Financial Toxicity and Health-Related Quality of Life Profile of Patients With Hematologic Malignancies Treated in a Universal Health Care System

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ABSTRACT

PURPOSE We investigated the association of financial toxicity (FT) with the health-related quality of life (HRQoL) profile of patients with hematologic malignancies treated in a universal health care system.

METHODS We did a secondary analysis of six multicenter studies enrolling patients with hematologic malignancies. FT was evaluated using the financial difficulties item of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30). Multivariable linear regression models were used to assess the mean differences in HRQoL scores between patients with or without FT, while adjusting for key potential confounding factors. We also examined the prevalence of clinically important problems and symptoms by the experience of FT, using established thresholds for the EORTC QLQ-C30. Multivariable binary logistic regression analysis was performed to explore the risk factors associated with FT.

RESULTS Overall, 1,847 patients were analyzed, of whom 441 (23.9%) reported FT. We observed statistically and clinically relevant worse scores for patients with FT compared with those without FT for all the EORTC QLQ-C30 scales. The three largest clinically relevant mean differences between patients with and without FT were observed in pain (Δ = 19.6 [95% CI, 15.7 to 23.5]; P < .001), social functioning (Δ = −18.9 [95% CI, −22.5 to −15.2]; P < .001), and role functioning (Δ = −17.7 [95% CI, −22.1 to −13.3]; P < .001). Patients with FT tended to report a higher prevalence of clinically important problems and symptoms across all EORTC QLQ-C30 scales. In the univariable and multivariable analyses, the presence of FT was associated with the presence of comorbidities, an Eastern Cooperative Oncology Group performance status ≥1, and not receiving a salary.

CONCLUSION Patients with hematologic malignancies treated in the setting of a universal health care system who experience FT have a worse HRQoL profile compared with those without FT.

ACCOMPANYING CONTENT

Appendix

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INTRODUCTION

Financial toxicity (FT), a term used to indicate the material, behavioral, and/or psychosocial consequences of direct (eg, out-of-pocket [OOP] expenses) and indirect (eg, the reduced/lost income) cancer-related costs faced by patients and their families,[1,2] is a growing concern in oncology.[3-5]

FT has been associated with worse health-related quality of life (HRQoL),[6-10] worse mental/emotional well-being,[7,8,10,11] higher symptom burden,[10] as well as shorter survival.[6,12] For example, in a large pooled analysis of prospective trials, Perrone et al[6] found that patients with greater FT at baseline also reported worse HRQoL outcomes, and those who developed FT during or after treatment had a higher risk of death. However, most evidence stems from studies conducted in patients with solid tumors, with scanty evidence for patients with hematologic malignancies. Moreover, the few studies conducted in this population were carried out in the United States,[13,14] which does not have a universal health care system.

CONTEXT

Key Objective

To investigate the association of financial toxicity (FT) with the health-related quality of life (HRQoL) profile of patients with hematologic malignancies treated in a universal health care system.

Knowledge Generated

Nearly one fourth of patients report FT, and their HRQoL profile is worse compared with those patients without FT. Not receiving a salary, having comorbidities, and a worse performance status are associated with FT.

Relevance

This study shows that, even in the context of a universal healthcare coverage, FT is still an important issue for a considerable percentage of patients with hematologic malignancies, and it is associated with HRQoL impairments. Efforts to quantify the magnitude of the problem across specific hematologic cancer populations and to identify solutions to address this growing concern are needed.

Systematic reviews have suggested that FT may also negatively affect patients living in countries with a universal health care system[15,16] and have noted the paucity of studies on the impact of FT on patients with hematologic malignancies. However, in several analyses, patients with hematologic malignancies were combined with patients with solid tumors.[15,16] Regardless of the health care system,[17,18] it has been observed that patients with hematologic cancers have higher level of medical care utilization and financial hardship in affording care compared with patients with solid tumors.[19] This may be due to frequent need for blood and platelet transfusion support requiring visits to the clinic, the high prevalence of fatigue that may limit the capacity to work, or the long periods of hospitalization to recover from intensive chemotherapy.[20] Because of these differences, dedicated analyses and interventions on FT experienced by patients with hematologic malignancies are necessary.[21]

Our main objective was to investigate the association of FT and HRQoL profile of adult patients with hematologic malignancies treated in a universal health care system. Secondary objectives were to assess the prevalence of clinically important problems and symptoms by the presence of FT and to explore socioeconomic and clinical factors independently associated with FT.

METHODS

Study Design and Patients

We performed a secondary analysis by merging data sets from six multicenter studies conducted by the Italian Group for Adult Hematologic Diseases (GIMEMA).[22-27] This pooled data set contained socioeconomic, clinical and patient-reported outcomes (PROs) data of patients with myelodysplastic syndromes (MDS), acute promyelocytic leukemia (APL), chronic myeloid leukemia (CML), and relapsed/refractory multiple myeloma (RRMM). For each included study except one, we used for the analysis the HRQoL baseline assessment (details of data sets used are provided in Appendix Table A1, online only). Considering that the effect of FT on patients' lives depends on the sociocultural context and the health care and social welfare system,[28] only patients enrolled in Italian centers from these studies were considered. Ethical committee approval was obtained from each participating center and all patients provided written informed consent.

Assessment of FT and HRQoL

The presence of FT was evaluated through the financial difficulties item of the well-validated European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30),[29] which asks, "During the last week, has your physical condition or medical treatment caused you financial difficulties?" The possible responses are not at all, a little, quite a bit, and very much. Patients who did not answer to this question were excluded from our analysis. Raw scores were converted to a scale ranging from 0 to 100, with higher values indicating higher perceived financial difficulties.[30] Patients were considered to have FT if they reported any level of financial difficulties, that is, if their score in this scale was above the threshold for clinical importance identified by Giesinger et al.[31] Thresholds for clinical importance have been established to improve the interpretation of the EORTC QLQ-C30 scores in clinical practice and research. These thresholds allow identification of patients who exhibit a clinically important problem or symptom that limit their daily lives, cause worry to them, their partners, or their families, or require help or care.[31] Measurement of FT using the financial difficulties item of the EORTC QLQ-C30 was previously used in other studies.[6,32,33]

HRQoL was evaluated using the functioning and symptoms scales and the global health status/QoL (GHS/QoL) scale of

the EORTC QLQ-C30, which was used in all the six studies selected for this analysis. The following clinical and socioeconomic variables were selected on the basis of their potential impact on FT: age at study entry (continuous), time since diagnosis (continuous), sex (female *v* male), comorbidities (0 *v* ≥1), Eastern Cooperative Oncology Group (ECOG) performance status (0 *v* ≥1), level of education (low, ie, up to compulsory school, *v* medium, ie, up to high school, *v* high, ie, university degree or higher), living arrangements (living alone *v* living with others), and receiving a salary (yes *v* no). Patients receiving, at the time of study entry, a salary for a paid job (ie, employed) or those retired receiving a pension, were classified as patients receiving a salary. Students, homemakers, and unemployed were classified as patients not receiving a salary.

Statistical Analysis

We classified patients into two groups (with and without FT) on the basis of the above-mentioned threshold for the EORTC QLQ-C30 financial difficulties.[31] Patients' characteristics were reported, overall and by presence of clinically meaningful FT, as median and IQR, counts and percentages according to the variable. We assessed differences in the two groups in the main characteristics by Pearson's chi-square tests or Wilcoxon-Mann-Whitney tests, depending on the type of variable. Multivariable linear regression models were used for each EORTC QLQ-C30 scale to assess the mean differences in HRQoL scores between patients with or without FT while controlling for potential confounding factors. The raw scores for each scale were transformed to a linear scale ranging from 0 to 100. A higher score represents a higher level of functioning and GHS/QoL or higher symptom severity. The clinical relevance of between-groups (ie, with or without FT) differences in mean scores was evaluated according to the scale-specific clinically relevant differences for the EORTC QLQ-C30, identified by Cocks et al.[34] These thresholds rely on expert judgment and allow determination of whether a clinically relevant difference between groups is small, medium, or large.[34] To evaluate a possible dose-response effect of FT on HRQoL, as previously observed in patients with solid tumors,[10] we performed an additional descriptive analysis by dividing patients into three groups: those without FT, those with little FT, and those with quite a bit/very much FT. Prevalence of clinically important problems and symptoms at the patient level was also evaluated by presence of FT, using the criteria identified by Giesinger et al.[31] This analysis was also performed by dividing the patients into the same three groups. Univariable and multivariable binary logistic regression analyses were performed to determine the independent socioeconomic and clinical factors associated with FT. First, any factor having a significant univariate test at some arbitrary level (ie, *P* value cutoff point of .05) was selected as a candidate for the multivariable analysis. Next, a backward elimination iterative process removed factors from the multivariable model if they were not significant. Finally, odds ratio (OR) and associated 95% CIs were estimated for the significant factors. All statistical tests were two-sided with type I error $\alpha = .05$. Because of the exploratory nature of the research shown in this manuscript, we did not adjust for multiple testing. Statistical analyses were performed using SAS statistical software, version 9.4 (SAS Institute, Cary, NC).

RESULTS

Patient Characteristics

Overall, 1,847 patients with hematologic malignancies were included in this analysis. Of these, 566 (30.6%) were patients with CML, 514 (27.8%) with MDS, 402 (21.8%) with RRMM, and 365 (19.8%) with APL. Almost one of four patients (n = 441, 23.9%) reported having FT. The median age of patients at study entry was 67.2 years (IQR, 55.1-75.4), and more than a half (n = 1,026, 55.5%) were males. At study entry, 427 (23.4%) patients were not receiving a salary. Compared with patients with FT, patients without FT were more likely to have a high level of education (16.0% without FT *v* 11.1% with FT). Most patients (n = 1,092, 59.1%) had at least one comorbidity, and 657 (42.2%) had an ECOG ≥1. Compared with patients without FT, patients with FT more commonly had at least one comorbidity (63.3% with FT *v* 57.8% without FT; $P = .043$) and an ECOG ≥1 (54.7% with FT *v* 38.2% without FT; $P < .001$). Additional details are reported in Table 1.

Adjusted Mean Differences in HRQoL Scores Between Patients With and Without FT

The HRQoL profile of patients varied by presence of FT. Statistically and clinically meaningful worse scores were observed for patients with FT compared with those without FT, across all HRQoL scales (Table 2). In symptoms scales, the top three largest clinically meaningful differences were observed for pain (Δ = 19.6 [95% CI, 15.7 to 23.5]; $P < .001$), fatigue (Δ = 14.8 [95% CI, 11.0 to 18.6]; $P < .001$), and dyspnea (Δ = 12.9 [95% CI, 8.7 to 17.1]; $P < .001$). In the functioning scales, the top three largest clinically meaningful differences were observed for social functioning (Δ = −18.9 [95% CI, −22.5 to −15.2]; $P < .001$), role functioning (Δ = −17.7 [95% CI, −22.1 to −13.3]; $P < .001$), and emotional functioning (Δ = −15.1 [95% CI, −18.6 to −11.5]; $P < .001$). Clinically meaningful worse scores for patients with FT than patients without FT were also observed in GHS/QoL (Δ = −12.0 [95% CI, −15.1 to −8.7]; $P < .001$).

Descriptive analysis to examine the possible dose-response of FT on HRQoL revealed that, for all the EORTC QLQ-C30 scales, HRQoL scores worsened in parallel to increasing levels of FT (Fig 1). For example, with respect to patients without FT, those with little FT reported a 14.1 lower score in social functioning (a medium clinically relevant difference), and those with quite a bit/very much FT a 29.9 lower score (a large clinically relevant difference). Likewise, for pain the difference was 15.9 (a medium clinically relevant difference) and 28.2 (a large clinically relevant difference) for patients with little FT and quite a bit/very much FT, respectively.

TABLE 1. Characteristics of Patients, Overall and by Financial Toxicity

Patient Characteristic	Overall (N = 1,847)	Patients Without FT (n = 1,406)	Patients With FT (n = 441)	*P*
Sex, No. (%)				.744
Male	1,026 (55.5)	784 (55.8)	242 (54.9)	
Female	821 (44.5)	622 (44.2)	199 (45.1)	
Age at study entry, years				.623
Median (IQR)	67.2 (55.1-75.4)	67.5 (55.0-75.6)	66.3 (55.6-74.6)	
Time since diagnosis, years				.496
Median (IQR)	2.0 (0.3-7.0)	2.1 (0.3-7.2)	1.9 (0.3-6.4)	
Living arrangements, No. (%)				.508
Living alone	245 (13.5)	182 (13.2)	63 (14.4)	
Living with others	1,569 (86.5)	1,196 (86.8)	373 (85.6)	
Missing	33	28	5	
Receiving a salary, No. (%)				<.001
Yes	1,399 (76.6)	1,091 (78.6)	308 (70.3)	
No	427 (23.4)	297 (21.4)	130 (29.7)	
Missing	21	18	3	
Education, No. (%)				.012
Low (up to compulsory school)	813 (45.4)	595 (43.8)	218 (50.5)	
Intermediate (up to high school)	712 (39.7)	546 (40.2)	166 (38.4)	
High (university degree or higher)	266 (14.9)	218 (16.0)	48 (11.1)	
Missing	56	47	9	
ECOG performance status, No. (%)				<.001
0	900 (57.8)	730 (61.8)	170 (45.3)	
≥1	657 (42.2)	452 (38.2)	205 (54.7)	
Missing	290	224	66	
Comorbidity at study entry, No. (%)				.043
No	755 (40.9)	593 (42.2)	162 (36.7)	
Yes (≥1)	1,092 (59.1)	813 (57.8)	279 (63.3)	
Type of hematologic malignancy, No. (%)				<.001
APL	365 (19.8)	278 (19.8)	87 (19.7)	
CML	566 (30.6)	468 (33.3)	98 (22.3)	
MDS	514 (27.8)	386 (27.4)	128 (29.0)	
RRMM	402 (21.8)	274 (19.5)	128 (29.0)	

Abbreviations: APL, acute promyelocytic leukemia; CML, chronic myeloid leukemia; ECOG, Eastern Cooperative Oncology Group; FT, financial toxicity; MDS, myelodysplastic syndrome; RRMM, relapsed refractory multiple myeloma.

Prevalence of Clinically Important Problems and Symptoms by FT

The prevalence of clinically important problems and symptoms was significantly higher in patients with FT than those without FT across all scales of the EORTC QLQ-C30 (Appendix Fig A1). The most prevalent clinically important functional impairment and symptom for patients with FT were, respectively, physical functioning (73.4%, *v* 45.6% for patients without FT) and dyspnea (64.5%, *v* 42.7% for patients without FT). The largest difference in the prevalence of clinically important problems and symptoms between patients with and without FT were found in emotional functioning (34.1 percentage points) and pain (33.9 percentage points).

Prevalence of clinically important problems and symptoms increased with increasing levels of FT. For example, prevalence of fatigue was twofold higher for patients with a little FT and threefold higher for patients with quite a bit/very much FT compared with those without FT (23.2%, 46.6%, and 65.8%, respectively, for patients without FT, with little FT, and with quite a bit/very much FT). Further details are reported in Figure 2.

Socioeconomic and Clinical Factors Associated With FT

In the univariable analyses, the following factors were associated with FT: having at least one comorbidity (OR, 1.26; $P = .043$), an ECOG performance status ≥1 (OR, 1.95; $P < .001$), the level of education (OR, 0.60; $P = .004$; high level *v* low

TABLE 2. Adjusted Mean Differences in EORTC QLQ-C30 Scales of Patients With and Without Financial Toxicity

EORTC QLQ-C30	Patients With FT (n = 441)	Patients Without FT (n = 1,406)	Mean Difference (95% CI)	*P*	Clinical Relevance
Functioning scales and GHS/QoL					
Physical functioning	64.0	78.3	−14.3 (−17.7 to −11.0)	<.001	Medium
Role functioning	61.7	79.4	−17.7 (−22.1 to −13.3)	<.001	Small
Emotional functioning	63.2	78.3	−15.1 (−18.6 to −11.5)	<.001	NA[a]
Cognitive functioning	71.5	83.7	−12.2 (−15.8 to −8.7)	<.001	Medium
Social functioning	68.6	87.5	−18.9 (−22.5 to −15.2)	<.001	Large
GHS/QoL	59.0	71.0	−12.0 (−15.1 to −8.7)	<.001	Medium
Symptoms					
Fatigue	46.3	31.5	14.8 (11.0 to 18.6)	<.001	Medium
Nausea/vomiting	12.5	7.7	4.8 (2.3 to 7.2)	<.001	Small
Pain	36.7	17.1	19.6 (15.7 to 23.5)	<.001	Large
Dyspnea	32.5	19.6	12.9 (8.7 to 17.1)	<.001	Medium
Insomnia	36.6	25.8	10.8 (5.9 to 15.7)	<.001	Small
Appetite loss	18.8	10.5	8.3 (4.4 to 12.0)	<.001	Small
Constipation	20.7	14.9	5.8 (1.4 to 10.3)	<.001	Small
Diarrhea	18.3	10.8	7.5 (3.8 to 11.2)	<.001	Medium

NOTE. A higher score represents a higher level of functioning and GHS/QoL or higher symptom severity. Means were adjusted by a multivariable linear regression model including age at study entry, sex, type of hematologic malignancy, time since diagnosis, presence of comorbidities, ECOG performance status, level of education, living arrangements, and receiving a salary.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; GHS, global health status; FT, financial toxicity; NA, not applicable; QoL, quality of life.
[a]No threshold was provided by Cocks et al.[34]

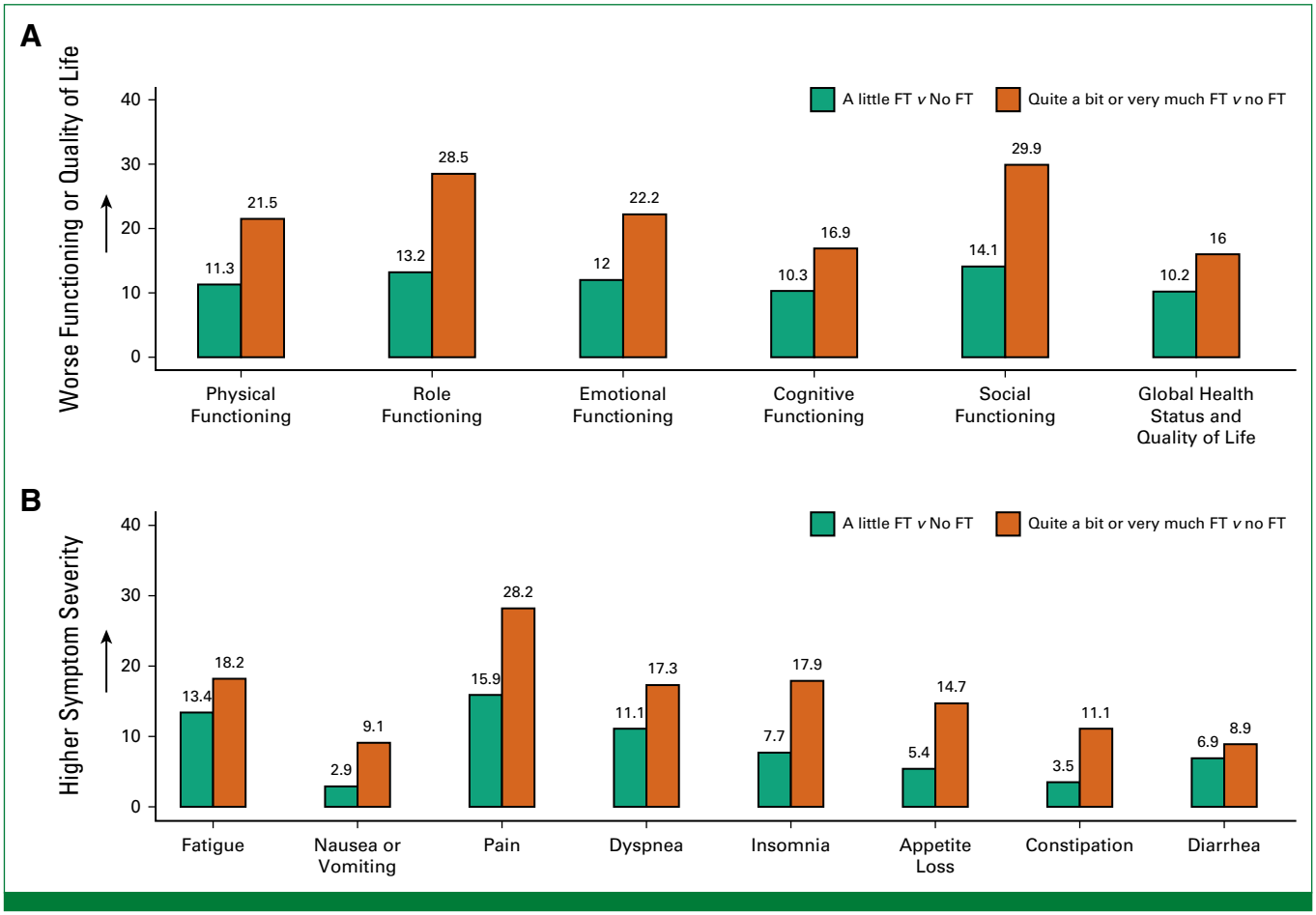

FIG 1. Adjusted mean differences in EORTC QLQ-C30 (A) functioning and global health status/quality of life scales and (B) symptoms scales by severity of financial toxicity. Means were adjusted by a multivariable linear regression model including age at study entry, time since diagnosis, sex, type of hematologic malignancy, presence of comorbidities, ECOG performance status, level of education, living arrangements, and receiving a salary. For descriptive purposes the differences of the functioning scales were multiplied by −1. ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; FT, financial toxicity.

level of education), not receiving a salary (OR, 0.65; $P < .001$; patients with *v* those without a salary), and the type of hematologic malignancy (RRMM with respect to all the other hematologic malignancies). In the multivariable analysis, the presence of FT remained independently associated with comorbidities (OR, 1.27; $P = .048$), an ECOG performance status ≥1 (OR, 1.66; $P < .001$), not receiving a salary (OR, 0.60; $P < .001$; patients with *v* those without a salary), and the type of hematologic malignancy (RRMM with respect to MDS and CML; Table 3).

DISCUSSION

We found that approximately one fourth of patients with hematologic malignancies treated within a universal health care system report FT and that their HRQoL profile is typically worse compared with those patients without FT.

Our results are broadly in keeping with those found in patients with solid tumors, both in the Italian[6] and the US context,[10] indicating that FT is associated with worse HRQoL and symptom burden, as measured with the EORTC QLQ-C30.

The increasing price of new therapies and the remarkable treatment advances that translated into improved survival for many patients with hematologic cancers have led to increasing health care expenditures, contributing to rising costs for societies and higher financial burden for patients.[35] Some patients, for example, those with acute leukemias, are an extremely vulnerable population for FT, as they frequently receive aggressive treatments that require intensive, high-cost health care use.[36,37] However, FT may also affect patients with chronic leukemias, such as those with CML, and patients may decide to delay or miss clinical appointments or prescription medication because of economic burden.[13]

Although these problems have been mainly highlighted in the United States, we have demonstrated that FT is also an

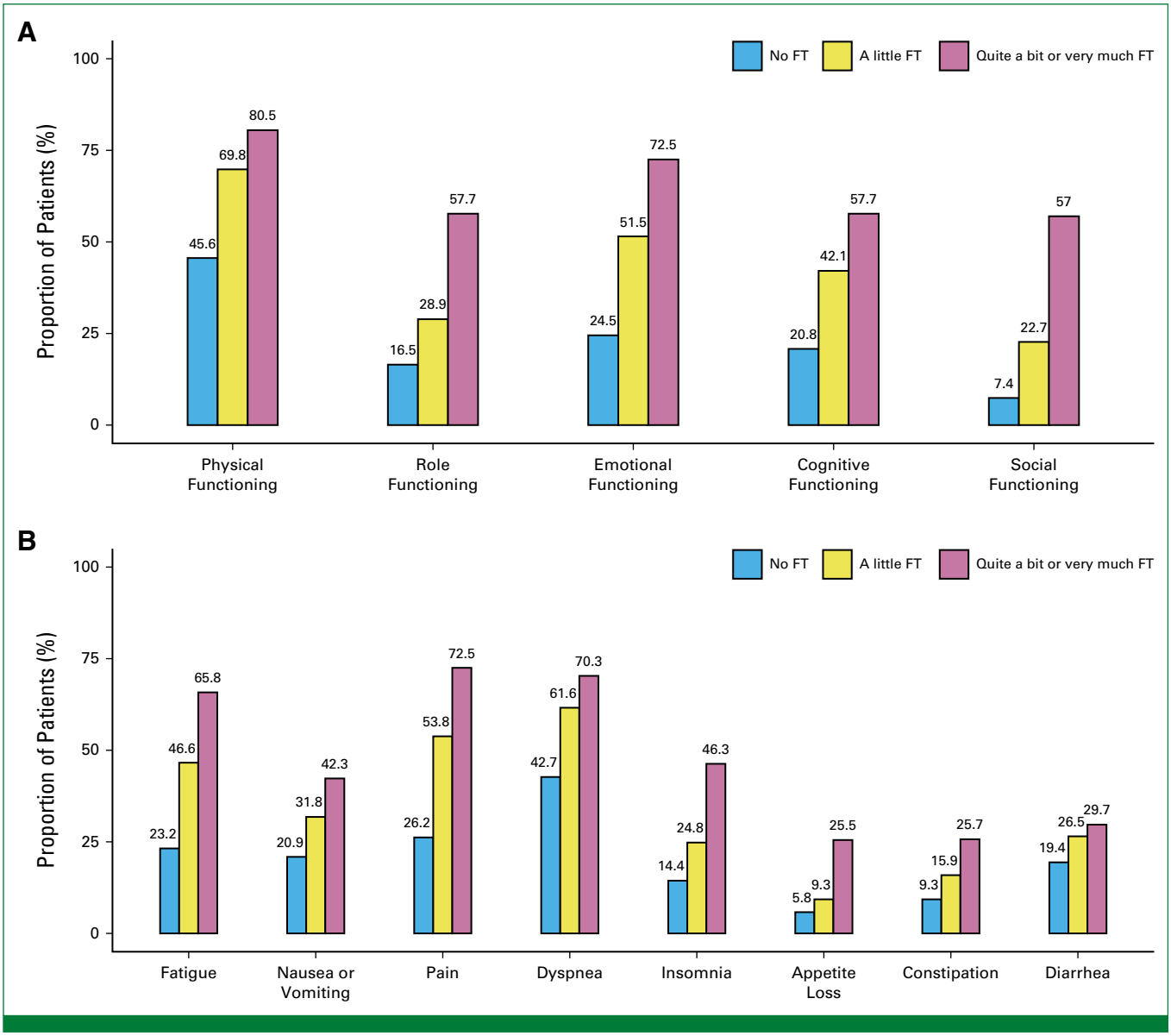

FIG 2. Prevalence of clinically important problems and symptoms in EORTC QLQ-C30 (A) functioning scales and (B) symptoms scales, by severity of financial toxicity. EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; FT, financial toxicity.

important issue in patients treated in a universal health care system. Even in this setting, some inefficiencies (eg, public hospitals not able to provide diagnostic services on time, regional inequalities) may determine the use of private health care or renunciation of care because of high OOP expenses.[38,39] In 2019, about 74% of the health care expenditure in Italy was funded by the National Health System and 26% by private sources. The share of private health spending has increased over the past decade (in 2010, it was 21.5%) and is mostly driven by the OOP payments.[40] A survey conducted on Italian patients wih cancer found that the yearly average OOP costs is more than 1,800 € and is mainly driven by diagnostic examinations, transportation, specialist examinations, nononcologic drugs, and accommodations.[41] Another study conducted among Italian patients with cancer found that 90% of those who took medications to control treatment toxicities paid for at least part of these drugs.[42] The most frequently assumed medicines were those for controlling pain, and these were significantly associated with financial distress.[42] In our analysis, pain was the most prevalent clinically relevant symptom among patients with higher levels of FT, and further studies should focus on the role that this symptom may have on patients' FT. Additionally, cancer survivors may have faced difficulty obtaining financial services like loans or mortgages as, at the time of conduction of the studies, Italy

TABLE 3. Factors Associated With the Likelihood of Experiencing Financial Toxicity

	Univariable Analysis		Multivariable Analysis	
Variable	OR (95% CI)	*P*	OR (95% CI)	*P*
Age (continuous)	1.00 (0.99 to 1.01)	.787	NA	NA
Times since diagnosis (continuous)	0.99 (0.97 to 1.01)	.206	NA	NA
Comorbidity (≥1 *v* 0)	1.26 (1.01 to 1.57)	.043	1.27 (1.01 to 1.61)	.048
ECOG performance status (≥1 *v* 0)	1.95 (1.54 to 2.46)	<.001	1.66 (1.29 to 2.13)	<.001
Sex (female *v* male)	1.04 (0.84 to 1.29)	.744	NA	NA
Level of education				
Medium *v* low	0.83 (0.66 to 1.05)	.116	NA	NA
High *v* low	0.60 (0.42 to 0.85)	.004	NA	NA
Living arrangements (living alone *v* living with others)	0.90 (0.66 to 1.23)	.509	NA	NA
Receiving a salary (yes *v* no)	0.65 (0.51 to 0.82)	<.001	0.60 (0.47 to 0.78)	<.001
Type of hematologic malignancy				
APL *v* RRMM	0.67 (0.49 to 0.92)	.014	0.75 (0.48 to 1.18)	.218
CML *v* RRMM	0.45 (0.33 to 0.61)	<.001	0.44 (0.32 to 0.61)	<.001
MDS *v* RRMM	0.71 (0.53 to 0.95)	.021	0.72 (0.53 to 0.97)	.030

NOTE. For the variable education: low = primary school or less, medium = up to a secondary school diploma, high = higher than a secondary school diploma. For the variable receiving a salary: yes = employed or retired, no = unemployed, homemaker, or student.
Abbreviations: APL, acute promyelocytic leukemia; CML, chronic myeloid leukemia; ECOG, Eastern Cooperative Oncology Group; MDS, myelodysplastic syndrome; NA, not applicable; OR, odds ratio; RRMM, relapsed refractory multiple myeloma.

had not yet adopted a law recognizing the right to be forgotten for cancer survivors, which would have forbidden insurance companies from taking into account patients' medical history.[43] For all these reasons, health disparities increase, as the most vulnerable patients, such as the unemployed or those in poor socioeconomic conditions, may be less protected even in a universal health care system. The impact on clinical and HRQoL outcomes for these patients may be substantial. As highlighted in the literature, there may be a dose-response relationship between financial problems and QoL.[10,44] In our study, we have shown not only that hematologic patients with FT had worse HRQoL compared with those without FT but also that higher levels of FT correlate with worse HRQoL. FT can have different grades of severity, and the application of a standardized grading system for FT has been proposed to help quantify this problem and facilitate shared decision making.[45]

In an effort to better understand potential determinants of FT, our exploratory multivariable analysis revealed that being without a salary, having a higher performance status, and having comorbidities increase the chances of suffering FT. These findings are not surprising, given that working-aged patients may lose the ability to work during treatment for hematologic malignancies, putting them at risk of suffering reduced incomes. Likewise, patients with comorbidities or worse physical health are likely to bear higher OOP costs for additional medicines or visits. Our findings are in keeping with the literature, which identified younger age, unemployment, and lower income as the most common risk factors for FT in patients with hematologic malignancies.[14] Even if the extent to which risk factors determine FT may differ between countries such as United States and those with a universal health care system, Pauge et al[16] found that most risk factors overlap. Future studies should more precisely identify the risk factors underlying FT in the setting studied in our work, taking into account that these often reflect the preexisting social determinants of health.[46] Acknowledging, understanding, and quantifying FT are the first steps to identify possible solutions, which will require involvement of many stakeholders including patients, clinicians, policymakers, and researchers.[4,47] Screening for FT and financial navigation are examples of interventions that have been proposed and have been associated with increased HRQoL and survival.[37,48]

Our study has limitations. The cross-sectional design did not allow us to establish causal relationship between FT and HRQoL. Also, we did not collect data on types and amount of direct and indirect costs sustained by the patients, which would have provided additional insights. Furthermore, the heterogeneity of the hematologic malignancies in our population could have confounded the results; for example, the population of patients with RRMM is likely to be an older population with a higher burden of adverse effects because of ongoing therapy, whereas the population of patients with CML in remission is likely to have a lower burden of office visits, treatment-related adverse effects, and OOP costs, so the findings of this study may have been different if large numbers of patients with these different diseases had been analyzed. Future studies will have to elucidate the various impacts of different hematologic malignancies and treatments on FT. Finally, we measured FT using a single-item question, which might not have fully captured the burden of

FT. In this respect, we note that an Italian PRO questionnaire for measuring FT has been recently developed,[49] and future studies in this area will have to implement this measure to get a better understanding on the relationships between FT and patient outcomes. Our study has also strengths. To the best of our knowledge, this is one of the largest sample of patients with hematologic malignancies treated in a universal health care system for which the impact of FT on HRQoL was assessed. Given the large variability of our sample, we showed that FT is an issue regardless of type and status of hematologic malignancy. Furthermore, the use of the financial difficulties item of the EORTC QLQ-C30 questionnaire for measuring FT has allowed us to use established thresholds for defining clinically important financial difficulties.[31]

In conclusion, FT is a relevant issue in patients with hematologic malignancies treated in a universal health care system, and major efforts should be made in future studies to quantify the magnitude of the problem across specific hematologic cancer populations.

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APPENDIX

TABLE A1. Clinical Characteristics of Patient Populations Included in the Pooled Analysis

APL	CML	MDS	RRMM
Study 1 Type of study: long-term follow-up of two previous clinical trials Patients: long-term survivors (diagnosed >5 years ago and treated with ATRA + idarubicin) and in complete remission	Study 1 Type of study: observational Patients: in first-line treatment for < 3 years with oral TKI	Type of study: observational Patients: patients receiving MDS-related therapy since 2 months	Type of study: observational Patients: patients with MM who have received at least one previous line of therapy and are considered as RRMM according to IMWG criteria
Study 2 Type of study: long-term follow-up of a previous RCT Patients: long-term survivors (treated with ATRA-ATO or ATRA + chemotherapy) and in complete remission	Study 2 Type of study: observational Patients: in first-line therapy with first- or second-generation TKI, and patients in second or greater line of therapy with any TKI		

NOTE. For each study, we considered the baseline assessment, that is the first assessment after patient registration, except for the MDS study.
Abbreviations: APL, acute promyelocytic leukemia; ATO, arsenic trioxide; ATRA, all-trans retinoic acid; CML, chronic myeloid leukemia; IMWG, International Myeloma Working Group; MDS, myelodysplastic syndrome; MM, multiple myeloma; RCT, randomized controlled trial; RRMM, relapsed refractory multiple myeloma; TKI, tyrosine kinase inhibitor.

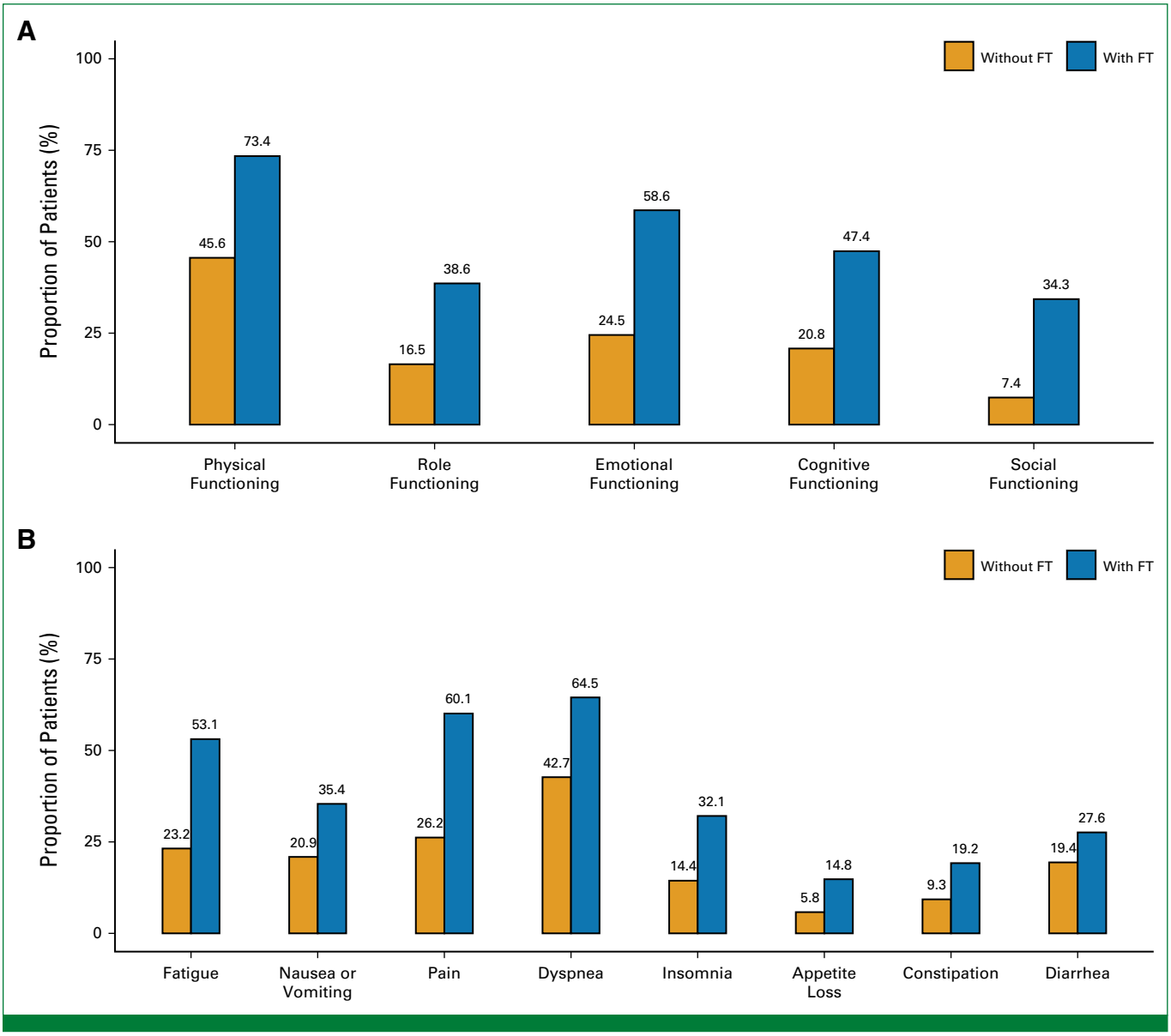

FIG A1. Prevalence of clinically important problems and symptoms in EORTC QLQ-C30 (A) functioning scales and (B) symptoms scales, in patients with and without financial toxicity. All differences in proportions between the two groups were significant. FT, financial toxicity.