2b**).

EFA on the 9-outcome correlation matrix was first performed in the restricted sample of 116 subjects with complete information, because of the presence of the job item Q99. PAF assumptions on the 9 outcome items were met with very good parameters (KMO = 0.82 and Bartlett's test of sphericity, p-value <.001). Two items were excluded because of low communality (see appendix for details). With 7 outcome items, two initial eigenvalues were >1 and explained 66% of the total variance; both could be interpreted as expression of financial burden, the first one being more correlated with items mirroring an actual severe

burden while the second one appeared more correlated with worries about the future. This interpretation was reinforced when oblique Promax rotation was applied (see appendix).

In the full sample (KMO = 0.87 and Bartlett's test of sphericity, p-value <.001), with missing imputation for the job-related item, similar findings were observed. The same seven items were retained, but only one factor >1 was extracted that explained 57% of the total variance; factor loadings and communalities are reported in the appendix (EFA on outcome paragraph).

Thus, the PROFFIT FT-score includes 7 outcome items. The Cronbach alpha coefficient for the PROFFIT FT-score was 0.85 in the restricted sample and 0.87 in the full sample, indicating that the correlation between the items and the score is consistently reliable. Correlations between each single item of the FT-score and the total score (after removal of the single item), ranged from 0.37 to 0.73 in the restricted sample, and from 0.53 to 0.74 in the full sample (**Table S3**).

Similarly, assumptions on the 15 determinants items were met with satisfactory parameters (KMO = 0.68 and Bartlett's test of sphericity, p-value <0.001). PAF on the determinant items eliminated 6 items because of low communality and showed that the other 9 items were only mildly related, without a clear definition of any factor, hence they were retained as single items (see appendix – EFA on determinants paragraph - for more details).

Therefore, the final PROFFIT instrument includes the FT-score (consisting of 7 items) and 9 single items assessing possible determinants of FT. In **Table 2**, both the Italian items and the English translation are reported. The postulated causal structure for PROFFIT is reported in **Figure 1**.

We excluded from the test-retest analysis all questionnaires administered more than 35 days (n=52) after the first ones because of the possibility that more than one cycle of treatment

could had been given during the interval. However, due to cyclic structure of ongoing anticancer treatment, most retest questionnaires were actually administered later than the planned one-week interval from the first assessment. Within 132 cases of the full sample, median time between test and retest was 21 days; ICC and Cohen's weighted K coefficients of the FT-score were excellent, being equal to 0.81 and 0.82, respectively. Considering each singular item, all ICCs and K coefficients were good, ranging from 0.52 and 0.79 (**Table S4).**

Associations of FT-score with baseline characteristics of patients are reported in **Table S5**. Significant and relevant differences were found in accordance with Italian macro-region, age, education level and family disease burden.

DISCUSSION

Financial toxicity has been initially described in the US as a factor negatively affecting cancer patients during their journey, in several ways.[7] Particularly, both QoL and survival have been reported to be worse among patients facing with financial hardships and bankruptcy. [16 17] This might be not surprising given that the US health system prevalently requires out of pocket co-payment of medical expenses, and that the cost of cancer treatment has been steadily increasing. [18]

On the contrary, we were surprised when we earlier observed that financial problems (measured by the EORTC QLQ-C30 questionnaire) were associated with worse QoL and shorter survival also among Italian cancer patients, who actually live in a country with a 74% public coverage of healthcare system. [5 19] However, the extreme simplicity of the single-item #28 of the EORTC QLQ-C30 questionnaire did not allow further understanding of the determinants of the phenomenon. Therefore, we decided to develop an instrument to describe financial toxicity more thoroughly and to explore potential determinants, within the Italian public health system, where the dynamics should be different as compared with a prevalently private health system like the US one. [20 21].

The Italian health care system was shaped, since 1978, as a National Health Service (NHS) model, where the State is the most important financer, via general tax levies. [22] The NHS model prevails in Northern and Southern European Countries, whereas Central Europe is mostly characterized by social insurance-based model, funded by payroll taxes. Regardless the model, the European health care systems are characterized by a high proportion of healthcare expenditure covered by compulsory public programs, ranging from 66% in Spain to 78% in UK, compared to 49% in the USA. [19] The Italian NHS is decentralised, since regions are responsible for healthcare budget. [22] In Europe decentralisation does not depend on the healthcare system model: both NHS-shaped models (eg. UK vs Spain) and

social-Insurance models (eg. France vs Germany) are centralised vs decentralised respectively. Italy shows a lower intermediation of private expenditure than the other major European countries: in 2018 out-of-pocket expenditure accounted for 89% of private expenditure in Italy, compared to 40%, 55% and 75% in Germany, France and UK/Spain respectively. [23] The mean yearly amount of out-of-pocket expenses for cancer patients was estimated in the same year to be 1841 euros within a survey conducted by the Federazione italiana delle Associazioni di Volontariato in Oncologia – FAVO. [24]

Here we report the PROFFIT questionnaire that, to the best of our knowledge, is the first instrument fully published from a European country, and that is candidate to be cross-culturally adapted and validated in other countries with health systems similar to the Italian public health system. The PROFFIT questionnaire includes the FT-score (consisting of 7 items) and 9 single items assessing possible determinants of FT. In principle, the 7-item FT-score could be immediately generalizable to every system, once validity has been confirmed, while the 9 single-item determinants are strictly dependent on the healthcare system. The latter ones, that are lacking in other tools like COST, were acknowledged by patients in the cognitive interviews and should be the variable part of the questionnaire to be assessed in the various frameworks. In terms of construct validity, the PROFFIT score appears to be sensitive to patients' differences (e.g. Italian macro-regions, age, education level and family burden of disease), while, on the contrary, the time from cancer diagnosis has no impact on that score. However, together with other clinical questions, differences will be further validated in a larger independent sample in the ongoing step 4 of the project by using confirmatory analysis.

The need to have a specific instrument to measure financial toxicity has been previously addressed in the US by the Investigators who produced and validated the Comprehensive Score for Financial Toxicity (COST) instrument [25 26] .

The methodology applied to develop PROFFIT is similar to that applied for the COST development, as both followed the ISPOR guidelines. [10 11] Nevertheless, the content of the two instruments differ, according to the three domains (psychological response, material conditions and coping behaviours) proposed by Altice et al. to describe financial hardship. [27] Indeed, while 8 of the 11 items of the COST version 1 questionnaire fall into the "affect" theme and the psychological response domain, 11 out of the 16 PROFFIT items pertain to the material conditions domain. This marked difference supports that the sociocultural context and the health and social care systems may significantly affect the causes and the consequences of financial problems of cancer patients. [20 21] Recently, the COST-FACIT version 2) has been developed. In this version, an additional item was added to reflect overall financial wellbeing (https://wizard.facit.org/index.php?option=com_facit&view=search&searchPerformed=1 accessed August 18th, 2021). However, this additional item was not included in the calculation of the summary score in the original validation study [25-26] and this makes difficult to make any comparisons with the US context, at the present time.

Therefore, specific instruments should be used within different contexts, and an analysis of differences between social and health systems should be done before choosing which instrument might be more appropriate for measuring financial toxicity. An instrument like PROFFIT, including several items related to determinants of financial toxicity, may be helpful to identify potential targets for action; and such targets, indeed, might be not immediately identified within a public health system that should cover all the needs of cancer patients. Namely, items related to transportation costs, to medical expenses not adequately covered

by the public health system and the items pertaining to the quality of medical and non-medical staff and the communication among them clearly indicate some roadmaps of intervention that should be addressed within projects of education, organisation and financial support of various compartments of the welfare system.

Around one third of patients did not respond to items related to job activities. For this reason, we performed correlation analysis separately for job-related items and for all the other items, and approached EFA using both a restricted sample, including only subjects answering all items, and the full sample, involving all subjects, where missing responses were imputed based on responses to the other valid items. We did that, according to the protocol, for both increasing the power of the analysis and as a sensitivity analysis of findings in the restricted sample. We chose to input the average score rather than the minimum score because the latter could be true for retired people (at least in the Italian population), but not for younger people without job. Further, this choice is consistent with the calculus of the score, where the missing items are not considered in the denominator. Accordingly, the restricted sample might be most sensitive to financial distress deriving from job loss or reduction but would not be representative of the real-world cancer patient population due to the selective exclusion of older patients, and generalizability would be reduced. On the contrary, the full sample, that is representative of the general cancer patient population might be less sensitive to relevance of job problems. We will further investigate the impact of job conditions in larger multicentre clinical studies through a more detailed definition of job categories, including all the types of unemployment that led to missing responses.

Notwithstanding a longer than planned interval between test and retest questionnaire administration, that might in principle reduce reproducibility, a good reliability was observed with all the items.

While usually a fixed time window is indicated in patient reported outcomes to define the period of interest, we decided not to use a fixed temporal frame to which refer the response. The decision was prompted by the consideration that in the final PROFFIT questionnaires, some of the items represent patient-reported experiences, rather than pure outcomes, and might derive from the accumulation of problems over the time. This should make the instrument more sensitive for cross-sectional studies, where it is not strictly important to define whether responses refer to a precise time window. Of course, when PROFFIT will be used as a tool within prospective trials comparing different treatment strategies, a fixed time might be indicated. The flexibility proposed by the PROFFIT aims to facilitate its use in healthcare settings alongside routine psycho-oncological assessments for stress and quality of life where stress/financial anxiety could represent a new construct to be systematically assessed as recently suggested.[28] The PROFFIT will be also able to monitor patients' social conditions including work and family status, dimensions that seems extremely sensitive to FT. [29 30]

According to the protocol, larger studies are planned to confirm criterion and construct validity of the PROFFIT instrument, and to assess the responsiveness of the tool [12] over the course of the disease and in different types of patients. In the meanwhile, the questionnaire is available for all Investigators wishing to cross-validate it into different languages and countries. No fee will be required for using the questionnaire for purely academic studies, but registration of the protocols will be required and written agreements with the National Cancer Institute of Naples, Italy, will be requested.

In conclusion, financial toxicity is a major problem in oncology also within a universal healthcare system, hence the availability of specific and validated instruments is crucial to better understand its causes and its relationship with different aspects of cancer disease. Ultimately, data generated via this newly developed tool will provide insights on how to

collaborate in the fight against financial toxicity, and hopefully improve the outcomes of cancer patients.

Table 1. Characteristics of participating patients

	Full sample N = 184	Restricted sample N = 116
Gender, n (%)		
Female	108 (58,7)	63 (54,3)
Male	76 (41,3)	53 (45,7)
Age, median (range)	59 (29-82)	55 (29-74)
Age category, n (%)		
<=60	94 (51,1)	72 (62,1)
>60	90 (48,9)	44 (37,9)
Macro-region of the participating institution, n (%)		
North	71 (38,6)	46 (39,7)
Center	15 (8,2)	9 (7,8)
South	71 (38,6)	43 (37,1)
Islands	27 (14,7)	18 (15,5)
Education level, n (%)		
Elementary school	23 (12,5)	8 (6,9)
Middle school	57 (31,0)	33 (28,4)
High school/degree	104 (56,5)	75 (64,7)
Marital status, n (%)		
Married	132 (71,7)	82 (70,7)
Other	52 (28,3)	34 (29,3)
With dependent family members, n (%)		
No	107 (58,2)	60 (51,7)
Yes	77 (41,8)	56 (48,3)
Family members with cancer or chronic disease, n (%)		
No	82 (44,6)	52 (44,8)
Yes	102 (55,4)	64 (55,2)
Working status, n (%)		
Working	84 (45,7)	82 (70,7)
Not working	100 (54,3)	34 (29,3)
Distance (km) from the hospital, median (range)	20 (1-430)	25 (1-286)
Time (years) from initial diagnosis, n (%)		
≤1	80 (43,5)	54 (46,6)
1-5	65 (35,3)	38 (32,8)
≥5	39 (21,2)	24 (20,7)

Table 1. Characteristics of participating patients

	Full sample N = 184	Restricted sample N = 116
Previous treatment, n (%)		
Surgery	129 (70,1)	81 (69,8)
Chemotherapy	157 (85,3)	94 (81,0)
Target-based agents	55 (29,9)	37 (31,9)
Immunotherapy	38 (20,7)	28 (24,1)
Hormonal therapy	31 (16,8)	18 (15,5)
Radiotherapy	43 (23,4)	28 (24,1)
Last/ongoing treatment, n (%)		
Chemotherapy	135 (73,4)	79 (68,1)
Target-based agents	18 (9,8)	13 (11,2)
Immunotherapy	25 (13,6)	19 (16,4)
Hormonal therapy	5 (2,7)	4 (3,4)
Radiotherapy	1 (0,5)	1 (0,9)
Primary tumour site, n (%)		
Breast	59 (32,1)	36 (31,0)
Lower_gastrointestinal tract	51 (27,7)	24 (20,7)
Genito-urinary	34 (18,5)	27 (23,3)
Thoracic	18 (9,8)	13 (11,2)
Upper_gastrointestinal tract	13 (7,1)	10 (8,6)
Other	9 (4,9)	6 (5,2)

Table 2. Final PROFFIT instrument

Item type and number	Italian version	**English translation** (for comprehension only)
Outcome items (FT-score)		
1.	Sono in grado di sostenere le mie spese mensili senza difficoltà (ad esempio per affitto, elettricità, telefono…)	I can afford my monthly expenses without difficulty (for example rent, electricity, phone…)
2.	La mia malattia ha ridotto le mie disponibilità economiche	My illness has reduced my financial resources
3.	Sono preoccupato dei problemi economici che potrei avere in futuro a causa della malattia	I am concerned by the economic problems I may have in the future due to my illness
4.	La mia condizione economica incide sulle mie possibilità di curarmi	My economic situation affects the possibility of receiving medical care
5.	Ho ridotto le spese per attività ricreative come vacanze, ristoranti o spettacoli per affrontare le spese della mia malattia	I have reduced my spending on leisure activities such as holidays, restaurants or entertainment in order to cope with expenses related to my illness
6.	Ho ridotto le spese per acquisti essenziali (ad esempio il cibo) per affrontare le spese per la mia malattia	I have reduced spending on essential goods (for example food) in order to cope with expenses related to my illness
7.	Sono preoccupata/o di non riuscire a lavorare a causa della mia malattia	I am worried that I will not be able to work due to my illness
Determinant items (single items)		
8.	Il Servizio Sanitario Nazionale copre tutti i costi sanitari associati alla mia malattia	The National Health Service covers all health costs related to my illness
9.	Ho sostenuto spese per una o più visite private per la mia malattia	I have paid for one or more private medical examinations for my illness
10.	Ho sostenuto spese per farmaci supplementari o integratori per la mia malattia	I have paid for additional medicines or supplements related to my illness
11.	Devo sostenere spese per cure integrative a mio carico (es. fisioterapia, psicoterapia, cure odontoiatriche)	I have to pay for additional treatment myself (for example physiotherapy, psychotherapy, dental care)
12.	Il centro di cura è lontano dalla mia abitazione	The treatment centre is a long way from where I live
13.	Ho dovuto sostenere rilevanti costi di trasporto per curarmi	I have spent a considerable amount of money on travel for treatment
14.	Il personale sanitario (cioè medici, infermieri, etc.) ha agevolato il percorso di cura	Medical staff (that is doctors, nurses etc.) have been helpful throughout my medical care
15.	Il personale ospedaliero amministrativo (cioè centro di prenotazione, segreterie, etc.) ha agevolato il percorso di cura	Staff in hospital administration (that is for booking appointments, secretaries, etc.) have been helpful throughout my medical care
16.	C'è stata comunicazione tra i medici e le strutture sanitarie che mi seguono	Medical staff and medical facilities I attended communicated with each other

Legend of figure

Figure 1. Postulated causal structure for PROFFIT tool

Acknowledgments

See appendix.

Authors contribution

FP obtained funding. SR, JB, CG and FP drafted the manuscript. MDM, FE, VM, LF, DG, LDC, FDL, EI, FT, LG, CJ, CMV, and MCP contributed to manuscript writing. MDM, VM, DG, DB, SC, CP, LDM, VZ, AAC, RB, AG and FP contributed to patients' enrolment. SR, LA, LG, CG and FP performed statistical analysis and drafted the manuscript. All Authors contributed to the manuscript and approved the final version.

Data

Data will be made available upon request to the corresponding author.

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Ethical approval statement

The study protocol was initially approved by the Ethics Committee of the National Cancer Institute of Naples, that acted as coordinating Ethics Committe. Date of first approval is October 18, 2017 and code of approval is 18/17oss. Thereafter, the protocol was approved by Ethics Committee at each participating centre.

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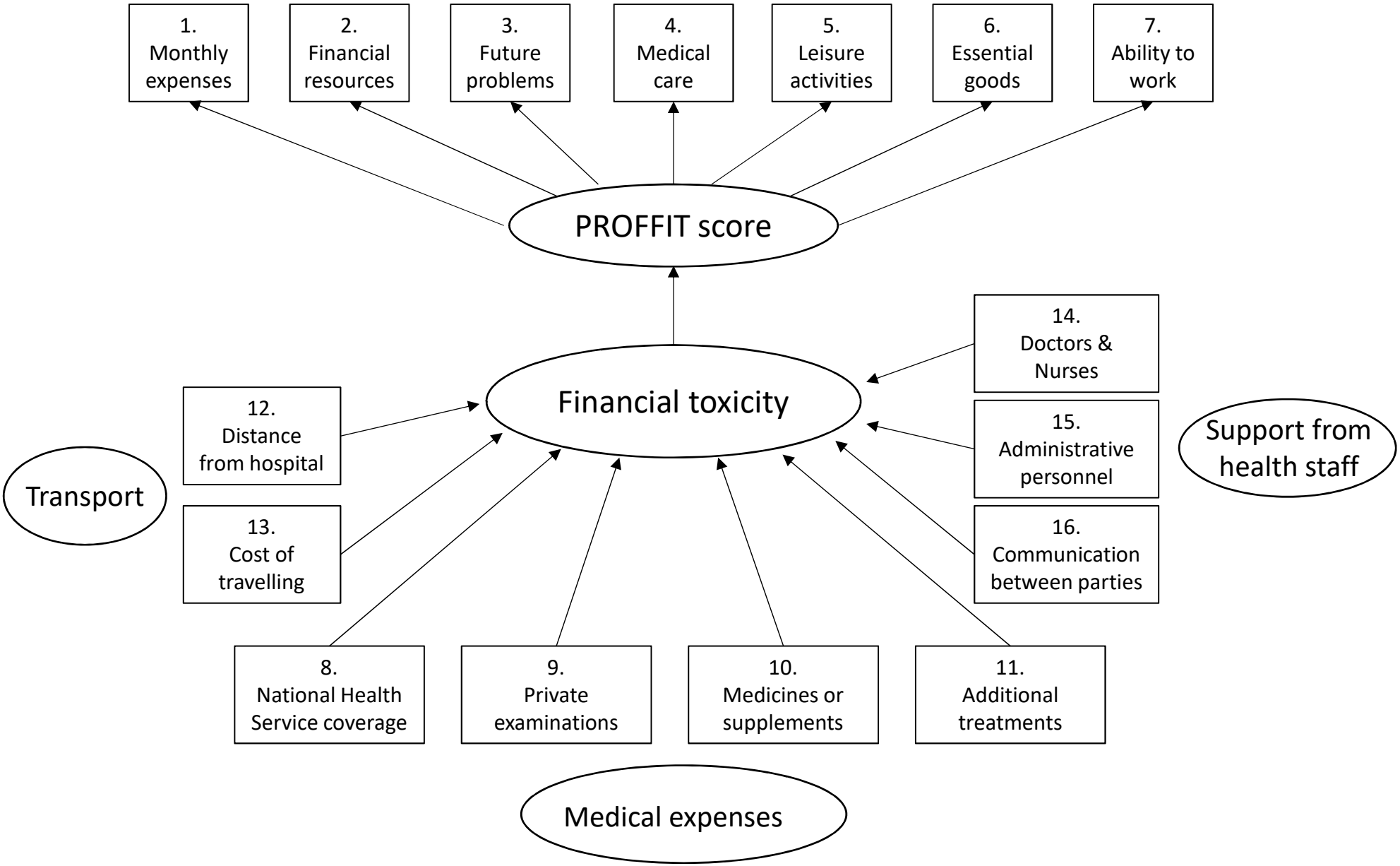
1. Monthly expenses
2. Financial resources
3. Future problems
4. Medical care
5. Leisure activities
6. Essential goods
7. Ability to work
PROFFIT score
Financial toxicity
14. Doctors & Nurses
15. Administrative personnel
16. Communication between parties
Support from health staff
12. Distance from hospital
13. Cost of travelling
Transport
8. National Health Service coverage
9. Private examinations
10. Medicines or supplements
11. Additional treatments
Medical expenses

Figure 1.

A cross-sectional study to develop and describe psychometric characteristics of a patient-reported instrument (PROFFIT) for measuring financial toxicity of cancer within a public healthcare system

Appendix

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Steering Committee and participating Investigators

The PROFFIT Steering Committee includes: Francesco Perrone, Jane Bryce, Ciro Gallo, Silvia Riva, Fabio Efficace, Francesco De Lorenzo, Elisabetta Iannelli, Laura Del Campo, Francesca Traclò, Massimo Di Maio (also as representative of AIOM – Associazione Italiana di Oncologia Medica), Luciano Frontini, Vincenzo Montesarchio (also as representative of CIPOMO – Collegio Italiano dei Primari di Oncologia Medica Ospedalieri), Diana Giannarelli, Lara Gitto, Claudio Jommi, Concetta Maria Vaccaro.

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Scoring procedure

Responses to PROFFIT items are coded in four categories of agreement with the statement of each item, scoring from 1 to 4:
1 - I do not agree at all, 2 - I agree partially, 3 - I agree substantially, 4 - I very much agree.

PROFFIT results are reported as a FT-score (including items #1 to #7) and nine separate items for FT determinants. All the scores are normalised to 0-100%, where 100 indicates the highest toxicity.

For **calculation of the FT-score**, including items #1 to #7, the following steps should be followed:

- Reverse the score for Item #1 according to the following formula

$$X_{1-reverse} = 5 - X_1$$

where X_1 is the response given to item #1.

- Calculate the FT-score according to the following formula

$$\frac{X_{1-reverse} + X_2 + X_3 + X_4 + X_5 + X_6 + X_7 - Y}{3 \times Y} \times 100$$

where X is the response given for each item and Y is the number of items with valid response; if Y is 3 or less the score should be considered missing. At least 4 valid responses are needed to calculate the FT-score.

Examples of calculation of FT score

Item: response	Intermediate	Final FT score
Example 1		
#1: I very much agree (4) #2: I agree partially (2) #3: I agree substantially (3) #4: I do not agree at all (1) #5: I agree partially (2) #6: I agree substantially (3) #7: I do not agree at all (1)	$X_{1-reverse} = 5 - 4 = 1$	$\frac{1+2+3+1+2+3+1-7}{3\times 7}\times 100 = 38$
Example 2.		
#1: I do not agree at all (1) #2: I very much agree (4) #3: I agree substantially (3) #4: I agree substantially (3) #5: I do not agree at all (1) #6: I agree partially (2) #7: MISSING	$X_{1-reverse} = 5 - 1 = 4$	$\frac{4+4+3+3+1+2-6}{3\times 6}\times 100 = 61$

For calculation of the score for items #8, #14, #15 and #16 use the following formula

$$\frac{4 - X_j}{3} \times 100$$

where X is the response given and *j* is the item (8, 14, 15, or 16).

For calculation of the score for items #9, #10, #11, #12, #13 use the following formula

$$\frac{X_j - 1}{3} \times 100$$

where X is the response given and *j* is the item (9, 10, 11, 12 or 13).

Examples of calculation of single determinants scores

Item: response	Final single score
Example 3.	
#8: I do not agree at all (1) #14: I agree substantially (3)	$\frac{4-1}{3} \times 100 = 100$ $\frac{4-3}{3} \times 100 = 33$
Example 4.	
#9: I very much agree (4) #13: I agree partially (2)	$\frac{4-1}{3} \times 100 = 100$ $\frac{2-1}{3} \times 100 = 33$

Table S1. List of items in the pre-final instrument

Item ID in the pre-final instrument	*Item ID in the final instrument*	*Item*
Q1		Ho rapidamente trovato la struttura dove curarmi
Q2		Il tempo necessario per la diagnosi è stato breve
Q5		Ho sentito molto il peso della burocrazia (ad esempio per prenotare visite o per usufruire di benefici assistenziali, previdenziali e lavorativi)
Q26	10	Ho sostenuto spese per farmaci supplementari o integratori per la mia malattia
Q27	9	Ho sostenuto spese per una o più visite private per la mia malattia
Q28	11	Devo sostenere spese per cure integrative a mio carico (es. fisioterapia, psicoterapia, cure odontoiatriche)
Q49	8	Il Servizio Sanitario Nazionale copre tutti i costi sanitari associati alla mia malattia
Q68	1	Sono in grado di sostenere le mie spese mensili senza difficoltà (ad esempio per affitto, elettricità, telefono…)
Q76	3	Sono preoccupata/o dei problemi economici che potrei avere in futuro a causa della malattia
Q85	2	La mia malattia ha ridotto le mie disponibilità economiche
Q86	4	La mia condizione economica incide sulle mie possibilità di curarmi
Q90		I miei problemi economici mi preoccupano
Q95		La mia famiglia ha dovuto sostenere i costi di trasporto, vitto e alloggio per curarmi in una città diversa da quella in cui vivo
Q99	7	Sono preoccupata/o di non riuscire a lavorare a causa della malattia
Q102		Ho perso molti giorni lavorativi a causa della mia malattia
Q103		Non riesco a guadagnare come prima per via della mia malattia
Q106		Ho dovuto smettere di lavorare a causa della mia malattia
Q107		Ho ridotto le ore al lavoro a causa della mia malattia
Q111	14	Il personale sanitario (cioè medici, infermieri, etc.) ha agevolato il percorso di cura
Q112	15	Il personale ospedaliero amministrativo (cioè centro di prenotazione, segreterie, etc.) ha agevolato il percorso di cura
Q113	16	C'è stata comunicazione tra i medici e le strutture sanitarie che mi seguono
Q114		Il medico di famiglia ha agevolato il percorso di cura
Q121	5	Ho ridotto le spese per attività ricreative come vacanze, ristoranti o spettacoli per affrontare le spese della mia malattia
Q122	6	Ho ridotto le spese per acquisti essenziali (ad esempio il cibo) per affrontare le spese per la mia malattia
Q138		I servizi di trasporto per raggiungere l'ospedale (mezzi pubblici, parcheggi) sono scarsi
Q139		Ho dovuto sostenere i costi di trasporto, vitto e alloggio per curarmi in una città diversa da quella in cui vivo
Q140	13	Ho dovuto sostenere rilevanti costi di trasporto per curarmi
Q141	12	Il centro di cura è lontano dalla mia abitazione
Q151		È stato facile ottenere le agevolazioni economiche a cui ho diritto (ad esempio esenzione dal ticket, assegni o pensioni di invalidità)
Q156		So che la mia malattia mi dà diritto ad agevolazioni economiche (ad esempio esenzione dal ticket, assegni o pensioni di invalidità)

Questionnaire development

The first step of the analysis was estimating the between-item correlation matrix. Because of the ordinal nature of the items the pairwise Spearman rank correlation coefficients (r_s) were used.

We ascertained that there were about a third (68/184, 37%) of missing responses for the five job items from patients, who declared themselves retired or jobless (i.e. househusbands, housewives or individuals in search of employment); thus we decided to estimate two separate bivariate correlation matrices, one limited to job items, where only the 116 cases without missing information were used (**Table S2a below**), and one for all the other items, where the complete sample of 184 cases was used (**Table S2b below**).

For every pair, whose r_s >0.65, the item with the greater score in the previously published importance analysis was retained.

At the end of this preliminary analysis, six items (Q103, Q106, Q107, Q90, Q95, Q139) were excluded, because r_s was greater than 0.65, leading to 9 outcome and 15 determinant items for subsequent analyses. Out of the five job items, two were retained, one outcome (Q99) and one determinant (Q102).

Table S2. Spearman correlation coefficients between items

Table S2a. Job items

	Q99	Q102	Q103	Q106	Q107
Q99	1				
Q102	0,63	1			
Q103	0,72	0,66	1		
Q106	0,55	0,50	0,60	1	
Q107	0,56	0,67	0,67	0,78	1

Table S2b. All other items

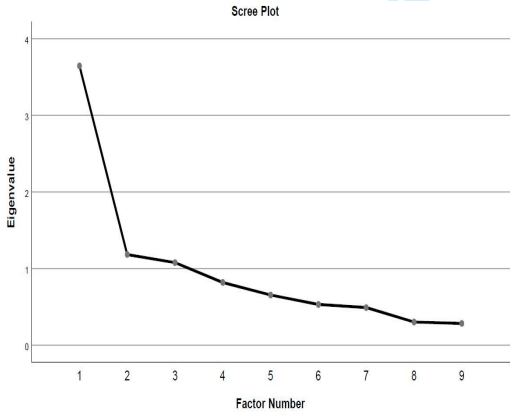
	Q1	Q2	Q5	Q26	Q27	Q28	Q49	Q68	Q76	Q85	Q86	Q90	Q95	Q111	Q112	Q113	Q114	Q121	Q122	Q138	Q139	Q140	Q141	Q151	Q156
Q1	1																								
Q2	0,29	1																							
Q5	-0,08	-0,05	1																						
Q26	-0,18	-0,13	0,22	1																					
Q27	-0,16	-0,04	0,33	0,30	1																				
Q28	-0,07	-0,03	0,40	0,36	0,40	1																			
Q49	0,18	0,15	-0,23	-0,46	-0,27	-0,41	1																		
Q68	0,09	0,15	-0,03	-0,25	-0,09	-0,13	0,34	1																	
Q76	-0,22	-0,10	0,21	0,41	0,29	0,29	-0,32	-0,45	1																
Q85	-0,18	-0,04	0,27	0,46	0,31	0,37	-0,41	-0,41	0,65	1															
Q86	-0,24	-0,11	0,27	0,40	0,39	0,34	-0,46	-0,44	0,56	0,57	1														
Q90	-0,21	-0,15	0,16	0,34	0,22	0,26	-0,29	-0,53	0,71	0,67	0,70	1													
Q95	-0,23	-0,10	0,19	0,25	0,29	0,30	-0,23	-0,12	0,20	0,33	0,28	0,21	1												
Q111	0,35	0,25	-0,26	-0,26	-0,30	-0,29	0,38	0,14	-0,11	-0,17	-0,31	-0,13	-0,17	1											
Q112	0,25	0,10	-0,12	-0,20	-0,15	-0,16	0,41	0,10	-0,17	-0,18	-0,31	-0,14	-0,10	0,53	1										
Q113	0,21	0,13	-0,20	-0,05	-0,45	-0,22	0,22	0,00	-0,11	-0,07	-0,22	-0,15	-0,11	0,43	0,33	1									
Q114	0,15	0,09	-0,23	-0,10	-0,17	-0,24	0,12	0,25	-0,24	-0,12	-0,24	-0,24	0,02	0,37	0,38	0,28	1								
Q121	-0,21	-0,15	0,12	0,31	0,36	0,28	-0,21	-0,41	0,57	0,59	0,48	0,62	0,28	-0,06	-0,09	-0,17	-0,10	1							
Q122	-0,08	-0,09	0,09	0,36	0,25	0,31	-0,37	-0,47	0,48	0,49	0,64	0,66	0,33	-0,15	-0,17	-0,15	-0,10	0,57	1						
Q138	-0,08	-0,05	0,28	0,25	0,22	0,27	-0,30	-0,17	0,24	0,34	0,31	0,31	0,08	-0,24	-0,23	-0,03	-0,15	0,18	0,34	1					
Q139	-0,23	-0,02	0,18	0,28	0,33	0,36	-0,25	-0,19	0,26	0,36	0,34	0,23	0,69	-0,14	-0,10	-0,07	-0,02	0,30	0,42	0,15	1				
Q140	-0,17	-0,04	0,27	0,30	0,33	0,29	-0,27	-0,21	0,28	0,41	0,33	0,31	0,59	-0,20	-0,10	-0,02	-0,04	0,38	0,45	0,27	0,66	1			
Q141	-0,14	0,02	0,16	0,09	0,11	0,10	-0,02	-0,08	0,11	0,18	0,12	0,12	0,34	-0,04	0,04	0,05	-0,13	0,10	0,18	0,11	0,45	0,55	1		
Q151	0,10	0,11	-0,15	-0,21	-0,15	-0,11	0,27	0,24	-0,20	-0,29	-0,29	-0,24	-0,09	0,18	0,20	0,17	0,20	-0,22	-0,21	-0,10	-0,18	-0,18	-0,07	1	
Q156	0,15	0,27	-0,02	-0,14	-0,03	-0,07	0,33	0,39	-0,18	-0,22	-0,32	-0,25	-0,07	0,22	0,23	0,20	0,18	-0,15	-0,32	-0,22	-0,13	-0,08	0,01	0,35	1

Exploratory Factor Analysis (EFA)

EFA on Outcome

EFA on the 9-outcome correlation matrix was performed by Principal Axis Factor (PAF) extraction option of SPSS, with VARIMAX rotation, in the sample of 116 subjects with complete information, because of the presence of the job item Q99.
The items considered at the start were Q5, Q68, Q76, Q85, Q86, Q99, Q121, Q122, Q151.
In the initial factor solution, three factors met the Kaiser criterion of eigenvalue >1 and accounted for 66% of the variance, the first axis alone explaining 41% of the total variance (see Table and scree plot below).

Factor	Total	% of variance	Cumulative %
1	3.645	40.501	40.501
2	1.185	13.163	53.665
3	1.079	11.986	65.651
4	0.819	9.105	74.756
5	0.656	7.286	82.042
6	0.533	5.927	87.969
7	0.492	5.470	93.439
8	0.304	3.383	96.821
9	0.286	3.179	100.000



Communalities and unrotated factor loadings are reported in the table below.

	Communalities			Factor		
	Initial	Extraction		1	2	3
Q5	0.133	0.31		0.261	0.203	-0.448
Q68	0.233	0.266		-0.452	0.248	-0.020
Q76	0.574	0.653		0.793	0.152	-0.027
Q85	0.605	0.729		0.819	0.238	0.034
Q86	0.510	0.677		0.723	-0.305	-0.248
Q99	0.248	0.344		0.424	0.387	0.119
Q121	0.471	0.593		0.704	0.118	0.290
Q122	0.437	0.623		0.630	-0.458	0.131
Q151	0.089	0.116		-0.265	-0.018	0.214

The item Q151 shows communality <0.20, Child 2006), and factor loadings <0.3 (Field, 2013) with all three factors, and was removed from further analyses.

Analogously at the next step the item Q5 was removed (communality = 0.072).

Eventually, seven items were retained with two factors meeting the Kaiser criterion of eigenvalue >1.

Communalities and factor loadings after Varimax rotation in the reduced sample of 116 patients are reported below. Many items cross loaded on both axes, that seemed both expression of financial burden: after rotation, the first one was more correlated with items mirroring an actual severe burden (Q68, Q86, Q122), while the second one appeared more correlated with worries about the future.

	Communalities			Factor	
	Initial	Extraction		1	2
Q68	0.222	0.269		-0.498	-0.145
Q76	0.570	0.648		0.468	0.655
Q85	0.600	0.737		0.413	0.753
Q86	0.491	0.588		0.719	0.266
Q99	0.247	0.356		0.012	0.596
Q121	0.470	0.510		0.397	0.594
Q122	0.426	0.566		0.735	0.159

The previous interpretation might imply that some correlation between axes would be expected. Thus, the oblique Promax rotation was applied. The same seven-item final solution was found with two factors meeting the Kaiser criterion of eigenvalue >1, and findings were reinforced. The factor loadings with Promax rotation are reported below.

	Factor	
	1	2
Q68	-0.549	0.047
Q76	0.248	0.616
Q85	0.129	0.766
Q86	0.764	0.004
Q99	-0.292	0.753
Q121	0.191	0.571
Q122	0.839	-0.140

The same analysis was repeated in the whole sample, replacing the missing information on the Q99 job in the 68 cases with the average score of the other items. We did that, according to the protocol, for both increasing the power of the analysis and as a sensitivity analysis of findings in the restricted sample. We chose to input the average score rather than the minimum score (that would sound *I am not worried at all that I will not be able to work due to my illness*) because it could be true for retired people (at least in the Italian population), but not for younger people without job. We think, indeed, that imputing the minimum score would definitely bias the score toward the null, while imputing the average could possibly only slightly overestimate the financial issues. Further, this choice is consistent with the calculus of the score, where the missing items are not considered in the denominator. This question will be further dealt with in the next validation steps.
In the full sample similar and stronger results were found: items Q151 and Q5 were removed because of low communalities (both <0.10). With the eventual 7-item analysis only the first axis met the Kaiser criterion of eigenvalue >1. Communalities and factor loadings in the complete sample are reported below. With one factor extracted no rotation was needed.

	Communalities			Factor
	Initial	Extraction		1
Q68	0.309	0.309		-0.556
Q76	0.555	0.622		0.788
Q85	0.582	0.647		0.805
Q86	0.534	0.547		0.739
Q99	0.318	0.273		0.522
Q121	0.494	0.537		0.733
Q122	0.506	0.485		0.697

Therefore, the PROFFIT FT-score includes 7 outcome items.

EFA on Determinants

EFA on the 15-outcome correlation matrix was performed by Principal Axis Factor (PAF) extraction option of SPSS, with VARIMAX rotation, in the sample of 116 subjects with complete information, because of the presence of the job item Q102.

The items considered at the start were Q1, Q2, Q26, Q27, Q28, Q49, Q102, Q111, Q112, Q113, Q114, Q138, Q140, Q141, Q156. In principle, the 15 determinants could be expression of three categories: (i) direct medical expenses (Q26, Q27, Q28, Q49), (ii) indirect costs due to travelling needs for medical care (Q138, Q140, Q141), (iii) indirect costs due to bureaucracy (Q1, Q2, Q111, Q112, Q113, Q114, Q156), plus a single job item (Q102).

In the initial factor solution, five factors met the Kaiser criterion of eigenvalue >1 and accounted for 62% of the variance (Table below), but the first axis explained only the 26% of the total variance.

Factor	Total	% of variance	Cumulative %
1	3.869	25.793	25.793
2	1.851	12.341	38.133
3	1.403	9.356	47.490
4	1.135	7.567	55.057
5	1.041	6.943	62.000
6	0.975	6.502	68.503
7	0.825	5.501	74.004
8	0.766	5.104	79.107
9	0.664	4.425	83.532
10	0.583	3.885	87.417
11	0.554	3.696	91.113
12	0.416	2.774	93.887
13	0.364	2.426	96.313
14	0.326	2.171	98.484
15	0.227	1.516	100.000

The job item Q102 had the smallest communality (0.183) and was removed. All the other items had complete responses, thus it seemed meaningless to continue in the restricted sample, and the subsequent analysis was only performed in the complete sample, where all of the responses were available.

The initial factor solution with 14 items in the full sample is reported below. Almost nothing changed: five factors met the Kaiser criterion of eigenvalue >1 and accounted for 63% of the variance, and the first axis explained only the 26% of the total variance.

Factor	Total	% of variance	Cumulative %
1	3.571	25.508	25.508
2	1.712	12.232	37.740
3	1.290	9.211	46.951
4	1.223	8.733	55.684
5	1.078	7.703	63.387
6	0.869	6.207	69.594
7	0.776	5.543	75.136
8	0.735	5.253	80.389
9	0.649	4.635	85.023
10	0.554	3.954	88.978
11	0.451	3.219	92.197
12	0.413	2.949	95.146
13	0.373	2.662	97.808
14	0.307	2.192	100.000

At the next steps items Q1, Q2, Q156, Q138 and Q114 were removed in turn because of small communalities, leading to the final solution with nine items and four factors retained. Communalities and factor loadings in the complete sample are reported below.

	Communalities			Factor		
	Initial	**Extraction**	**1**	**2**	**3**	**4**
Q26	0.305	0.425	0.628	-0.113	0.124	0.050
Q27	0.374	0.597	0.350	0.010	0.183	0.664
Q28	0.335	0.453	0.604	-0.048	0.137	0.259
Q49	0.393	0.576	-0.660	0.372	-0.012	-0.045
Q111	0.369	0.487	-0.210	0.592	-0.081	-0.294
Q112	0.333	0.610	-0.144	0.765	0.039	-0.049
Q113	0.319	0.556	0.001	0.332	0.059	-0.665
Q140	0.426	0.741	0.283	-0.069	0.803	0.105
Q141	0.316	0.449	0.009	0.033	0.669	0.005

Seemingly the first axis is related to direct medical expenses, the second axis to health bureaucracy items and the third axis to travelling costs, but some cross load on the factors is present.

Therefore we decided to retain the nine determinant items as single items in the final questionnaire.

Convergent validity

We said above that the PROFFIT FT-score includes 7 outcome items. In the table below correlation between each item and the total score of the scale, removing that item from the sum (convergent validity), is reported. Correlations are quite good, all r_s being greater than 0.5 in the full sample.

Table S3. Spearman correlation coefficients between each item and total score*

Item number	Full sample (N=184)	Restricted sample (N=116)
1	0.5325	0.5243
2	0.7360	0.7267
3	0.7251	0.7158
4	0.6646	0.6559
5	0.6887	0.6765
6	0.6712	0.6626
7	0.5537	0.3684

*calculated removing each item from the sum

Repeatability

Agreement between repeated measurements was assessed by intra-class correlation coefficient (ICC) and weighted Cohen's Kappa coefficient. Scores were stable enough over time, with ICCs ranging from 0.56 and 0.79. ICC was equal to 0.81 for the FT-score.

Table S4. Test-retest results

	ICC	Weighted K	Agreement %
Outcome items			
Item 1	0.70	0.70	95.7
Item 2	0.68	0.68	93.7
Item 3	0.56	0.56	90.7
Item 4	0.64	0.64	93.2
Item 5	0.65	0.65	91.0
Item 6	0.65	0.65	93.9
Item 7	0.79	0.81	94.4
FT-score	*0.81*	*0.82*	*97.4*
Determinant items			
Item 8	0.61	0.61	94.4
Item 9	0.72	0.72	94.2
Item 10	0.65	0.65	93.0
Item 11	0.61	0.62	92.4
Item 12	0.79	0.79	96.6
Item 13	0.78	0.78	92.2
Item 14	0.53	0.52	96.5
Item 15	0.59	0.58	95.0
Item 16	0.61	0.61	93.9

Table S5. Association of FT score with baseline characteristics of patients

	Median	(IQR)	P (Mann-Whitney)
All patients	38.1	(23.8-57.1)	
Region of the hospital			**0.005**
North	**28.6**	**(14.3-47.6)**	
Center	**33.3**	**(23.8-61.9)**	
South	**42.9**	**(23.8-57.1)**	
Islands	**52.4**	**(33.3-57.1)**	
Gender			0.932
Female	38.1	(23.8-57.1)	
Male	33.3	(23.8-52.4)	
Age category			**0.005**
<=65	**42.9**	**(23.8-57.1)**	
>65	**26.2**	**(14.3-47.6)**	
Education level			**0.018**
Elementary/Middle school	**42.9**	**(23.8-57.1)**	
High school/degree	**33.3**	**(19.0-50.0)**	
Cohabitant/Married			0.298
No	33.3	(23.8-52.4)	
Yes	38.1	(23.8-57.1)	
With dependent family members			0.060
No	33.3	(19.0-52.4)	
Yes	42.9	(28.6-57.1)	
Family members with cancer or chronic disease			**0.017**
No	**31.0**	**(19.0-52.4)**	
Yes	**42.9**	**(23.8-57.1)**	
Working status			0.531
Not working	33.3	(19.0-52.4)	
Working	38.1	(23.8-57.1)	
Site of treatment			0.134
Within the region of residency	38.1	(23.8-57.1)	
Outside the region of residency	28.6	(19.0-42.9)	
Time (years) from initial diagnosis			0.920
≤1	38.1	(23.8-57.1)	
1-5	33.3	(23.8-52.4)	
≥5	33.3	(19.0-61.9)	
Previous surgery			0.175
No	42.9	(23.8-61.9)	
Yes	33.3	(23.8-52.4)	
Last/ongoing anticancer treatment at registration			0.546
Chemotherapy	38.1	(23.8-57.1)	
Target-based agents	40.5	(23.8-52.4)	
Immunotherapy	28.6	(9.5-47.6)	
Hormonal therapy	38.1	(33.3-42.9)	
Radiotherapy	28.6	(28.6-28.6)	

Reporting checklist for cross sectional study.

Based on the STROBE cross sectional guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cross sectionalreporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	3-4

Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	#3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	#4	Present key elements of study design early in the paper	6
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	11
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants.	6
	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	6
Bias	#9	Describe any efforts to address potential sources of bias	7-8

Study size	#10	Explain how the study size was arrived at	6
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	7
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	7-8
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	7-8
Statistical methods	#12c	Explain how missing data were addressed	8
Statistical methods	#12d	If applicable, describe analytical methods taking account of sampling strategy	8
Statistical methods	#12e	Describe any sensitivity analyses	7-8
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	11
Participants	#13b	Give reasons for non-participation at each stage	11

Participants	#13c	Consider use of a flow diagram	Considered but deemed useless
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	11 (Table 1)
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	11
Outcome data	#15	Report numbers of outcome events or summary measures. Give information separately for exposed and unexposed groups if applicable.	Not applicable
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Not applicable
Main results	#16b	Report category boundaries when continuous variables were categorized	Not applicable
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable

Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	11-13
Discussion			
Key results	#18	Summarise key results with reference to study objectives	15
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	16-17
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	15-16
Generalisability	#21	Discuss the generalisability (external validity) of the study results	18
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	22