

ORIGINAL ARTICLE

PATIENT-REPORTED FINANCIAL TOXICITY WITHIN THE ITALIAN PUBLIC HEALTHCARE SYSTEM: A SINGLE CENTER CROSS-SECTIONAL ANALYSIS IN PATIENTS WITH CANCER

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ABSTRACT

PROFFIT (Patient Reported Outcome for Fighting Financial Toxicity of cancer) questionnaire has been developed in Italy, within a universal healthcare system, for measuring financial toxicity (FT) in patients with cancer and understanding its determinants. Our aim was to describe the amount of FT in patients with cancer, by using the PROFFIT questionnaire, in subjects treated in a public Italian institution. Between May and July 2021 we administered, on one-off basis with a cross-sectional approach, the

PROFFIT questionnaire to 167 outpatients receiving active anticancer treatment at the Oncology Day Hospital of Ordine Mauriziano Hospital, Turin, Italy. Answers were matched with relevant clinical and demographic characteristics.

Median FT score in the overall population was 23.81 (IQR 14.29-47.62). FT score was significantly higher in younger patients, in those with worse educational level, in private employees and unemployed, and in subjects with economically dependent familiars.

No significant differences were found according to gender, time from diagnosis, type of tumor, type of treatment and disease setting. There was a significant association between FT score and the presence of economic damage due to COVID-19 for the patient or the family: median FT score was 14.29,

33.33 and 47.61 for those declaring no damage, a little damage and much damage ($p < 0.001$).

Our analysis, conducted during the COVID-19 pandemic, shows that financial toxicity is not negligible in patients with cancer, also in Italy, a country with universal healthcare system.

KEY WORDS

Financial toxicity; patient-reported outcomes; cancer; Italian health system; PROFFIT.

IMPACT STATEMENT

We administered the PROFFIT questionnaire to 167 outpatients receiving active anticancer treatment at Mauriziano Hospital, Turin, Italy, showing that financial toxicity is not negligible in patients with cancer, also in a country with universal healthcare system.

INTRODUCTION

Financial toxicity (FT) experienced by patients after a diagnosis of cancer has been increasingly discussed and reported worldwide, within countries with different healthcare systems (1-7). Initially, FT has been described in the US, as a factor negatively affecting cancer patients (2). In detail, both QoL and survival have been reported to be worse among patients facing with financial hardships and bankruptcy (8, 9). This is not surprising, considering that the US health system requires out of pocket co-payment of medical expenses and that the cost of cancer treatments has significantly increased in recent years.

The need of a specific instrument to measure FT has been previously addressed in the US, with the development and validation of the Comprehensive Score for Financial Toxicity (COST) instrument (10, 11). However, differently from US, Italy has a public health system, where patients should not directly sustain the expenses related to diagnosis and treatment of cancer. Since 1978, the Italian health care system is designed with a National Health Service model, where the State is the most important financer, via general tax levies. Some years ago, financial difficulties among Italian cancer patients enrolled in 16 clinical trials have been reported in a not negligible proportion of subjects, showing a relevant association with worse quality of life and overall survival (1). Namely, using the answer to item 28 of EORTC QLQ C30 ("Has your physical condition or medical treatment caused you financial difficulties?"), that analysis showed that patients reporting some degree of financial burden at baseline had a higher chance of wors-

ening global quality of life (QoL) during the treatment, and that patients, who developed financial toxicity during treatment, had a statistically significant shorter survival (1).

Therefore, in 2018, in order to develop an instrument for measuring and understanding the determinants of FT in patients with cancer, sensitive to dimensions of a universal healthcare system, the multicentre PROFFIT (Patient Reported Outcome for Fighting Financial Toxicity of cancer) project was started (12-14). That project led to the production of the PROFFIT questionnaire which is, to the best of our knowledge, the first instrument for FT fully published from a European country.

With the aim of describing the amount of FT in patients with cancer treated in a public Italian institution, we administered the PROFFIT questionnaire to outpatients receiving active treatment at the Oncology Day Hospital of Ordine Mauriziano Hospital, in Turin, Italy.

METHODS

Patients

PROFFIT questionnaire was administered, in paper format, to adult outpatients who were receiving any type of active systemic treatment (chemotherapy, targeted agents, immune checkpoint inhibitors, hormonal treatment) for a solid tumor. Both patients who were starting a treatment and those who were already on treatment were eligi-

ble. Patients were eligible independently of tumor stage, and both patients receiving a (neo)adjuvant treatment and those with advanced disease were included in the analysis.

PROFFIT questionnaire

The PROFFIT questionnaire includes the FT-score (consisting of 7 items) and 9 single items assessing possible determinants of FT. Among the latter ones, 4 items are related to medical expenses (coverage by National Health service; private visits and examinations; medicines and/or supplements; additional expenses), 2 items are related to transportation (distance from hospital and costs of transportation), and 3 items are related to support from health system (doctors and nurses; administrative staff; communication among parties). Responses to PROFFIT items are coded in 4 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).

In addition to the 16 PROFFIT items, information about economically relevant factors (education level, marital status, living alone, presence of dependents among family members, working status, economic damage from COVID-19 pandemic) were collected too, with dedicated questions added to the paper questionnaire. After the collection, each questionnaire was transcribed by an author (G.G.) into an electronic Excel database, and main clinical characteristics (gender, age, time from cancer diagnosis, type of primary tumor, type of anticancer treatment and disease setting) were collected by the same author from patient's electronic medical records.

Statistical issues

PROFFIT results are reported as a FT-score (including items #1 to #7) and 9 separate items for FT determinants. According to the methodology previously described, all the scores are normalised to 0-100%, where 100 indicates the highest toxicity (14). For calculation of the FT-score, including items #1 to #7, the following steps should be followed: (1) 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; (2) 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. 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).

There was no formal sample size planning for this study. Statistical analyses were essentially descriptive. Categorical variables are described with frequencies and percentages. PROFFIT scores were reported both as mean (and standard deviation) and median (an interquartile range, IQR). FT scores were compared between groups by Mann-Whitney test (for variables with 2 groups) and Kruskal Wallis test (for variables with more than 2 groups). All statistical tests were two-tailed and p-values less than 0.05 were considered statistically significant. Because of the exploratory nature of this analysis, adjustment for multiple item comparisons was not performed. Analyses were performed with SPSS for Windows, version 27.0.

Ethical issues

Our institution was involved in the development and validation of the PROFFIT questionnaire: the study protocol was initially approved by the Ethics Committee of the National Cancer Institute of Naples, which acted as coordinating Ethics Committee, and was subsequently approved by our Ethics Committee. Following the development of PROFFIT questionnaire within the clinical trial, we administered the same questionnaire to patients routinely treated at our center. Before filling questionnaires, all patients signed a written consent for the treatment of personal data, in an anonymous format.

RESULTS

Between May and July 2021, we administered the PROFFIT questionnaire to 170 patients treated at Oncology Day Hospital, Mauriziano Hospital, Turin, Ita-

ly. Three patients were excluded because they were not receiving active anticancer treatment, so the remaining 167 patients were eligible for the analysis. Of them, 24 patients (14.4%) compiled the questionnaire on the day of treatment line start, further 28 (16.8%) had started that line of treatment less than 1 month before, and the remaining 115 (68.9%) had started their line of treatment more than 1 month before.

Main demographic and clinical characteristics of patients included in the analysis are shown in **table I**. Participants were mostly females (110, 65.9%), and median age was 66 years (range 34-87), with 79 patients (47.3%) under 70 years and the remaining 88 (52.7%) older than 70. About half of the patients (82, 49.1%) were resident in the city of Turin, while the remaining 85 (50.9%) were resident outside the city. More than half (59.9%) of the patients had a high level of education (high school or degree), and 108 (65.1%) were married. Forty-one patients (24.6%) lived alone, and 41 patients (24.6%) had 1 or more dependents among family members. In terms of employment status, more than half of the patients (98, 59.4%) were retired, 20 (12.1%) public employees, 19 (11.5%) private employees; 17 (10.3%) were unemployed. Time from tumor diagnosis was lower than 1 year in 90 (53.9%) of patients. The most common tumors were gastrointestinal cancers (71, 42.5%, namely 25 colorectal cancers and 46 upper tract cancers), breast cancer (38, 22.8%), gynecologic cancers (20, 12.0%) and lung cancer (18, 10.8%). Most common treatments received at the time of PROFFIT administration were chemotherapy (123, 73.7%), targeted drugs (20, 12.0%) and immune checkpoint inhibitors (20, 12.0%). Most patients were receiving treatment for advanced disease, as first-line (78, 46.7%) or second-line and beyond (39, 23.4%).

Detailed answers and scores for each of the items included in the PROFFIT questionnaire are reported in **table II**. When asked about their "ability of affording monthly expenses (e.g., rent, electricity, phone) without difficulty", 51 patients (30.5%) declared not agreeing at all or only partially. Proportion of patients declaring substantial or very much agreement was 27.5% for the statement "My illness has reduced my financial resources"; 35.9% for the statement "I am concerned by the economic problems I may have in the future due to my illness" and 15.6% for the statement "My economic situation affects the possibility of receiving medical care". In addition, proportion of patients declaring substantial or very much agreement was 26.3% for the

statement "I have reduced my spending on leisure activities such as holidays, restaurants or entertainment in order to cope with expenses related to my illness", 12.0% for the statement "I have reduced spending on essential goods (e.g., food) in order to cope with expenses related to my illness" and 30.5% for the statement "I am worried that I will not be able to work due to my illness". Excluding retired patients from this latter item, proportion of patients declaring substantial or very much worry of not being able to work due to the illness rised to 47.8%.

Based on the above described outcome items, mean FT score in the 167 patients was 29.28 (SD 21.78), and median score was 23.81 (IQR 14.29-47.62), as reported in **table II**. Distribution of FT scores in the whole series of patients is reported in **figure 1**. The association of FT score with patients' characteristics is reported in **table III**. FT score was

	N	%
All patients	167	
GENDER		
Male	57	34.1%
Female	110	65.9%
AGE		
Younger than 70 years	79	47.3%
Older than 70 years	88	52.7%
RESIDENCE		
City of Turin	82	49.1%
Outside Turin	85	50.9%
EDUCATION LEVEL		
Primary (elementary)	22	13.2%
Middle school	45	26.9%
High school	72	43.1%
Degree	28	16.8%
MARITAL STATUS (1 MISSING)		
Married	108	65.1%
Divorced	16	9.6%
Cohabiting	7	4.2%
Unmarried	13	7.8%
Widow(er)	22	13.3%
LIVING ALONE		
No	126	75.4%
Yes	41	24.6%
WITH DEPENDENT FAMILY MEMBERS		
No	126	75.4%
Yes	41	24.6%

Table I. Patients' characteristics. (Continued).

	N	%
WORKING STATUS (2 MISSING)		
Public employee	20	12.1%
Private employee	19	11.5%
Free lance	11	6.7%
Retired	98	59.4%
Unemployed	17	10.3%
ECONOMIC DAMAGE FROM COVID-19		
Not at all	89	53.3%
Quite a bit	63	37.7%
Very much	15	9.0%
TIME FROM CANCER DIAGNOSIS		
Less than 12 months	90	53.9%
More than 12 months	77	46.1%
TYPE OF TUMOR		
Thoracic	18	10.8%
Breast	38	22.8%
Gastrointestinal, colorectal	25	15.0%
Gastrointestinal, non colorectal	46	27.5%
Genito-urinary	15	9.0%
Gynecologic	20	12.0%
Other	5	3.0%
TYPE OF TREATMENT		
Chemotherapy +/- other	123	73.7%
Targeted agents	20	12.0%
Immunotherapy	20	12.0%
Hormonal treatment	4	2.4%
DISEASE SETTING		
(Neo)adjuvant	50	29.9%
Advanced, first-line	78	46.7%
Advanced, second- / further lines	39	23.4%

Table 1. Patients' characteristics.

significantly associated with age (worse in younger patients), educational level (better in graduated subjects), occupational status (worse in private employees and in unemployed subjects), presence of economically dependent familiars. On the other hand, there was no significant association of FT score with sex, marital status, time from tumor diagnosis, type of tumor, type of treatment and setting of disease. As expected, there was a significant association between FT score and the presence of economic damage due to COVID for the patient or

the family (**figure 2**). Namely, median FT score was 14.29, 33.33 and 47.61 for those declaring no damage, a little damage and much damage.

As for determinants of FT, when asked if "the National Health Service covers all health costs related to their illness", 66 patients (39.5%) declared not agreeing at all or only partially. Proportion of patients declaring substantial or very much agreement was 34.7% for the statement "I have paid for one or more private medical examinations for my illness", 46.7% for the statement "I have paid for additional medicines or supplements related to my illness" and 26.9% for the statement "I have to pay for additional treatment (e.g., physiotherapy, psychotherapy, dental care) myself". As for expenses related to distance from the treatment centre and related costs, proportion of patients declaring substantial or very much agreement was 33.5% for the statement "The treatment centre is a long way from where I live" and 25.1% for "I have spent a considerable amount of money on travel for treatment". As expected, answers to these 2 questions were significantly related to the residence of patients: proportion declaring substantial or very much agreement to the former statement was 11.0% among patients resident within Turin vs. 55.3% among those resident outside Turin, while for the latter statement proportion was 13.4% vs. 36.5%, respectively. As for support from the health staff, proportion of patients who declared not agreeing at all or only partially was 4.2% for the statement "Medical staff (i.e., doctors, nurses, etc.) have been helpful throughout my medical care", 10.8% for "Staff in hospital administration (i.e., for booking appointments, secretaries) have been helpful throughout my medical care" and 12.0% for "Medical staff and medical facilities I attended communicated with each other".

DISCUSSION

This analysis shows that FT in patients with cancer treated at a public institution in Italy, during the COVID-19 pandemic, was not negligible. When testing the association between patients' characteristics and impact of financial toxicity, FT score was significantly higher in younger patients (i.e. subjects of working age), in those with worse educational level, in private employees and unemployed patients, and in subjects with economically dependents among their family members. On the other hand, no significant differences were found

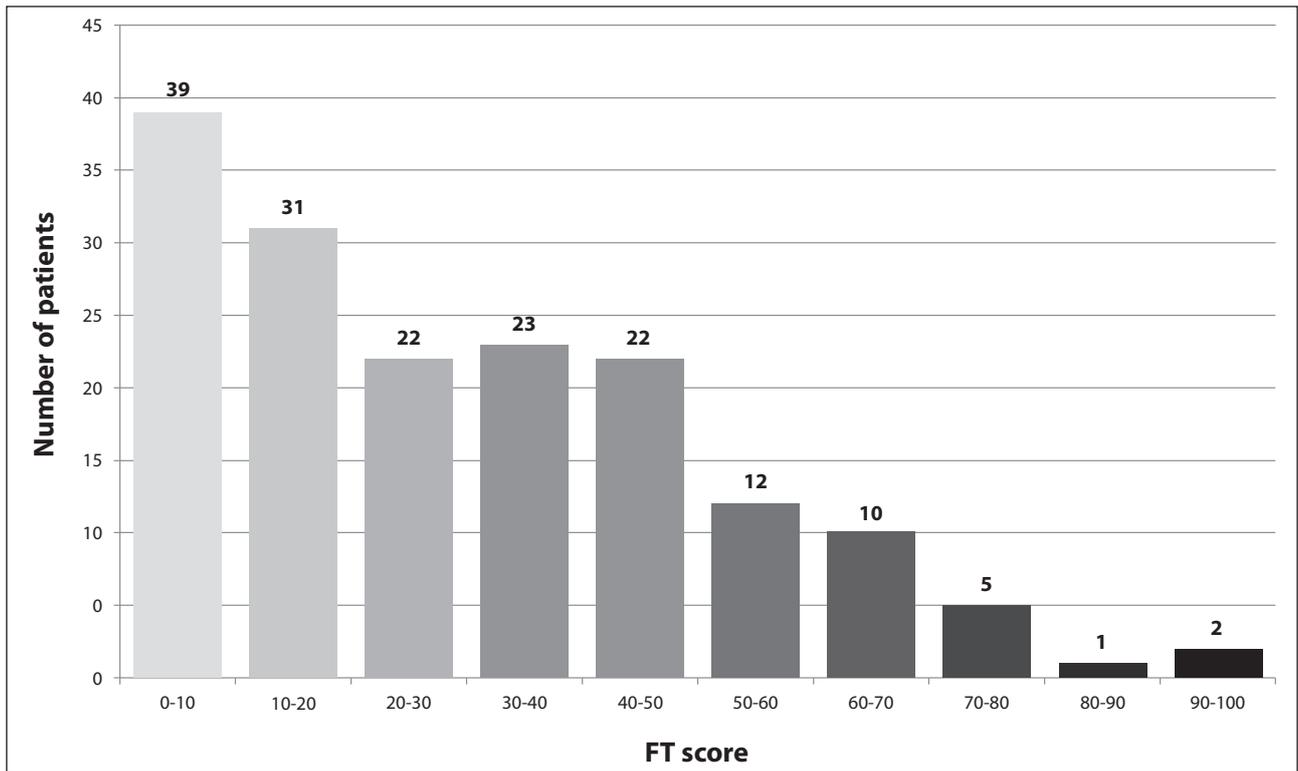


Figure 1. Distribution of Financial Toxicity score, based on the first 7 items of PROFFIT questionnaire, in the 167 patients included in the analysis. The score is normalised from 0 to 100, where 100 indicates the highest financial toxicity.

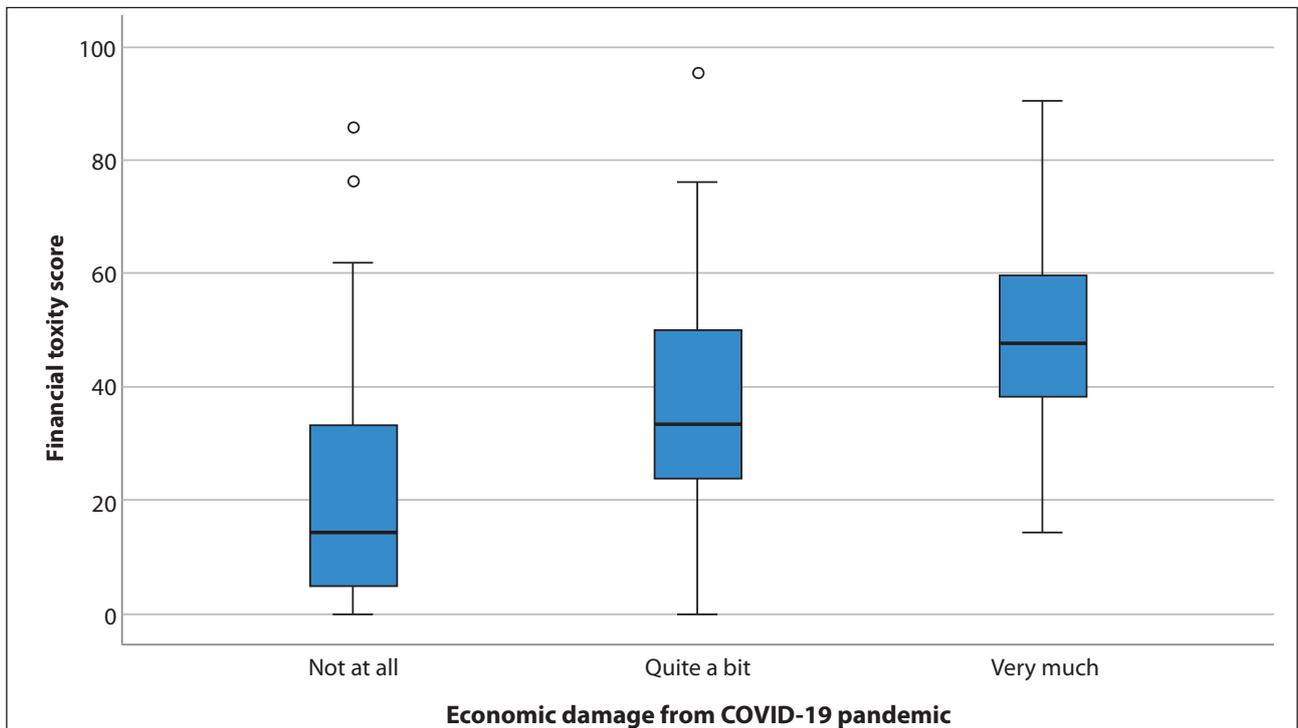


Figure 2. Box plot of Financial Toxicity score in the 167 patients included in the analysis, according to economic damage from COVID-19 pandemic. The thick line in the middle is the median. The top and bottom box lines show the first and third quartiles. The whiskers show the maximum and minimum values, with the exceptions of outliers (circles).

according to gender, time from diagnosis, type of tumor, type of treatment and disease setting.

As expected, there was a significant association between FT score and the presence of economic

		1 - I DO NOT AGREE AT ALL	2 - I AGREE PARTIALLY	3 - I AGREE SUBSTANTIALLY	4 - I VERY MUCH AGREE	SCORE	
						MEAN (SD)	MEDIAN (IQR)
OUTCOME ITEMS (FT SCORE)							
1	I can afford my monthly expenses without difficulty (e.g., rent, electricity, phone...)	16 (9.6%)	35 (21.0%)	69 (41.3%)	47 (28.1%)	29.28 (21.78)	23.81 (14.29-47.62)
2	My illness has reduced my financial resources	64 (38.3%)	57 (34.1%)	36 (21.6%)	10 (6.0%)		
3	I am concerned by the economic problems I may have in the future due to my illness	49 (29.3%)	58 (34.7%)	40 (24.0%)	20 (12.0%)		
4	My economic situation affects the possibility of receiving medical care	94 (56.3%)	47 (28.1%)	18 (10.8%)	8 (4.8%)		
5	I have reduced my spending on leisure activities such as holidays, restaurants or entertainment in order to cope with expenses related to my illness	81 (48.5%)	42 (25.1%)	21 (12.6%)	23 (13.8%)		
6	I have reduced spending on essential goods (e.g., food) in order to cope with expenses related to my illness	123 (73.7%)	24 (14.4%)	18 (10.8%)	2 (1.2%)		
7	I am worried that I will not be able to work due to my illness	87 (52.1%)	29 (17.4%)	25 (15.0%)	26 (15.6%)		
DETERMINANT ITEMS (SINGLE ITEMS)							
8	The National Health Service covers all health costs related to my illness	26 (15.6%)	40 (24.0%)	65 (38.9%)	36 (21.6%)	44.51 (32.85)	33.33 (33.3-66.67)
9	I have paid for one or more private medical examinations for my illness	65 (38.9%)	44 (26.3%)	32 (19.2%)	26 (15.6%)	37.13 (36.48)	33.33 (0-66.67)
10	I have paid for additional medicines or supplements related to my illness	39 (23.4%)	50 (29.9%)	51 (30.5%)	27 (16.2%)	46.51 (33.92)	33.33 (33.33-66.67)
11	I have to pay for additional treatment myself (e.g., physiotherapy, psychotherapy, dental care)	78 (46.7%)	44 (26.3%)	26 (15.6%)	19 (11.4%)	30.54 (34.60)	33.33 (33.33-66.67)
12	The treatment centre is a long way from where I live	59 (35.3%)	52 (31.1%)	35 (21.0%)	21 (12.6%)	36.93 (34.33)	33.33 (0-66.67)
13	I have spent a considerable amount of money on travel for treatment	78 (46.7%)	47 (28.1%)	25 (15.0%)	17 (10.2%)	29.54 (33.62)	33.33 (0-66.67)
14	Medical staff (i.e., doctors, nurses, etc.) have been helpful throughout my medical care	1 (0.6%)	6 (3.6%)	36 (21.6%)	124 (74.3%)	10.18 (18.91)	0 (0-33.33)
15	Staff in hospital administration (i.e., for booking appointments, secretaries, etc.) have been helpful throughout my medical care	5 (3.0%)	13 (7.8%)	43 (25.7%)	106 (63.5%)	16.78 (25.58)	0 (0-33.33)
16	Medical staff and medical facilities I attended communicated with each other	9 (5.4%)	11 (6.6%)	41 (24.6%)	106 (63.5%)	17.96 (28.04)	0 (0-33.33)

Table II. Answers to the 16 items of the PROFFIT questionnaire (n = 167 patients).

damage due to COVID for the patient or the family. The PROFFIT questionnaire has been developed in Italy, so in this analysis it was used within the specific context which led to its development and validation (12-14). This is particularly important for an instrument

which aims to measure determinants of financial burden, which can be largely different among countries with different health systems (16). Moreover, the inclusion in PROFFIT of several items related to determinants of FT may be helpful to identify potential targets

for action, both at a local and a national level. Despite Italian public health system should cover all the needs of cancer patients, we showed that many patients declare some trouble with several potential determi-

nants of FT. For instance, items related to transportation show that a minority of patients declared a long distance between home and the hospital, and relevant costs for transportation, with higher proportion, as

	N	FINANCIAL TOXICITY SCORE		
		MEAN (SD)	MEDIAN (IQR)	
ALL PATIENTS	167	29.28 (21.78)	23.81 (14.29-47.62)	
Sex				0.52
Male	57	27.90 (21.92)	23.81 (9.52-42.86)	
Female	110	30.00 (21.77)	23.81 (14.29-47.62)	
Age				0.002
Younger than 70 years	79	34.54 (22.33)	14.29-47.62)	
Older than 70 years	88	24.57 (20.27)	19.05 (9.52-36.90)	
Residence				0.99
City of Turin	82	29.97 (23.84)	23.81 (9.52-47.62)	
Outside Turin	85	28.63 (19.71)	23.81 (14.29-42.86)	
Education level				0.024
Primary (elementary)	22	29.65 (19.82)	33.33 (14.29-48.81)	
Middle school	45	31.32 (21.06)	33.33 (14.29-47.62)	
High school	72	32.28 (23.76)	30.95 (14.29-42.86)	
Degree	28	18.03 (15.68)	14.29 (9.52-19.05)	
Marital status				0.58
Married	108	28.53 (21.63)	23.81 (14.29-42.86)	
Divorced	16	35.42 (19.67)	40.48 (16.67-52.38)	
Cohabiting	7	27.21 (27.45)	9.52 (4.76-57.14)	
Unmarried	13	34.07 (26.36)	23.81 (14.29-64.29)	
Widow(er)	22	26.84 (20.50)	21.43 (9.52-44.05)	
Living alone				0.38
No	126	28.38 (21.47)	23.81 (14.29-42.86)	
Yes	41	32.06 (22.76)	33.33 (11.90-50.00)	
With dependent family members				0.006
No	126	26.76 (21.30)	23.81 (9.52-42.86)	
Yes	41	37.05 (21.65)	33.33 (21.49-52.38)	
Working status				0.011
Public employee	20	26.90 (21.92)	16.67 (14.29-38.10)	
Private employee	19	40.85 (21.26)	42.86 (23.81-52.38)	
Free lance	11	33.77 (17.75)	23.81 (19.05-47.62)	
Retired	98	24.83 (20.07)	23.81 (8.33-39.29)	
Unemployed	17	36.69 (24.44)	33.33 (16.67-57.14)	
Economic damage from COVID-19				< 0.001
Not at all	89	20.81 (19.47)	14.29 (4.76-33.33)	
Quite a bit	63	36.73 (19.68)	33.33 (23.81-52.38)	
Very much	15	48.25 (20.90)	47.61 (33.33-66.67)	
Time from cancer diagnosis				0.44
Less than 12 months	90	30.58 (22.37)	26.19 (14.29-47.62)	
More than 12 months	77	27.78 (21.12)	23.81 (9.52-42.86)	

Table III. Financial toxicity score in the whole population and according to patients' characteristics. (Continued).

	N	FINANCIAL TOXICITY SCORE		
		MEAN (SD)	MEDIAN (IQR)	
ALL PATIENTS	167	29.28 (21.78)	23.81 (14.29-47.62)	
Type of tumor				0.38
Thoracic	18	28.31 (28.92)	23.81 (4.76-48.81)	
Breast	38	34.84 (23.49)	35.71 (14.29-52.38)	
Gastrointestinal	71	29.18 (21.07)	28.57 (9.52-42.86)	
<i>Colorectal</i>	25	22.29 (20.05)	14.29 (4.76-38.10)	
<i>Non colorectal</i>	46	32.92 (20.86)	33.33 (14.29-47.62)	
Genito-urinary	15	21.27 (16.58)	19.05 (4.76-33.33)	
Gynecologic	20	25.24 (17.69)	23.81 (14.29-33.33)	
Other	5	32.38 (13.64)	33.33 (19.05-45.24)	
Type of treatment				0.63
Chemotherapy +/- other	123	29.11 (21.39)	23.81 (14.29-47.62)	
Targeted agents	20	30.24 (23.60)	33.33 (5.95-46.43)	
Immunotherapy	20	31.90 (23.44)	23.81 (14.29-46.43)	
Hormonal treatment	4	16.67 (19.25)	16.67 (0-33.33)	
Disease setting				0.96
(Neo)adjuvant	50	29.05 (21.39)	23.81 (14.29-47.62)	
Advanced, first-line	78	29.73 (21.95)	26.19 (14.29-44.05)	
Advanced, second- /further lines	39	28.69 (22.48)	23.81 (9.52-42.86)	

Table III. Financial toxicity score in the whole population and according to patients' characteristics.

expected, among those living outside the city of Turin. The majority of patients treated at Mauriziano Hospital come from Turin city and neighbouring municipalities, but this issue can be even higher at institutions which treat a higher number of patients coming from other provinces or regions (17). As a general rule, with the exception of those patients who are included in a clinical trial which is only available at our center, we usually propose all patients to be treated in the hospital closest to home, to avoid a negative impact on quality of life and to reduce financial and logistical burden related to transportation issues. As for additional medical expenses not covered by the public health system, these have been declared by a not negligible proportion of patients included in our analysis. On the other hand, we were particularly satisfied by the overall answers to the last 3 items of PROFFIT, pertaining to the quality of assistance by medical and administrative staff and to the efficiency of communication among the different operators. Our Hospital is in Turin, in a Region where the oncologic network ("Rete Oncologica") is considered well established since many years, and this should, at least in principle, assure the efficiency of the diagnostic, therapeutic and assistance path for patients which come to our hospital with a suspect of

cancer diagnosis. Of course, this does not necessarily reflect this issue in all other Italian Regions, considering that the degree of implementation of oncologic networks is not the same in the whole country. From this point of view, the larger study currently ongoing within the PROFFIT project (NCT03473379), involving our hospital among many other Italian institutions, distributed among the Italian macro-regions (North, Centre, South, Islands) could be helpful to describe differences, if any, among different parts of the country. Beyond the single-center dimension discussed above, our analysis has some important limitations. Firstly, it was based on a single questionnaire, administered on a one-off basis, and patients reported about their FT in different moments of their disease trajectory. All respondents were on active treatment (mostly chemotherapy, but not exclusively), but time from cancer diagnosis, time from treatment start and disease setting (adjuvant vs. advanced) were quite heterogeneous. Of course, the cross-sectional approach adopted in this analysis allows a rough comparison between different categories (e.g. adjuvant vs. advanced, shorter vs. longer time from cancer diagnosis), but not the description of changes over time in the same patient. Within

the PROFFIT project, an ongoing study with the repeated administration of questionnaires during the course of patients' treatment will allow a better description of the changes over time of FT.

Second, our results are unavoidably conditioned by the impact of COVID-19 emergency. The COVID-19 pandemic in Italy, like in all other countries, has produced a dramatic impact on the management of patients with cancer (15). Beyond the impact on patients' management in terms of treatment decisions, rules for access in the hospital *etc.*, COVID-19 pandemic, with social restrictions and limitations of economic activities, had major consequences on economic income of many people, potentially including patients with cancer and their families. All the questionnaires described here were administered between May and July 2021, just after the second and third waves of the pandemic emergency. This could represent a major limitation for the generalization of our results. Results could have been sensibly different 2 years before, and could be (hopefully) different in the near future, with the evolution / resolution of the pandemic emergency. However, we documented a strong association between FT score and the economic damage from COVID-19 declared by patients.

In conclusion, our analysis confirms that FT is not negligible in patients with cancer, also in a country with universal healthcare system like Italy, and in a Region like Piedmont, where the oncologic network is considered well established since many years. The PROFFIT questionnaire was successfully administered, with optimal compliance. This approach will hopefully provide insights on how to fight against FT, in order to improve the outcomes of cancer patients.

ETHICS

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There were no institutional or private fundings for this article.

Conflict of interests

Massimo Di Maio reports personal fees from Astra-Zeneca, Pfizer, Novartis, Roche, Takeda, Janssen, Eisai, Astellas, Merck Sharp & Dohme, Boehringer Ingelheim, grants from Tesaro - GlaxoSmithKline, outside the submitted work. Francesco Perrone reports grants and personal fees from Bayer, Astra Zeneca, Pierre Fabre, Roche, Incyte, MSD, Janssen Cilag, personal fees from Daichii Sankyo, Clovis,

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Availability of data and materials

The raw dataset used for the analysis reported in this article is available online as **Supplementary materials**.

Code availability

N/A.

Authors' contributions

FDV, GG, MDM contributed to the study conception and design. Material preparation and data collection were performed by FDV, GG, AB, LF, LP, VA and ST. The first draft of the manuscript was written by FDV, GG and MDM, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethical approval

Our institution was involved in the development and validation of the PROFFIT questionnaire: the study protocol was initially approved by the Ethics Committee of the National Cancer Institute of Naples, which acted as coordinating Ethics Committee, and was subsequently approved by our Ethics Committee. Following the development of PROFFIT questionnaire within the clinical trial, we administered the same questionnaire to patients routinely treated at our center.

Consent to participate

Before filling questionnaires, all patients signed a written consent for the treatment of personal data, in anonymous format.

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