ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ESMO OPEN SCIENCE FOR OPTIMAL CANCER CARE

ORIGINAL RESEARCH

Confirmatory validation analysis of the PROFFIT questionnaire to assess financial toxicity in cancer patients

L. Arenare[1], C. Porta[2,3], D. Barberio[4], S. Terzolo[5], V. Zagonel[6], S. Pisconti[7], L. Del Mastro[8,9], C. Pinto[10], D. Bilancia[11], S. Cinieri[12], M. Rizzo[3], G. Migliaccio[4], V. Montesarchio[13], L. Del Campo[14], F. De Lorenzo[14,15], E. Iannelli[14,16], F. Traclò[16†], L. Gitto[17], M. C. Vaccaro[18], L. Frontini[19], D. Giannarelli[20], J. Bryce[21], M. C. Piccirillo[1], C. Jommi[22], F. Efficace[23], S. Riva[24], M. Di Maio[5], C. Gallo[25] & F. Perrone[1*]

[1]Clinical Trial Unit, Istituto Nazionale Tumori, IRCCS, Fondazione G. Pascale, Napoli; [2]Interdisciplinary Department of Medicine, Università degli Studi 'A. Moro', Bari; [3]Polyclinic Consortium University Hospital, Bari; [4]Departmental Structure of Clinical Psycho-oncology, Istituto Nazionale Tumori, IRCCS, Fondazione G. Pascale, Napoli; [5]Department of Oncology, Università di Torino, AO Ordine Mauriziano, Torino; [6]Oncology Unit 1, Istituto Oncologico Veneto, IOV, IRCCS, Padova; [7]Oncology Unit, Ospedale S. G. Moscati, Statte TA; [8]Medical Oncology, IRCCS Ospedale Policlinico San Martino, Genova; [9]Department of Internal Medicine and Medical Specialties (DIMI), Università di Genova, Genova; [10]Medical Oncology, AUSL-IRCCS di Reggio Emilia, Reggio Emilia; [11]Medical Oncology, Azienda Ospedaliera San Carlo, Potenza; [12]Medical Oncologiy, Ospedale Perrino, Brindisi; [13]Medical Oncology, Azienda Ospedaliera Specialistica dei Colli, Napoli; [14]Federazione Italiana delle Associazioni di Volontariato in Oncologia (FAVO), Rome; [15]European Cancer Patient Coalition (ECPC), Brussels; [16]Associazione Italiana Malati di Cancro (AIMAC), Roma; [17]Department of Economy, Università degli Studi di Messina, Messina; [18]Welfare and Health Department, Centro Studi Investimenti Sociali (CENSIS), Roma; [19]Federation of Italian Cooperative Oncology Groups (FICOG), Milano; [20]Epidemiology and Biostatistics, GSTeP, Fondazione Policlinico Universitario A. Gemelli, IRCCS, Roma, Italy; [21]Ascension St. John Clinical Research Institute, Tulsa, USA; [22]Department of Pharmaceutical Sciences, Università del Piemonte Orientale, Novara; [23]Gruppo Italiano per le Malattie Ematologiche dell'Adulto (GIMEMA) Health Outcomes Research Unit, Roma, Italy; [24]St Mary's University, Twickenham, London, UK; [25]Professor Emeritus Medical Statistics, Università degli Studi della Campania 'Luigi Vanvitelli', Napoli, Italy

Available online 5 December 2023

Background: The Patient Reported Outcome for Fighting FInancial Toxicity (PROFFIT) questionnaire was developed to measure financial toxicity (FT) and identify its determinants. The aim of the present study was to confirm its validity in a prospective cohort of patients receiving anticancer treatment.

Patients and methods: From March 2021 to July 2022, 221 patients were enrolled at 10 Italian centres. Selected items of the EORTC-QLQ-C30 questionnaire represented the anchors, specifically, question 28 (Q-28) on financial difficulties, and questions 29-30 measuring global health status/quality of life (HR-QOL). The study had 80% power to detect a 0.20 correlation coefficient (r) between anchors and PROFFIT-score (items 1-7, range 0-100, 100 indicating maximum FT) with bilateral alpha 0.05 and 80% power. Confirmatory factor analysis was conducted. FT determinants (items 8-16) were described.

Results: Median age of patients was 65 years, 116 (52.5%) were females, 96 (43.4%) had low education level. Confirmatory factor analysis confirmed goodness of fit of the PROFFIT-score. Significant partial correlation of PROFFIT-score was found with Q-28 ($r = 0.51$) and HR-QOL ($r = -0.23$). Mean (SD) PROFFIT-score at baseline was 36.5 (24.9); it was statistically significantly higher for patients living in South Italy, those with lower education level, those who were freelancer/unemployed at diagnosis and those who reported significant economic impact from the COVID-19 pandemic. Mean (SD) scores of determinants ranged from 17.6 (27.1) for item 14 (support from medical staff) to 49.0 (36.3) for item 10 (expenses for medicines or supplements). PROFFIT-score significantly increased with worsening response to determinants.

Conclusions: External validation of PROFFIT-score in an independent sample of patients was successful. The instrument is now being used in clinical studies.

Key words: financial toxicity, PROFFIT, quality of life, patient reported outcomes, health economics

INTRODUCTION

Financial toxicity (FT) of cancer was initially reported in the United States where it is described as the problems a patient may have related to the cost of medical care.[1,2] Such problems may lead to patients' bankruptcy, and may be associated with worse clinical outcomes, including worse quality of life and shorter survival.[3-5]

*Correspondence to: 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. Tel: +39 081 17770274

E-mail: f.perrone@istitutotumori.na.it (F. Perrone).

†Deceased.

However, in recent years, FT has been further described in other countries, characterized by different healthcare systems.[6-8]

In Italy, using individual data from 16 randomized trials, we found that patients reporting financial hardship at baseline had a higher chance of worsening global quality of life (QoL) response after treatment, and that patients who worsened FT during treatment had a shorter survival.[9]

Considering that socio-cultural barriers can affect degree and determinants of FT in cancer patients, context-specific tools may be more sensitive to capturing FT and more useful to suggest preventive policies.[10,11] Therefore, in 2018, we started the Patient Reported Outcome for Fighting FInancial Toxicity of cancer (PROFFIT) project to develop a tool for measuring and understanding financial toxicity related to cancer and/or its treatments within a healthcare system providing universal health coverage.[12-14] The final instrument contains 16 items, 7 of which (number 1 to 7) were combined after exploratory factor analysis in a PROFFIT-score estimating the amount of the financial distress, and 9 were retained as single items, indicating possible determinants of the financial hardship, roughly pertaining to three major areas, e.g. medical expenses (items 8 to 11), transportation (items 12 and 13) and support from the health staff (items 14 to 16). We herein report the subsequent step of the PROFFIT project, consisting of a confirmatory analysis of the external validity of the final instrument, in a cohort of patients receiving anticancer treatment, using validated quality of life tools as anchors.

PATIENTS AND METHODS

This study represents the fourth task of the protocol (clinicaltrials.gov NCT03473379) that was approved by independent ethical review boards at enrolling centres and performed according to International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guidelines.[15,16] Cancer patients for this study were prospectively enrolled; due to heterogeneity of the planned patient population in terms of type and stage of cancer, and type of treatment, data on typical oncological outcomes (response, time to progression and survival) were not collected.

The project was overseen by a Steering Committee including multidisciplinary researchers and patients representative of patients' associations.

Eligibility criteria

Patients $\geq$18 years of age, with a histological or cytological confirmed diagnosis of solid cancer or haematological malignancy, and ready to start a medical treatment (chemotherapy, target agents, immunotherapy, hormonal treatment, radiotherapy or combinations of such therapies) were eligible; patients were eligible whichever the line (neoadjuvant/adjuvant, first line, second or further line) of the treatment they were going to start. Written informed consent was required.

Power calculation and planned sample size

To demonstrate a Pearson correlation coefficient of 0.20 between PROFFIT-score and health-related quality of life (HR-QOL) score (measured with items 29-30 of the EORTC-QLQ-C30 questionnaire), with bilateral alpha 0.05 and 80% power, at least 194 patients were required and 220 were planned to account for possible missing data.

Instruments and data collection

PROFFIT questionnaire is reported in Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2023.102192.

EORTC-QLQ-C30 questionnaire was used as the anchor to test criterion validity, particularly question 28 (Q-28), measuring financial problems, and questions 29-30 which form the global health status/quality of life scale (HR-QOL).[17]

Due to COVID-19 pandemic a further question, not planned in the protocol, was proposed to explore whether COVID-19 impacted on patients' economic situation, with the following possible answers: not at all, a little, very much.

Questionnaires could be administered either as paper document or as digital version on tablet, according to centre choice.

Data on baseline and anamnestic characteristics of patients were collected by researchers during the first visit, after the informed consent procedure, and were inputted in a dedicated electronic case report form within the web-based platform for management of clinical trials hosted at the coordinating centre at the National Cancer Institute of Naples, Italy.

Statistical analysis

Descriptive statistics were used to report characteristics of enrolled patients. Continuous variables were described with median values and interquartile range (IQR) or mean values and standard deviation (SD), as appropriate; categorical variables were expressed in terms of absolute numbers and percentage.

Compliance was described for PROFFIT and EORTC-QLQ-C30 questionnaires.

Education level was categorised as none, primary, lower secondary, upper secondary and tertiary (including any type of degree higher than upper secondary).[18] Performance status of patients was classified as 0 (fully active, able to carry on all pre-disease performance without restriction) or $\geq$1 (any condition worse than 0), according to the ECOG (Eastern Cooperative Oncology Group) scale.[19]

Confirmatory factory analysis was done to validate the factor-analytic structure of PROFFIT-score found in the previous task. Several indices were used: root mean squared error of approximation (RMSEA, values $<$0.05, from 0.05-0.10 and $>$0.10 representing close fit, acceptable fit, and poor approximate fit, respectively); comparative fit index (CFI) and Tucker-Lewis index (TLI), both ranging from 0 (poor fit) to 1 (perfect fit), values $>$0.95 and $>$0.90

representing good and acceptable fit, respectively; standardised root mean squared residual (SRMR) was calculated (values <0.05 representing very good fit).[20]

The Cronbach's alpha was used to test the internal consistency of the PROFFIT-score with the seven items on which it is built; estimates of $\alpha > 0.70$ were considered acceptable.

External validity of baseline PROFFIT-score was tested using two different anchors: the financial difficulties question (Q-28) and the global QoL scale (HR-QOL based on questions 29 and 30) of the EORTC QLQ-C30 questionnaire. For the latter, the baseline assumption was that a high degree of financial problems correlates with worse quality of life, and a threshold correlation of 0.20 was defined as relevant. Partial correlation coefficients were calculated in a multivariable model including sex, age, performance status, geographic region, education level, working status, and line of treatment as potential confounding factors. Unplanned sensitivity analyses were performed adding COVID-19 economic impact to the multivariable model.

Associations between characteristics of patients and baseline PROFFIT-score or financial toxicity determinants were evaluated using Mann-Whitney or Kruskal-Wallis test.

Associations between baseline PROFFIT-score and financial toxicity determinants were evaluated using Jonckheere-Terpstra test to account the ordinal nature of the studied variables.

All analyses were considered significant with an alpha level of 0.05. Statistical analyses were performed with Stata 14 (Stata, College Station, TX).

RESULTS

From 3 March 2021 to 4 July 2022, 221 cancer patients were enrolled across 10 Italian centres. Median age was 66 years (IQR 57-73 years); 116 (52.5%) were females; 129 (58.4%) lived in South Italy; median distance from home to hospital was 18 km (IQR 1-41 km); 125 (56.6%) had a high level of education (upper secondary or tertiary); 65 (29.4%) had dependent family members; 62 (28.1%) were on permanent or temporary/flexible work at diagnosis, while 102 patients (46.2%) were retired; 147 (66.5%) patients had had their cancer diagnosis within the previous 12 months; 161 (72.9%) patients had at least one comorbidity, with hypertension (30.2% of patients) and endocrine disease (including diabetes, 12.6% of patients) being the most frequently reported; breast was the most frequent site of the primary tumour; around half of the patients (109, 49.3%) were receiving their first-line treatment; 120 (54.3%) of the patients had previously undergone a surgical intervention; 166 (75.1%) of the patients received chemotherapy during the study; 88 (39.9%) patients reported they had suffered an economic impact from COVID-19 pandemic (details reported in Table 1).

All the enrolled patients filled in the PROFFIT questionnaire; one patient did not complete EORTC-QLQ-C30, and, in addition, there were four missing responses to Q-28 and two missing responses to questions 29-30. Overall, 58/221 patients (26.2%) filled in the questionnaires using the digital version on tablet; among these patients, median time spent to answer the PROFFIT was 3 min and 19 s (IQR: 2 min and 52 s − 3 min and 55 s), while it was 4 min and 5 s (IQR: 3 min and 34 s − 4 min and 46 s) for the EORTC-QLQ-C30. Responses given to each item of the PROFFIT questionnaire are summarized in Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2023.102192.

Confirmatory factor analysis indicated that the PROFFIT-score identified the latent FT factor. Namely, the analysis showed an acceptable fit in terms of RMSEA (0.074, 90% confidence interval 0.037-0.110, with a 0.125 probability of RMSEA <0.05), an excellent fit in terms of CFI (0.973) and of TLI (0.960) and a very good fit according to SRMR (0.041). The Cronbach's alpha coefficient was 0.86.

Correlation between PROFFIT-score and EORTC anchors is graphically represented in Figure 1. Correlations were positive with financial difficulties (increasing PROFFIT-score with increasing/worsening response to Q-28) and negative with HR-QOL (increasing PROFFIT-score with decreasing/worsening global HR-QOL).

Partial correlation coefficient of PROFFIT-score (r) with Q-28 was 0.51 ($P < 0.0001$), the only other covariate significantly correlated with Q-28 being the geographic region of residency ($r = 0.17$, $P = 0.01$). Partial correlation coefficient of PROFFIT-score and HR-QOL was -0.23 ($P = 0.0008$), in a model where worse ECOG performance status ($r = -0.18$, $P = 0.008$) and more advanced line of treatment ($r = -0.20$, $P = 0.003$) were also significantly correlated with HR-QOL. Sensitivity analyses adding COVID-19 economic impact confirmed the results, even if COVID-19 economic impact was significantly correlated with both Q-28 ($r = 0.14$, $P = 0.045$) and HR-QOL ($r = -0.16$, $P = 0.02$).

Distribution of PROFFIT-score and of determinants is reported in Figure 2. Overall, mean (SD) PROFFIT-score was 36.5 (24.9); mean (SD) scores of determinants ranged from 17.6 (27.1) for item 14 (support from medical staff) to 49.0 (36.3) for item 10 (expenses for medicines or supplements).

PROFFIT-score was statistically significantly higher in South Italy, in patients with lower education level, freelancer/craftsman/trader or housewife/unemployed at diagnosis and in those who reported very much economic impact from COVID-19 outbreak (Table 2). PROFFIT-score tended to be higher with worsening response to determinants; the trend was statistically significant with items 8 to 11 (indicating various types of medical expenses), 12 and 13 (related to transportation); among items 14, 15 and 16, statistical significance was strong for the latter (communication among medical staffs and medical facilities) but less strong for the former two (helpfulness of medical staff and of administrative staff, Table 3).

Associations between each determinants and select baseline characteristics of patients are summarized in Supplementary Tables S3-S5, available at https://doi.org/10.1016/j.esmoop.2023.102192. Several statistically significant associations were observed between worse scores of determinants and female sex (items 8, 15, 16), residency in South Italy (items 8, 9, 11, 14-16), lower education level,

Table1. Characteristics of 221 participating patients

	n	(%)
Sex at birth		
Female	116	(52.5)
Male	105	(47.5)
Age, years		
<65	106	(48.0)
≥65	115	(52.0)
Macro-region where the patient lives		
North West	44	(19.9)
North East	48	(21.7)
South	129	(58.4)
Education level		
None	4	(1.8)
Primary	28	(12.7)
Lower secondary	64	(29.0)
Upper secondary	85	(38.5)
Tertiary	40	(18.1)
Living alone		
No	173	(78.3)
Yes	48	(21.7)
With dependent family members		
No	156	(70.6)
Yes	65	(29.4)
Family members with cancer or chronic disease		
No	119	(53.8)
Yes	102	(46.2)
Working status at diagnosis		
Permanent	57	(25.8)
Temporary/flexible work	5	(2.3)
Freelancer/craftsman/trader	21	(9.5)
Unemployed	9	(4.1)
Housewife	27	(12.2)
Retired	102	(46.2)
Reported economic damage from COVID-19		
Not at all	130	(58.8)
A little	64	(29.0)
Very much	24	(10.9)
Missing	3	(1.4)
Time (years) from initial diagnosis		
<1	147	(66.5)
≥1	74	(33.5)
Performance status at baseline		
0	146	(66.1)
≥1	75	(33.9)
Concomitant diseases at baseline		
None	60	(27.1)
1	85	(38.5)
2	45	(20.4)
3	18	(8.1)
≥4	13	(5.9)
Primary tumour site		
Breast	50	(22.6)
Lower gastrointestinal	44	(19.9)
Genito-urinary	40	(18.1)
Thoracic	20	(9.0)
Upper gastrointestinal	37	(16.7)
Other	30	(13.6)
Line of ongoing treatment		
Adjuvant/neoadjuvant	59	(26.7)
First line	109	(49.3)
Second or further line	53	(24.0)
Previous surgery	120	(54.3)
Previous chemotherapy	76	(34.4)
Previous target-based agents	29	(13.1)
Previous immunotherapy	21	(9.5)
Previous hormonal therapy	22	(10.0)
Previous radiotherapy	33	(14.9)
Ongoing chemotherapy	166	(75.1)
Ongoing target-based agents	51	(23.1)
Ongoing immunotherapy	48	(21.7)
Ongoing hormonal therapy	12	(5.4)
Ongoing radiotherapy	10	(4.5)

living alone, having no family member affected with chronic diseases (all with item 16), longer time from initial diagnosis (items 8, 10), worse performance status (items 8, 16), and more advanced line of treatment (item 8).

DISCUSSION

The primary purpose of this study was to externally validate the PROFFIT questionnaire within the framework of an universal healthcare coverage system and to examine its associations with financial difficulties, quality of life, and various determinants of financial toxicity.

The present study confirms validity of the PROFFIT questionnaire within a prospectively collected series of patients with solid tumours.

Particularly, confirmatory factor analysis substantiated the ability of the PROFFIT-score to capture the latent factor represented by financial toxicity by combining responses given to items 1 to 7 of the questionnaire, with a quite high reliability and internal consistency. This finding supports the robustness and credibility of the model postulated when PROFFIT was initially developed.[12]

Furthermore, the analysis of the correlations between PROFFIT-score and anchors from the EORTC-QLQ-C30 questionnaire, revealed an excellent partial correlation with its financial difficulties question ($r = |0.51|$) and with the global QOL scale ($r = |0.23|$). The former reaffirms the fact that the evidence on which this project is based (based on Q-28) is actually effectively captured by the PROFFIT-score. The latter supports the hypothesis and previous findings that financial toxicity may negatively impact patients' quality of life. The strength of such results comes from the use of multivariable analysis adjusting for potential confounders (sex, age, performance status, geographic region, education level, working status, and line of treatment); results remain valid even adjusting for a rough estimate of the financial impact of COVID-19. Further, correlation with the global QOL scale of the EORTC-QLQ-C30 is consistent with findings reported on the COST questionnaire in the USA.[21] Similarity of behaviour suggests that, regardless of the healthcare system, the association between FT and quality of life is consistent and might be true everywhere.

The PROFFIT questionnaire has the potential to assist physicians in patient care and decision-making. It provides a quantitative tool to assess financial toxicity, helping clinicians tailor patient care, provide financial counselling, and guide patients to relevant resources. Additionally, it can be a valuable tool for policymakers in addressing systemic issues related to financial difficulties within the healthcare system.

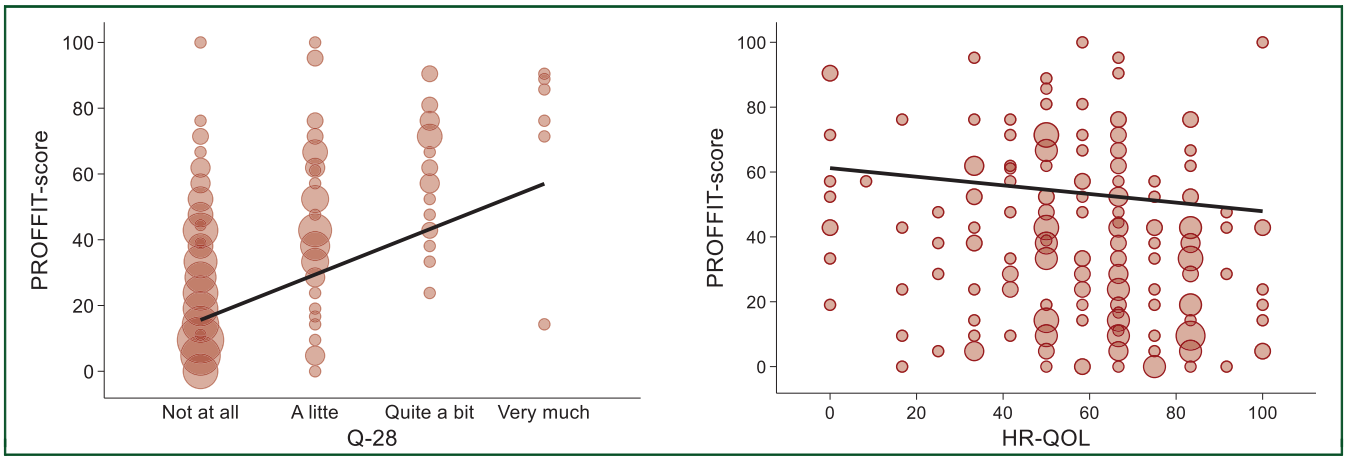

Figure 1. Correlation between PROFFIT-score and financial difficulties (Q-28, question 28 of the EORTC-QLQ-C30, on the left) and HR-QOL (questions 29/30 of the EORTC-QLQ-C30, on the right). Bubble size is proportional to frequency. Solid line represents regression lines.

The present study reports data of the third series of patients prospectively enrolled into the PROFFIT project; although none of these series was planned to be representative of a specific or general context, it is interesting to observe similarities regarding subgroups that have higher risk of financial toxicity in Italy.[12,22] These include patients who reside in South Italy, those younger than 65 years of age, those with a lower education level; consistently, FT is lower for those who work in the public sector (thanks to several protection rules) and for those who are retired, whose income is not affected by their incapacity to work. Also, there is consistency regarding the higher PROFFIT-score among those who reported further financial impact due to COVID-19.[22]

The nine items representing possible determinants of FT are a distinguishing figure of the PROFFIT questionnaire, as compared, for example, to the COST instrument where only 3 out of the 11 items represent material conditions, according to the definition given by Altice et al.[23,24] All the determinants were significantly associated with PROFFIT-score, as expected, although at a lower degree for items related to helpfulness of medical and administrative staffs. We suspect that a sort of deference toward the health-staff might affect patients during treatment; a similar trend, indeed, with few patients reporting problems of interaction with the health-staff was also found among the 184 patients involved in previous factor analysis (the one leading from pre-final to final questionnaire - data not reported) and among 167 patients interviewed in a single-centre study of PROFFIT.[12,22] For the future, the opportunity to investigate these determinants among patients who are in a phase of active treatment might be reviewed or anonymity should be warranted. These items, however, might still be important in cross-sectional studies enrolling patients not

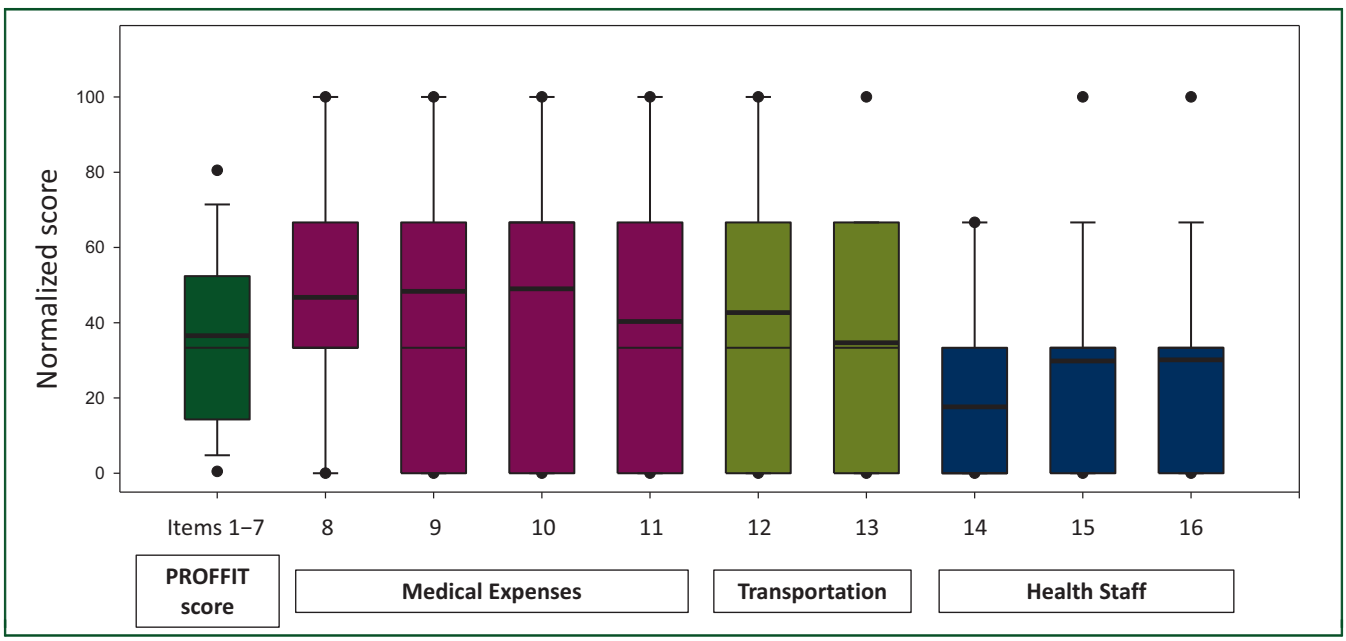

Figure 2. Box plots of distribution of PROFFIT-score and single items. Thicker lines represent mean values.

Table 2. PROFFIT-score by selected baseline characteristics. NA, not applicable

	n	PROFFIT-score Mean (SD)	*P*
Sex at birth			0.08
Female	116	39.4 (25.7)	
Male	105	33.4 (23.7)	
Age, years			0.10
<65	106	39.4 (24.5)	
≥65	115	33.9 (25.1)	
Macro-region where the patient lives			<0.001
North West	44	24.5 (19.9)	
North East	48	34.0 (24.8)	
South	129	42.7 (25.0)	
Education level			0.017
None/primary	32	44.0 (24.2)	
Lower secondary	64	34.6 (26.1)	
Upper secondary/tertiary	125	33.2 (24.3)	
Living alone			0.79
No	173	36.3 (25.5)	
Yes	48	37.4 (22.6)	
With dependent family members			0.19
No	156	35.1 (24.2)	
Yes	65	39.9 (26.3)	
Family members with cancer or chronic disease			0.37
No	119	37.9 (25.6)	
Yes	102	34.9 (24.0)	
Working status at diagnosis			<0.001
Permanent/temporary/flexible	62	32.5 (19.4)	
Freelancer/craftsman/trader	21	51.2 (28.6)	
Housewife/unemployed	36	48.5 (26.6)	
Retired	102	31.7 (24.1)	
Time (years) from initial diagnosis			0.87
<1	147	36.7 (24.8)	
≥1	74	36.1 (25.2)	
Performance status at baseline			0.54
0	146	35.8 (23.9)	
≥1	75	38.0 (26.8)	
Concomitant diseases at baseline			0.52
None	60	38.3 (27.8)	
≥1	161	35.9 (23.8)	
Primary tumour site			0.23
Breast	50	34.9 (24.7)	
Lower gastrointestinal tract	44	37.4 (26.0)	
Genito-urinary	40	32.9 (21.2)	
Thoracic	20	43.7 (25.1)	
Upper gastrointestinal tract	37	31.8 (23.8)	
Other	30	44.0 (28.3)	
Line of ongoing treatment			0.31
Adjuvant/neoadjuvant	59	33.3 (25.2)	
First line	109	39.1 (25.6)	
Second or further line	53	34.9 (22.8)	
Reported economic damage from COVID-19			<0.001
Not at all	130	31.0 (23.2)	
A little	64	36.8 (22.2)	
Very much	24	65.6 (21.0)	
Missing	3	NA	

Table 3. PROFFIT-score by response to items describing determinants

Number and item content	Mean PROFFIT-score	SD	*P*
8. The National Health Service covers all health costs…			0.006
Very much agree	25.4	24.9	
Agree substantially	40.7	23.5	
Agree partially	40.6	23.9	
Do not agree at all	38.1	25.0	
9. I have paid for one or more private medical examinations…			<0.001
Do not agree at all	27.4	18.7	
Agree partially	31.8	23.2	
Agree substantially	40.8	26.0	
Very much agree	46.9	27.1	
10. I have paid for additional medicines or supplements…			<0.001
Do not agree at all	30.3	27.1	
Agree partially	30.0	20.2	
Agree substantially	39.5	23.3	
Very much agree	46.8	25.7	
11. I have to pay for additional treatment myself (e.g. physiotherapy…			<0.001
Do not agree at all	26.9	22.8	
Agree partially	33.4	22.0	
Agree substantially	46.0	23.4	
Very much agree	46.5	27.0	
12. The treatment centre is a long way from where I live			<0.001
Do not agree at all	26.4	20.3	
Agree partially	36.1	22.9	
Agree substantially	40.3	26.7	
Very much agree	49.9	26.7	
13. I have spent a considerable amount of money on travel…			<0.001
Do not agree at all	25.4	19.1	
Agree partially	36.5	22.8	
Agree substantially	46.8	26.5	
Very much agree	56.6	25.0	
14. Medical staff (i.e. doctors, nurses, etc.) have been helpful…			0.048
Very much agree	34.6	25.3	
Agree substantially	37.9	23.3	
Agree partially	43.4	26.1	
Do not agree at all	46.2	25.6	
15. Staff in hospital administration have been helpful…			0.057
Very much agree	33.0	24.5	
Agree substantially	37.3	26.1	
Agree partially	39.6	19.4	
Do not agree at all	45.1	29.9	
16. Healthcare staff communicated well with each other…			<0.001
Very much agree	30.1	22.8	
Agree substantially	38.2	25.1	
Agree partially	43.2	27.2	
Do not agree at all	48.1	23.2	

undergoing active anticancer treatment, considering that 45 patients involved in the importance analysis during the development of PROFFIT ranked items 14 to 16 among the most important within the pre-final questionnaire.[14]

A recently reported survey of Italian cancer patients between 2017 and 2018 found that diagnostic examinations and transportations were the main components of the out-of-pocket costs sustained by cancer patients.[25] Actually, PROFFIT determinants do not directly refer to diagnostic examinations. Considering this as a limitation, we plan to further examine this matter in future studies to better understand the components of costs reported through response to items 8 to 11.

The PROFFIT project has until now included patients affected by a variety of tumour types. Such heterogeneity might prevent the identification of trends in specific patient populations and also prevents correlations of PROFFIT-score with prognosis, in terms of either quality of life or survival. Therefore, field-specific studies are now being planned in order to overcome this limitation. A project has started with

ovarian cancer patients (NCT06032975) and another is being planned with early breast cancer patients. Further studies are also warranted with patients with hematologic malignancies, considering the length of treatment with currently available oral therapies; such patients were in principle also eligible for the present study but they were actually not enrolled due to organizational issues.

To the best of our knowledge, PROFFIT is the first measure specifically developed for assessing financial toxicity and its determinants in settings with a public health system, which is a characteristic of many European countries. Therefore, we have validated its version in English and hope that other European groups may be interested in developing translations in other languages.[26]

Considering rising healthcare costs and the burden of cancer in public health systems, FT poses significant challenges of measurement and interpretation, and may adversely impact on patients' well-being, quality of life, and access to essential medical services. Validated instruments are required and, therefore, we believe that PROFFIT might assist physicians in clinical decision-making, tailoring patient care, providing financial counselling, and directing patients to relevant resources. Policy-makers might also be interested in using PROFFIT to design targeted interventions, address systemic issues contributing to financial toxicity, and implement policies that protect patients from financial distress.

In conclusion, the findings from this study emphasize the pressing need to address financial toxicity, given the increasing healthcare costs and the ongoing challenge of cancer within public health systems. The PROFFIT questionnaire, with its robust validation and proven effectiveness, holds the potential to become a very important tool for healthcare professionals in shaping clinical decisions and for policymakers in crafting targeted interventions and policies. By utilizing PROFFIT, we can strive to alleviate the adverse effects of financial toxicity on patients' overall well-being, quality of life, and their access to crucial medical services, thereby improving the healthcare experience for cancer patients and reducing the burden on healthcare systems.

ACKNOWLEDGEMENTS

This paper is dedicated to the lovely memory of Francesca Traclò, patient and representative of patients' associations, member of the Steering Committee of the study who died due to cancer progression while this manuscript was in preparation.

FUNDING

The work was supported by Fondazione Associazione Italiana per la Ricerca sul Cancro (AIRC), a non-profit Italian charity [grant number IG 2017 ID 20402]. AIRC had no role in writing the protocol and the manuscript and played no role in data analysis and interpretation.

DISCLOSURE

SC declared non-financial interests as President Italian Society of Medical Oncology (AIOM). LDC, FDL, and EI declared institutional grants or contracts from Novartis, Roche, AstraZeneca, Gilead Sciences, Viatris, Bristol Myers Squibb, Daiichi Sankyo Italia, GlaxoSmithKline, Ipsen, Servier, AbbVie, Boehringer Ingelheim Italia, Becton Dickinson Italia, Mylan, Clovis Oncology IT, Sandoz. LDM declared institutional grants or contracts from Eli Lilly, Novartis, Roche, Daiichi Sankyo, Seagen, Astrazeneca, Gilead, Pierre Fabre; and personal fees for consulting, honoraria, advisory or data safety monitoring board from Eli Lilly, Gilead, Daiichi Sankyio, Roche, Novartis, Pfizer, Astrazeneca, MSD, Seagen, Pierre Fabre, Eisai, Exact Science, Ipsen, GSK, Agendia, Stemline. MDM declared institutional grants or contracts from Tesaro/GlaxoSmithKline, Beigene, Exelixis, MSD, Pfizer and Roche. FE declared personal fees for consulting activities from AbbVie, Incyte, Janssen, Syros, Novartis. CJ declared institutional grants or contracts from Abbvie, AstraZeneca, Bayer, Biogen, Bristol Myers Squibb, Boehringer Ingelheim, Incyte, Janssen Cilag, Lundbeck, Merck Sharp & DohmeMerck Sharp & Dohme, Novartis, Roche, Pfizer, Sandoz, Sanofi; consulting fees from Amgen, Astrazeneca, Gilead, Incyte, Sanofi, Takeda; honoraria from MSD, Takeda; personal fees for participation on advisory boards from Amgen, Astrazeneca, BMS, Gilead, Incyte, Roche, Sanofi. FP declared institutional funding from Associazione Italiana per la Ricerca sul Cancro (AIRC) for the present study; institutional support or grants for clinical trials from Roche, Bayer, AstraZeneca, Pfizer, Incyte, Tesaro/GSK, Merck; personal fees for participation on advisory boards from Bayer, Pierre Fabre, AstraZeneca, Incyte, Ipsen, Clovis, Astellas, Sanofi, Roche, Pfizer. MCP declared institutional grants from Roche, AstraZeneca, Bayer; honoraria for educational activities from Astellas, Pfizer, Ipsen, AstraZeneca. CP declared consulting fees from Angelini Pharma, Astra Zeneca, BMS, Eisai, Ipsen, MSD; honoraria from Angelini PharmaAngelini Pharma, Astra Zeneca, BMS, Eisai, Ipsen, MSD. SR declared institutional grant from Moderna; honoraria from Roche. MR declared personal fees from MSD, Astra Zeneca, BMS, Eisai, Janssen-Cilag, Merck. MCV declared institutional grants from Roche, MSD, Novo Nordisk; leadership or fiduciary role within Health City Institute; Italian Barometer Diabetes Observatory (IBDO) Foundation, the Kore university Enna; Associazione Italiana Malattia di Alzheimer (AIMA). All other authors have declared no conflicts of interest.

DATA SHARING

Data are available at https://zenodo.org/record/8304766

REFERENCES

1. Khera N. Reporting and grading financial toxicity. *J Clin Oncol*. 2014;32(29):3337-3338.
2. NCI. Dictionary of Cancer Terms. Available at https://www.cancer.gov/publications/dictionaries/cancer-terms/def/financial-toxicity. Accessed November 2, 2023.

3. Lathan CS, Cronin A, Tucker-Seeley R, Zafar SY, Ayanian JZ, Schrag D. Association of financial strain with symptom burden and quality of life for patients with lung or colorectal cancer. *J Clin Oncol*. 2016;34(15):1732-1740.
4. Ramsey S, Blough D, Kirchhoff A, et al. Washington state cancer patients found to be at greater risk for bankruptcy than people without a cancer diagnosis. *Health Aff (Millwood)*. 2013;32(6):1143-1152.
5. Ramsey SD, Bansal A, Fedorenko CR, et al. Financial insolvency as a risk factor for early mortality among patients with cancer. *J Clin Oncol*. 2016;34(9):980-986.
6. Honda K, Gyawali B, Ando M, et al. A prospective survey of comprehensive score for financial toxicity in Japanese cancer patients: report on a pilot study. *Ecancermedicalscience*. 2018;12:847.
7. Longo CJ, Fitch MI, Banfield L, Hanly P, Yabroff KR, Sharp L. Financial toxicity associated with a cancer diagnosis in publicly funded healthcare countries: a systematic review. *Support Care Cancer*. 2020;28(10):4645-4665.
8. Poudyal BS, Giri S, Tuladhar S, Neupane S, Gyawali B. A survey in Nepalese patients with acute leukaemia: a starting point for defining financial toxicity of cancer care in low-income and middle-income countries. *Lancet Haematol*. 2020;7(9):e638-e639.
9. Perrone F, Jommi C, Di Maio M, et al. The association of financial difficulties with clinical outcomes in cancer patients: secondary analysis of 16 academic prospective clinical trials conducted in Italy. *Ann Oncol*. 2016;27(12):2224-2229.
10. Perrone F, Di Maio M, Efficace F, et al. Assessing financial toxicity in patients with cancer: moving away from a one-size-fits-all approach. *J Oncol Pract*. 2019;15(8):460-461.
11. Rotter J, Spencer JC, Wheeler SB. Financial toxicity in advanced and metastatic cancer: overburdened and underprepared. *J Oncol Pract*. 2019;15(4):e300-e307.
12. 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(10):e049128.
13. Riva S, Bryce J, De Lorenzo F, et al. Development and validation of a patient-reported outcome tool to assess cancer-related financial toxicity in Italy: a protocol. *BMJ Open*. 2019;9(9):e031485.
14. Riva S, Efficace F, Di Maio M, et al. A qualitative analysis and development of a conceptual model assessing financial toxicity in cancer patients accessing the universal healthcare system. *Support Care Cancer*. 2021;29(6):3219-3233.
15. Patrick DL, Burke LB, Gwaltney CJ, et al. Content validity–establishing and reporting the evidence in newly developed patient-reported outcomes (PRO) instruments for medical product evaluation: ISPOR PRO Good Research Practices Task Force report: part 2–assessing respondent understanding. *Value Health*. 2011;14(8):978-988.
16. Patrick DL, Burke LB, Gwaltney CJ, et al. Content validity–establishing and reporting the evidence in newly developed patient-reported outcomes (PRO) instruments for medical product evaluation: ISPOR PRO good research practices task force report: part 1–eliciting concepts for a new PRO instrument. *Value Health*. 2011;14(8):967-977.
17. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst*. 1993;85(5):365-376.
18. UNESCO. International. Standard Classification of Education (ISCED); 2011. Available at https://uis.unesco.org/en/topic/international-standard-classification-education-isced. Accessed November 2, 2023.
19. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982;5(6):649-655.
20. Fayers PM, Machin D. *Quality of Life: The Assessment, Analysis and Reporting of Patient-Reported Outcomes*. 3rd ed. John Wiey & Sons, Ltd.; 2016.
21. de Souza JA, Yap BJ, Wroblewski K, et al. Measuring financial toxicity as a clinically relevant patient-reported outcome: the validation of the COmprehensive Score for financial Toxicity (COST). *Cancer*. 2017;123(3):476-484.
22. De Vita F, Greco G, Sperti E, et al. Patient-reported financial toxicity within the Italian public healthcare system: a single center cross-sectional analysis in patients with cancer. *Ann Res Oncol*. 2022;2(2):94-115.
23. Altice CK, Banegas MP, Tucker-Seeley RD, Yabroff KR. Financial hardships experienced by cancer survivors: a systematic review. *J Natl Cancer Inst*. 2016;109(2):djw205.
24. de Souza JA, Yap BJ, Hlubocky FJ, et al. The development of a financial toxicity patient-reported outcome in cancer: the COST measure. *Cancer*. 2014;120(20):3245-3253.
25. Lillini R, De Lorenzo F, Baili P, et al. Out-of-pocket costs sustained in the last 12 months by cancer patients: an Italian survey-based study on individual expenses between 2017 and 2018. *Eur J Health Econ*. 2023;24(8):1309-1319.
26. Patel A, Perrone F, Ashcroft DM, Flaum N, Cook N, Riva S. Cross-cultural adaptation of the PROFFIT Instrument to measure financial toxicity in people living with cancer within a UK population. *J Cancer Policy*. 2023;38:100440.