BMJ Open

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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To cite: Riva S, Arenare L, Di Maio M, *et al*. 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. *BMJ Open* 2021;**11**:e049128. doi:10.1136/bmjopen-2021-049128

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-049128).

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Received 01 February 2021
Accepted 05 October 2021

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ABSTRACT

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

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

Participants From 8 October 2019 to 11 December 2019, 184 patients, aged 18 or more, who were receiving or had received within the previous 3 months active anticancer treatment were enrolled, 108 (59%) females and 76 (41%) males.

Intervention A 30-item prefinal 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 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 intraclass correlation coefficient and weighted Cohen's kappa coefficient).

Results After exploratory factor analysis, a score measuring FT (FT score) was identified, made by seven items dealing with outcomes of FT. The Cronbach's alpha coefficient for the FT score was 0.87 and the item-total correlation coefficients ranged from 0.53 to 0.74. Further, nine 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 of the 16 items retained in the final questionnaire.

Conclusions The Patient-Reported Outcome for Fighting FInancial Toxicity (PROFFIT) 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 number NCT03473379.

Strengths and limitations of this study

- ► Patient-Reported Outcome for Fighting FInancial Toxicity (PROFFIT) was developed as a reaction to the finding that financial problems affect the outcome of patients with cancer 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 recognised problem worldwide. While initial reports came from the USA, 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 patients with cancer enrolled in clinical trials, and their association with worse quality of life (QoL) and overall survival.[5] Using individual data from 16 randomised trials, we found that patients reporting some degree of financial burden at baseline had a higher chance of worsening global QoL response after treatment, and that patients, who developed FT during treatment, had a statistically significant shorter survival.[5]

Therefore, in 2018, we started the multicentre Patient-Reported Outcome for Fighting FInancial Toxicity of cancer (PROFFIT) project to develop a tool for measuring and understanding FT 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

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: (1) adult patients (>18 years), (2) histologically or cytologically confirmed diagnosis of any type of solid cancer or haematological malignancy, (3) medical treatment (chemotherapy, target agents, immunotherapy, hormonal treatment, radiotherapy or combinations of such therapies) ongoing or terminated within the previous 3 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 prefinal instrument (online supplemental appendix table S1).

Two groups of items were identified by the study steering committee: (1) outcome items (n=10), that is, 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), that is, 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's 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 (ie, 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 normalisation. 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's 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 online supplemental 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, that is, 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's rank correlation coefficient with correction for overlap, that is, 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 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 characterise 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 V.25.0 (SPSS) and with Stata V.14 (Stata).

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 and 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 prefinal questionnaire, and final analyses producing the final questionnaire (reported here); they are coauthor of this manuscript and of the previous manuscripts dealing with this project (LDC, FDL, EI and FT). They will also contribute in dissemination of the results of the project.

RESULTS

From 8 October 2019 to 11 December 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 (online supplemental appendix table S2a,b).

EFA on the nine-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 nine outcome items were met with very good parameters (KMO=0.82 and Bartlett's test of sphericity, p<0.001). Two items were excluded because of low communality (see online supplemental appendix for details). With seven 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 online supplemental appendix).

In the full sample (KMO=0.87 and Bartlett's test of sphericity, p<0.001), 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 online supplemental appendix (EFA on outcome paragraph).

Thus, the PROFFIT FT-score includes seven outcome items. The Cronbach alpha coefficient for the PROFFIT FT-score was 0.85 in the restricted sample and 0.87 in the

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)
Macroregion of the participating institution, n (%)		
North	71 (38,6)	46 (39,7)
Centre	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)
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)
Genitourinary	34 (18,5)	27 (23,3)
Thoracic	18 (9,8)	13 (11,2)
Upper astrointestinal tract	13 (7,1)	10 (8,6)
Other	9 (4,9)	6 (5,2)

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 (online supplemental appendix table S3).

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

Therefore, the final PROFFIT instrument includes the FT-score (consisting of seven items) and nine 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 1-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 to 0.79 (online supplemental appendix table S4).

Table 2 Final PROFFIT instrument

Item type and no	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 (eg, 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 (eg, 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 (eg, 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 (ie, 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 (ie, 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

FT, financial toxicity; PROFFIT, Patient-Reported Outcome for Fighting FInancial Toxicity.

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

DISCUSSION

FT has been initially described in the USA as a factor negatively affecting patients with cancer 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 copayment 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 patients with cancer, 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

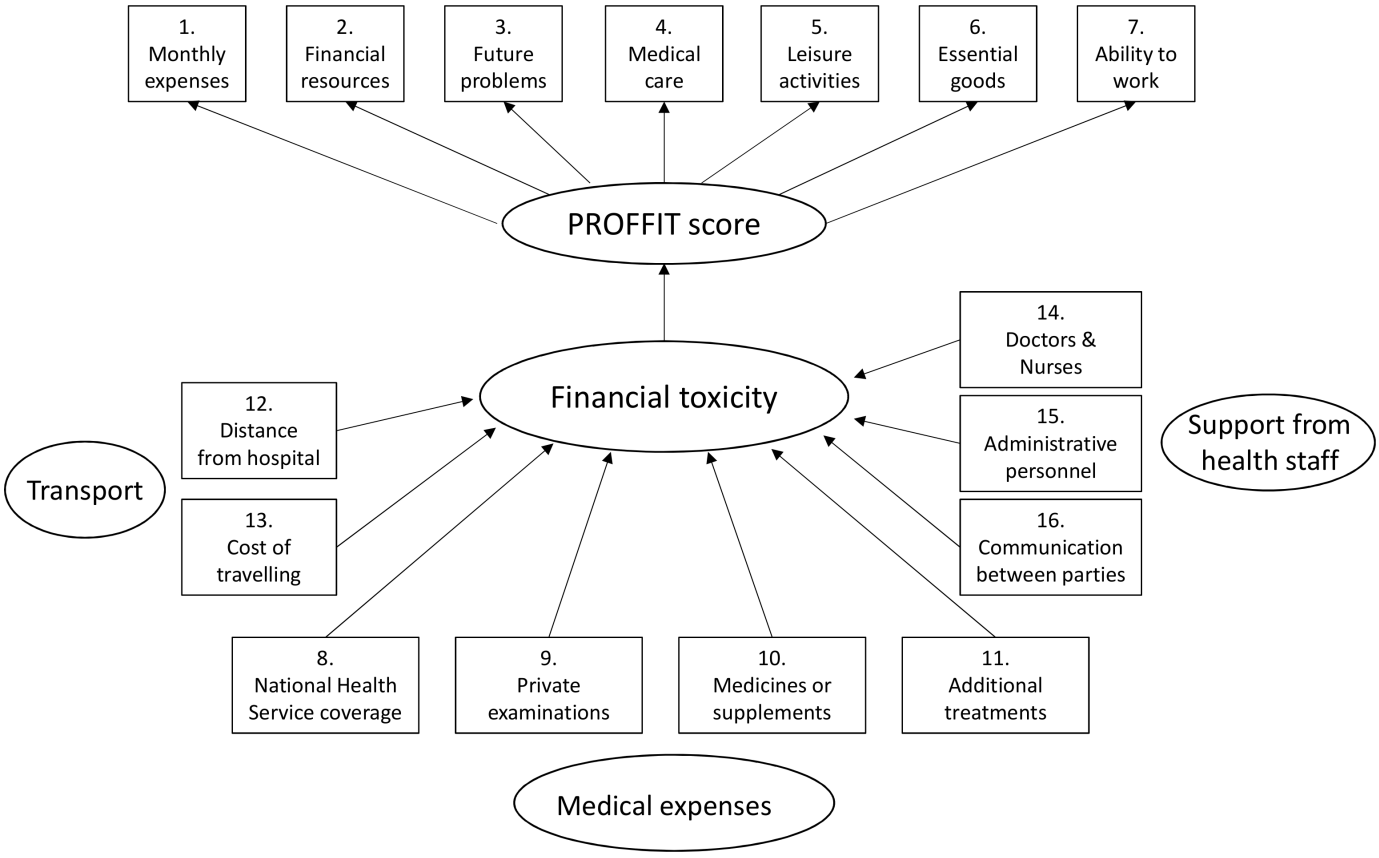

Figure 1 Postulated causal structure for PROFFIT tool. PROFIT, Patient-Reported Outcome for Fighting FInancial Toxicity.

to describe FT 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 healthcare 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 characterised by social insurance-based model, funded by payroll taxes. Regardless the model, the European healthcare systems are characterised by a high proportion of healthcare expenditure covered by compulsory public programmes, ranging from 66% in Spain to 78% in UK, compared with 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 versus 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 with 40%, 55% and 75% in Germany, France and UK/Spain, respectively.[23] The mean yearly amount of out-of-pocket expenses for patients with cancer was estimated in the same year to be €1841 within a survey conducted by the Federazione italiana delle Associazioni di Volontariato in Oncologia.[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 seven items) and nine single items assessing possible determinants of FT. In principle, the seven-item FT score could be immediately generalisable to every system, once validity has been confirmed, while the nine-single-item determinants are strictly dependent on the healthcare system. The latter ones, that are lacking in other tools like Comprehensive Score for Financial Toxicity (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 (eg, Italian macroregions, 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 FT has been previously addressed in the USA by the

investigators who produced and validated the 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 patients with cancer.[20 21] Recently, the COST-FACIT V.2 has been developed. In this version, an additional item was added to reflect overall financial well-being (https://wizard.facit.org/index.php?option=com_facit&view=search&searchPerformed=1 accessed 18 August 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 FT. An instrument like PROFFIT, including several items related to determinants of FT, 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 patients with cancer. 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 generalisability 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 QoL 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, FT 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 FT, and hopefully improve the outcomes of cpatients with cancer.

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Contributors 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. CG and FP are joint last authors. FP is responsible for the overall content as guarantor.

Funding The project is supported by Fondazione AIRC (Associazione Italiana per la Ricerca sul Cancro), a non-profit Italian charity, IG 2017 Id 20402.

Competing interests SR has received personal fees from CSL-Behring and GlaxoSmithKline Foundation. MDM has received personal fees from Bristol Myers Squibb, Merck Sharp & Dohme, Astra Zeneca, Janssen, Astellas, Pfizer, Eisai, Takeda. FE has received personal fees from AbbVie, BMS, Amgen, Orsenix, Takeda and research grant (Institution) from Amgen. VM has received personal fees from Bristol Myers Squibb and Italfarmaco; a member of his family is employee in Bayer. CJ has received personal fees from Amgen, Astra Zeneca, Biogen, Boehringer Ingelheim, Celgene, Gilead, GSK, Ipsen, Janssen-Cilag, Takeda and Sanofi. CMV has received personal fees from from Baxter, MSD, Novartis, Sanofi, Sanofi Genzyme. 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. LDM has received personal fees from Eli Lilly, Roche, MSD, Novartis, Genomic Health, Pierre Fabre, Pfizer, Seattle Genetics, Daiichi Sankyo, Astra Zeneca, Ipsen, Eisai. VZ has received personal fees from BMS, MSD, Eisai, Italfarmaco, Roche, Astellas Pharma, Servier, Astra Zeneca, MSD, Janssen, Ipsen and research grant (Institution) from Bayer, Roche, Eli Lilly, Astra Zeneca, BMS, Ipsen, Astellas. RB reports personal fees from Bayer, Astra Zeneca, Sanofi, Novartis, Amgen, Hoffmann La Roche, Pfizer, Janssen Cilag, Bristol Myers Squibb, Merck. MCP reports personal fees from Daichii Sankyo, personal fees from GSK, personal fees from MSD, grants from Roche, grants and personal fees from AstraZeneca, non-financial support from Bayer. FP has received personal fees from Bayer, Ipsen, Astra Zeneca, Bristol Myers Squibb, Sandoz, Incyte, Celgene, Pierre Fabre, Janssen-Cilag and research grants (Institution) from Astra Zeneca, Bayer, Roche, Merck, Pfizer, Incyte, Sanofi, BioClin, Tesaro. All the above disclosures are outside the submitted work. The other Authors have no conflict to disclose.

Patient consent for publication Not applicable.

Ethics approval 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 18 October 2017 and code of approval is 18/17oss. Thereafter, the protocol was approved by Ethics Committee at each participating centre.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

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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

Appendix

Index

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.

We acknowledge the contribution of the other personnel working at the Unità Sperimentazioni Cliniche of the Istituto Nazionale per lo Studio e la Cura dei Tumori, IRCCS Fondazione Pascale of Napoli: Adriano Gravina, Clorinda Schettino, Piera Gargiulo, Lucia Sparavigna, Giuliana Canzanella, Fiorella Romano, Valentina Barbato, Manuela Florio, Simona Bevilacqua, Gaetano Buonfanti, Alfonso Savio, Antonia Del Giudice, Teresa Ribecco, Marilena Martino, Giovanni De Matteis.

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- Oncologia traslazionale – I.R.C.C.S. Istituti Clinici Scientifici Maugeri, Pavia (Camillo Porta)
- U.O.C. Oncologia 1, Istituto Oncologico Veneto, IOV, IRCCS Padova (Vittorina Zagonel, Eleonora Bergo).

Italian to English translation was done thank to the voluntary contribution of Iain Halliday, Salvo Ciancitto, and Francesca Vigo (University of Catania, Dipartimento di Scienze Umanistiche), and Daniel Matheson (freelance translator).

A graphic logo (see below) has been created thanks to the voluntary contribution of Valeria Lepore, Pierpaola Borzacchiello, and Carla Langella (director), Design per la Valorizzazione Scientifica, Università della Campania Luigi Vanvitelli.

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.

Riva S, *et al. BMJ Open* 2021; 11:e049128. doi: 10.1136/bmjopen-2021-049128

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

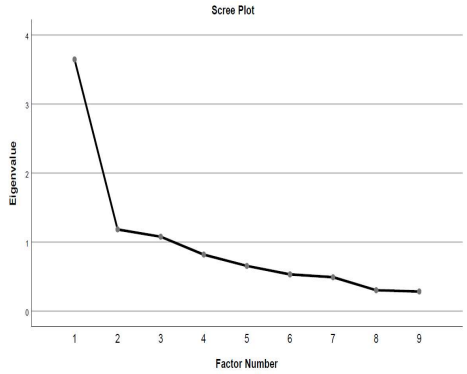
	Q1	Q2	Q5	Q26	Q27	Q28	Q49	Q68	Q76	Q85	Q86	Q90	Q95	Q111	Q112	Q113	Q114	Q121	Q122	Q138	Q139	Q140	Q141	Q151	Q156
Q1	1																								
Q2	0,29	1																							
Q5	-0,08	-0,05	1																						
Q26	-0,18	-0,13	0,22	1																					
Q27	-0,16	-0,04	0,33	0,30	1																				
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)	