

Explore the Factors Influencing Financial Toxicity in Patients with Digestive System Cancer Receiving Immunotherapy: A Cross-sectional Study

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Abstract

Purpose

Immune checkpoint inhibitors (ICIs) are novel treatments for digestive system cancers (DSCs); however, high treatment costs and immune-related adverse events (irAEs) may contribute to financial toxicity (FT). However, the evidence regarding the association between irAEs and FT remains limited. Thus, we aimed to investigate FT and examine irAEs and other associated factors in patients with DSCs receiving immunotherapy.

Methods

This cross-sectional study enrolled adults with DSCs receiving ICIs. IrAEs were assessed using the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE), and FT was measured using the COmprehensive Score for Financial Toxicity. Multiple regression analysis was performed to analyze factors significantly associated with FT.

Results

Among the 97 participants, most experienced mild irAEs, with a mean PRO-CTCAE score of 10.9. Overall, these patients reported relatively low FT (group mean, 27.9); however, 37.1% of the patients reported mild to moderate FT. The multiple regression model demonstrated that prior radiotherapy ($\beta = -0.327$), prior targeted therapy ($\beta = -0.271$), and married status ($\beta = 0.227$) were associated with FT. The model explained 33.8% of the variance in FT.

Conclusion

Patients with DSCs receiving immunotherapy experienced mild-to-moderate FT. Those who were unmarried and had a history of radiotherapy or targeted therapy had a higher FT. Routine FT screening should be integrated into oncology practice, particularly for patients without spousal support or with radio- or targeted therapy. Future longitudinal studies are required to clarify how different treatment trajectories influence FT over time.

Introduction

Digestive system cancers (DSCs)—including esophageal, gastric, liver, biliary tract, colorectal, and pancreatic cancers—account for approximately one-quarter of new cancer cases and one-third of cancer-related deaths worldwide, making them highly prevalent and fatal [1]. Despite advances in surgery, radiotherapy, chemotherapy, and targeted therapy, many DSCs remain difficult to treat owing to

therapeutic resistance and complex clinical presentations, often requiring intensive and expensive care and placing patients and their caregivers at a high risk of financial burden [2, 3].

Immune checkpoint inhibitors (ICIs) are innovative and important treatment options for DSCs and have demonstrated survival benefits [4]. However, the high costs associated with ICIs have raised concerns regarding the financial burden placed on patients and their families [2, 3]. Moreover, approximately 26.3% of patients with DSCs receiving ICI therapy experience immune-related adverse events (irAEs) during treatment [5], which may require prolonged monitoring, corticosteroid therapy, and second-line immunosuppression, increasing healthcare utilization and medical costs [6–8].

Financial toxicity (FT) encompasses both the material burden and financial distress associated with cancer care [9]. A recent large-scale study found that 45% of patients with DSCs experienced FT, indicating that financial distress remains an important concern in this population [3]. FT is an important issue in cancer care and may be associated with poorer quality of life, psychological distress, treatment delay or nonadherence, and increased mortality [10–12]. Younger age, lower household income, low educational level, unemployment, inadequate insurance protection, and being unmarried are associated with greater FT [3, 13–16]. Clinical and treatment-related factors, including advanced cancer stage, DSC type (e.g., anal, esophageal, or hepatobiliary cancer), symptom burden, and prolonged or multiple treatments, may further increase financial vulnerability through additional medical expenses, nonmedical costs, and loss of income [3, 8, 16, 17].

Healthcare coverage may modify but does not eliminate the financial consequences of cancer care. Studies conducted in countries with publicly funded or universal healthcare systems have shown that patients may still experience FT, suggesting that healthcare coverage may not fully protect patients from treatment-related financial burden [18, 19]. Taiwan's National Health Insurance (NHI) system provides broad coverage for routine cancer care and toxicity management [20]. The NHI began reimbursing ICIs for gastric cancer and hepatocellular carcinoma in 2019, although the reimbursement for these indications was suspended in 2020. Coverage was later expanded to first-line treatment for advanced hepatocellular carcinoma and gastric cancer in 2023–2024, followed by biliary tract cancer, and metastatic colorectal cancer with microsatellite instability-high or deficient mismatch repair in 2025. This progressive expansion has broadened NHI coverage for immunotherapy across major DSCs. However, patients for whom ICIs are clinically indicated but who do not meet the reimbursement criteria may face substantial out-of-pocket treatment costs [20]. This setting highlights the need to examine whether FT persists despite broad public coverage of routine cancer care and to identify the characteristics associated with greater financial vulnerability.

Although FT has been increasingly examined in patients with DSCs, previous studies have largely focused on patients with mixed gastrointestinal cancer or patients in other treatment contexts [3, 13, 14], whereas several real-world studies of ICI-related toxicities have primarily focused on healthcare utilization and medical costs rather than patients' perceived financial distress [6]. Consequently, little is known about whether irAEs and prior treatment exposure are associated with patients' perceived FT

during ICI therapy. Therefore, this study aimed to (1) explore the level and prevalence of FT in patients receiving immunotherapy for DSCs and (2) examine the association between demographic characteristics, disease factors, and patient-reported irAEs and FT.

Methods

2.1 Participants and settings

We conducted a cross-sectional study in the Oncology and Gastrointestinal ward in Taiwan between October 2024 and December 2025. Participants were included if they were (1) diagnosed with DSC; (2) aged > 18 years; (3) received immunotherapy at least once; (4) conscious, explicit, and able to communicate in Mandarin/Chinese or Taiwanese; and (5) agreed to participate in this study and provided written informed consent.

2.2 Data collection

This study was approved by the Institutional Review Board (IRB) of the study site (IRB no. 2023-03-005BC) prior to participant recruitment and data collection. The potential participants were screened by trained research assistants (RAs) based on the inclusion criteria. Participation commenced only after written informed consent was obtained. During data collection, if participants who were unable to complete the questionnaire independently owing to visual impairment or physical weakness, the RA administered the questionnaire by reading each item and its response options aloud. The participants provided verbal responses, which were recorded verbatim by the researcher.

2.3 Instruments

The following three structured questionnaires were used: (1) demographic and disease characteristics, (2) the Patient Reported Outcome Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE), and (3) the COMprehensive Score for financial Toxicity-Functional Assessment of Chronic Illness Therapy version 2 (COST).

Demographic data included sex, age (years), marital status, employment, educational level, monthly income, and private insurance.

Disease characteristics included NHI reimbursement for immunotherapy, out-of-pocket medical costs in the past month, diagnosis, history of radiation therapy, history of targeted therapy, ICI type, ICI combined with targeted therapy, and months since the first immunotherapy.

The **PRO-CTCAE** was used to assess irAEs. The items use five-point scales to rate symptom frequency (never, rarely, occasionally, frequently, almost constantly), severity (none, mild, moderate, severe, very severe), and interference (not at all, a little bit, somewhat, quite a bit, very much) over a 7-day recall period [21]. It can also assign composite grades based on an algorithm, ranging from 0 to 3 [22]. Thirty-two items, including 13 system-related categories (gastrointestinal [GI], respiratory, cardio-circulatory,

cutaneous, neurological, visual, cognitive, pain, mood, urinary, and systematic) were selected to assess irAEs based on a Delphi study conducted by Da Silva Lopes and Colomer-Lahiguera [23]. The sum of the irAE grades was 0–93 in this study. Construct validity was demonstrated, and test–retest reliability was strong (intraclass correlation coefficient, .53–.96; median, .76) [24]. The Chinese version was validated through cognitive interviewing [23]. It also showed good reliability, with a Cronbach’s alpha of 0.932.

The **COST**, developed and validated by de Souza et al. [25], was used to assess FT. It comprises 12 items, with seven reverse-scored items (items 2, 3, 4, 5, 8, 9, and 10), and item 12 is not included in the total score. Following the COST scoring guidelines, the sum of the completed item scores was multiplied by 11 and divided by the number of scored items answered. The total score ranged from 0 to 44, with lower scores indicating greater FT [25]. FT severity was classified as follows: grade 0 (no FT, ≥ 26), grade 1 (mild FT, > 14 –26), grade 2 (moderate FT, 1–14), and grade 3 (severe FT, 0). The scale demonstrated good internal consistency with a Cronbach’s α of 0.92 [25]. The Chinese version has been validated in Hong Kong and showed good reliability, with a Cronbach’s alpha of 0.860 [26]. It also showed good reliability in this study, with a Cronbach’s alpha of 0.836.

2.4 Statistical analyses

Data were analyzed using IBM SPSS Statistics version 29.0 (IBM Corp., Armonk, NY, USA). Numbers, percentages, and means with standard deviations (SDs) were used to describe participants’ demographic and clinical characteristics. The sum grade of the PRO-CTCAE was analyzed as a continuous variable to represent the overall severity of irAEs. Thirteen categories of irAEs were divided into two levels: grade 0 (no symptom reported) and $\geq$ grade 1 (symptom reported) as category variable to compare the severity of FT between those who have a symptom and those who do not. The COST was also analyzed as a continuous variable.

Two-tailed tests were used for bivariate and multivariable analyses. The Kolmogorov–Smirnov test was used to test the normality of FT before bivariate analysis, and the results showed that the distribution of FT scores was normal ($Z = 0.72$, $p = 0.200$). Therefore, an independent t-test, analysis of variance, and Pearson correlation were used to test the association among demographic and clinical characteristics, irAEs, and FT. Variables associated with FT in the bivariate analysis were entered into a multivariable linear regression model to identify independent factors associated with FT. Collinearity was assessed post hoc using the variance inflation factor (VIF). A VIF value < 10 indicated the absence of multicollinearity.

Sample size was estimated using G*Power version 3.1.9.4 for multiple linear regression analysis, with $\alpha = 0.05$ and power = 0.8. Because no prior studies have reported effect sizes related to FT in this population, a medium effect size of 0.20 for FT in this population and a medium effect size of 0.20 were adopted. With an estimated 10 predictors, the required sample size was 91 participants.

Results

3.1 Demographic and clinical characteristics

In total, 126 patients were approached for participation. Among them, 23 refused to participate because of an extended questionnaire completion time ($n = 7$), physical fatigue or discomfort ($n = 7$), unwillingness to complete the questionnaire ($n = 6$), perceived absence of symptoms ($n = 2$), or family members' concerns about the potential emotional impact on the patients ($n = 1$). Six patients were excluded during the analysis phase because of missing age data, resulting in a final sample of 97 patients included in the analysis.

The demographic and clinical characteristics are shown in Table 1. The mean age of the participants was 61.7 (SD = 11.2) years. Most participants were male ($n = 68$, 70.1%), married ($n = 75$, 77.3%), unemployed ($n = 63$, 66.0%), still had a monthly income ($n = 70$, 72.2%), and had private health insurance ($n = 70$, 72.2%). On average, the participants received immunotherapy for 8.9 months (SD = 10.2). Most immunotherapies were not covered by the NHI ($n = 64$, 66.0%). Sixteen participants declined to report their out-of-pocket medical expenditure during the previous month. Among the 81 participants who provided data, the two most common expenditure categories were no out-of-pocket expenditure ($n = 22$, 27.2%) and New Taiwan dollars (NT\$) 10,000–99,999 ($n = 22$, 27.2%). Most participants were diagnosed with liver cancer ($n = 53$, 54.6%). Most patients received chemotherapy ($n = 43$, 44.3%). The most commonly prescribed ICI was pembrolizumab ($n = 26$, 26.8%), and in most cases, the regimen did not include targeted therapy ($n = 57$, 58.8%).

Table 1
Descriptive Analysis of Demographic and Disease Characteristics (N = 97)

Characteristics	Mean	SD
Age	61.7	11.2
Education years	13.2	3.3
Months since first immunotherapy	8.9	10.2
Characteristics	n	%
Sex		
Male	68	70.1
Female	29	29.9
Marriage		
No / Divorced / Widow	22	22.7
Yes	75	77.3
Employ status		
No	64	66.0
Yes	33	34.0
Having monthly income		
No	27	27.8
Yes	70	72.2
Private health insurance		
No	27	27.8
Yes	70	72.2
NHI reimbursement		
Note. NHI: National Health Insurance. ICI: immune checkpoint inhibitor. NT\$: New Taiwan Dollar, 33 NT\$ ≈ 1 USD.		
^a Bile duct cancer included intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, and gallbladder cancer.		
^b Other cancer included esophagus cancer (n = 6), colorectal cancer (n = 3), and pancreatic cancer (n = 2).		
^c Other ICI included durvalumab (n = 9), pembrolizumab+ipilimumab (n = 1), and Zimberelimab+AB598 (n = 1).		

Characteristics	Mean	SD
No	64	66.0
Yes	33	34.0
Out-of-pocket medical costs in the past month (NT\$)		
0	22	27.2
1–9,999	16	19.8
10,000–99,999	22	27.2
≥ 100,000	21	25.9
Declined	16	
Cancer type		
Liver	53	54.6
Bile duct ^a	17	17.5
Gastric	16	16.5
Others ^b	11	11.4
History of surgery		
No	56	57.7
Yes	41	42.3
History of radiation therapy		
No	80	82.5
Yes	17	17.5
History of chemotherapy		
No	54	55.7
<i>Note.</i> NHI: National Health Insurance. ICI: immune checkpoint inhibitor. NT\$: New Taiwan Dollar, 33 NT\$ ≈ 1 USD.		
^a Bile duct cancer included intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, and gallbladder cancer.		
^b Other cancer included esophagus cancer (n = 6), colorectal cancer (n = 3), and pancreatic cancer (n = 2).		
^c Other ICI included durvalumab (n = 9), pembrolizumab+ipilimumab (n = 1), and Zimberelimab+AB598 (n = 1).		

Characteristics	Mean	SD
Yes	43	44.3
History of targeted therapy		
No	77	79.4
Yes	20	20.6
ICIs		
Pembrolizumab	26	26.8
Nivolumab	25	25.8
Atezolizumab	23	23.7
Durvalumab+Tremelimumab	13	13.4
Other ^c	11	11.3
ICI combined targeted therapy		
No	57	58.8
Yes	40	41.2
Note. NHI: National Health Insurance. ICI: immune checkpoint inhibitor. NT\$: New Taiwan Dollar, 33 NT\$ ≈ 1 USD.		
^a Bile duct cancer included intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, and gallbladder cancer.		
^b Other cancer included esophagus cancer (n = 6), colorectal cancer (n = 3), and pancreatic cancer (n = 2).		
^c Other ICI included durvalumab (n = 9), pembrolizumab+ipilimumab (n = 1), and Zimberelimab+AB598 (n = 1).		

3.2 The prevalence and level of financial toxicity

One response for item FT 10 was missing, and we followed the COST scoring guidelines to calculate the score; no statistical imputation was performed. The average COST score was 27.9 (SD = 9.9). Overall, 37.1% (n = 36) of the participants had a COST score < 26, indicating the presence of FT, with 26.8% (n = 26) experiencing mild FT (COST score, ≥ 14–26), whereas 10.3% (n = 10) were classified as having moderate FT (COST score, > 0–14).

3.3 Correlation between demographic and clinical characteristics and financial toxicity

The results of the bivariate analysis are presented in Table 2. Having a monthly income ($t=-2.053$, $p = 0.043$) and being married ($t=-2.067$, $p = 0.041$) were correlated with lower FT. In contrast, female sex ($t = 2.728$, $p = 0.008$) and history of radiation therapy ($t = 3.757$, $p < 0.001$) or targeted therapy ($t = 2.244$, $p = 0.034$) were associated with higher FT.

Table 2
Correlation between Demographic Characteristics and COST

Characteristics	n	Mean	SD	t/r/F	p
Age ^a	97			-0.023	0.824
Education years ^a	97			0.105	0.305
Gender ^b				2.728	0.008
Male	68	29.59	9.35		
Female	29	23.78	10.17		
Marriage ^b				-2.067	0.041
No / Divorced / Widow	22	24.07	9.59		
Yes	75	28.96	9.80		
Employ status ^b				-0.062	-0.950
No	63	27.81	10.03		
Yes	33	27.94	9.84		
Having monthly income ^b				-2.053	0.043
No	27	24.58	9.54		
Yes	70	29.11	9.84		
Private insurance ^b				-0.305	0.762
No	27	27.30	11.82		
Yes	70	28.07	9.17		
NHI reimbursement ^b				-1.655	0.101
No	64	26.67	10.16		
Yes	33	30.15	9.13		
Cancer type ^c				1.889	0.137
Liver	53	28.5	9.9		
Bile duct	17	22.9	7.7		
Gastric	16	29.1	9.7		
Note. ^a Using Pearson correlation test. ^b Using independent t test. ^c Using ANOVA.					

Characteristics	n	Mean	SD	t/r/F	p
Other	11	30.7	12.1		
History of surgery ^b				0.618	0.538
No	56	28.39	9.99		
Yes	41	27.12	9.89		
History of radiation therapy ^b				3.757	< 0.001
No	80	29.49	9.41		
Yes	17	20.15	8.78		
History of chemotherapy ^b				1.409	0.162
No	54	29.11	9.53		
Yes	43	26.27	10.27		
History of targeted therapy ^b				2.244	0.034
No	77	29.20	8.81		
Yes	20	22.65	12.26		
ICI combined targeted therapy ^b				-1.983	0.050
No	57	26.20	9.96		
Yes	40	30.20	9.48		
Note. ^a Using Pearson correlation test. ^b Using independent t test. ^c Using ANOVA.					

3.4 Correlation between patient-reported immune-related adverse events (irAEs), and financial toxicity

Overall, the irAEs were generally mild, with a mean total PRO-CTCAE score of 10.9 (SD = 8.6). The five most frequently reported symptom domains were GI irAEs (n = 75, 77.3%), systematic irAEs (n = 72, 74.2%), pain-related irAEs (n = 53, 54.6%), neurological irAEs (n = 48, 49.5%), and cutaneous irAEs (n = 48, 49.5%). In bivariate analysis, the sum grade of irAEs was not associated with FT ($r = -0.161$, $p = 0.115$), and having $\geq$ grade 1 cardio-circulatory-related symptoms ($t = 2.056$, $p = 0.042$) and visual-related symptoms ($t = 2.443$, $p = 0.016$) was correlated with more severe FT (Table 3).

Table 3
Descriptive Statistics and Correlations for Patient-Reported IrAEs and Financial Toxicity

Variable	n	%	Mean	SD	r / t	p
IrAE ^b	97				-0.161	0.115
Gastrointestinal-related irAEs					0.274	0.785
None	22	22.7	28.36	11.96		
≥grade 1	75	77.3	27.70	9.32		
Respiratory-related irAEs					1.334	0.185
None	64	66.0	28.81	10.60		
≥grade 1	33	34.0	25.99	8.26		
Cardio-circulatory-related irAEs					2.056	0.042
None	75	77.3	28.95	9.63		
≥grade 1	22	22.7	24.09	10.18		
Cutaneous-related irAEs					-0.104	0.917
None	49	50.5	27.75	10.28		
≥grade 1	48	49.5	27.96	9.64		
Neurological-related irAEs					0.209	0.835
None	49	50.5	28.06	10.58		
≥grade 1	48	49.5	27.64	9.30		
Visual-related irAEs					2.443	0.016
None	67	69.1	29.46	9.81		
≥grade 1	30	30.9	24.27	9.35		
Cognitive-related irAEs					1.151	0.253
None	60	61.9	28.76	9.34		
≥grade 1	37	38.1	26.38	10.76		
Pain-related irAEs					1.353	0.179
None	44	45.4	29.34	10.34		
≥grade 1	53	54.6	26.62	9.47		
Note. ^a Assessed by COST. ^b Assessed by PRO-CTCAE. IrAEs: Immune-related Adverse Events.						

Variable	n	%	Mean	SD	r / t	p
Mood-related irAEs					0.912	0.364
None	61	62.9	28.56	10.38		
≥grade 1	36	37.1	26.66	9.09		
Urinary-related irAEs					1.311	0.193
None	67	69.1	28.73	10.02		
≥grade 1	30	30.9	25.89	9.56		
Systematic irAEs					0.905	0.368
None	25	25.8	29.40	11.30		
≥grade 1	72	74.2	27.31	9.42		
Note. ^a Assessed by COST. ^b Assessed by PRO-CTCAE. IrAEs: Immune-related Adverse Events.						

3.5 Multiple linear regression analysis of demographic and clinical characteristics, patient-reported irAEs, and financial toxicity

Significant variables in the bivariate analysis were entered into a multiple linear regression model (Table 4). The results showed that being married was significantly associated with lower FT ($\beta = 0.227$, $p = 0.008$). In contrast, a history of radiotherapy ($\beta = -0.327$, $p < 0.001$) and targeted therapy ($\beta = -0.271$, $p = 0.003$) were significantly associated with higher FT. The model explained 33.8% of the variance in FT (adjusted $R^2 = 0.338$). Multicollinearity was not a concern, with VIF values ranging from 1.015 to 1.091.

Table 4
Multiple Linear Regression Analysis of Demographic Characteristics, Patient-Reported IrAEs, and Financial Toxicity

Characteristics	B	SE	95% CI		β	t	p
			LL	UL			
Gender							
Female	-3.617	1.853	-7.299	0.065	-0.168	-1.952	0.054
Male							
Marriage							
No / Divorced / Widow	5.337	1.979	1.406	9.268	0.227	2.697	0.008
Yes							
Having monthly income							
Yes	3.302	1.867	-0.407	7.011	0.150	1.769	0.080
No							
History of radiation therapy							
Yes	-8.473	2.199	-12.842	-4.105	-0.327	-3.854	< 0.001
No							
History of targeted therapy							
Yes	-6.619	2.040	-10.674	-2.565	-0.271	-3.244	0.002
No							
Cardio-circulatory-related irAEs							
None	-3.611	2.014	-7.612	0.390	-0.153	-1.793	0.076
≥grade 1							
Visual related irAEs							
None	-3.575	1.852	-7.255	0.105	-0.167	-1.930	0.057
≥grade 1							
Intercept	27.198	2.456	22.318	32.078		11.074	< 0.001
Note. B: unstandardized coefficients beta. CI = confidence interval; LL = lower limit; UL = upper limit.							

Characteristics	B	SE	95% CI		β	t	p
			LL	UL			
F(p)						7.989	< 0.001
R ²						0.621	
Adjusted R ²						0.338	
Note. B: unstandardized coefficients beta. CI = confidence interval; LL = lower limit; UL = upper limit.							

Discussion

Although immunotherapy is an expensive cancer treatment and is associated with potentially increased FT in patients with cancer [27, 28], our study found that patients with DSCs receiving ICIs experienced relative low FT (27.9 ± 9.9). Nevertheless, 37.1% of the patients experienced mild-to-moderate FT. In the multivariable analysis, marriage was associated with lower FT, whereas histories of targeted therapy and radiotherapy were associated with greater FT. Patient-reported irAEs were not independently associated with FT. These findings indicate that FT remains an important concern during immunotherapy and that patients without spousal support or with complex prior treatment histories may warrant particular attention.

To the best of our knowledge, this is the first study to specifically investigate FT in patients with DSCs receiving immunotherapy. Previous studies investigating FT among patients receiving immunotherapy have either examined pan-cancer populations [29] or primarily focused on patients with lung cancer receiving immunotherapy [28, 30]. We found that the mean COST score was higher than that reported in previous studies of patients with lung cancer actively receiving immunotherapy (COST = 21.41–25.64) [28, 30], indicating relatively lower FT in our study. This difference may partly reflect variations in healthcare financing and financial protection across healthcare systems from the USA, China, and Taiwan [28, 30]. Zhang et al. [30] noted that the high cost of immunotherapy might remain a source of financial burden when treatment is not fully covered by public health insurance. A similar reimbursement gap was observed in our study, with 66.0% of the participants not receiving NHI reimbursement for their current immunotherapy. Nevertheless, all participants in our study were enrolled in Taiwan's NHI, thereby reducing treatment-related out-of-pocket expenses even when the ICI itself is not reimbursed. In addition, 72.2% of the participants had supplemental private health insurance, which may have provided further financial protection. Compared with melanoma survivors approximately 2 years after completion of immunotherapy, who reported a higher mean COST score (30.0 ± 9.46), which indicated lower FT [27], patients receiving active treatment in our study experienced greater FT. This difference may reflect variation in treatment phase, as some treatment-related expenses may decrease after treatment completion [31]. However, these cross-study comparisons should be interpreted with caution because of differences in cancer type, treatment context, and healthcare financing.

Our study observed a lower FT compared with previous studies of patients with DSCs receiving surgery, chemotherapy, radiotherapy, or mixed cancer treatments (COST = 15–25.5) [3, 14, 32, 33]. Similarly, although 37.1% of the participants in our study experienced FT, this proportion was lower than the 45% reported in a large DSC cohort [3]. Previous DSC studies that reported greater FT frequently included patients with lower income, inadequate insurance coverage, or limited social support [3, 14, 32, 33]. In contrast, most participants in our study were married, had an income source, and had supplemental private insurance, suggesting that the financial resources of the participants may have also contributed to the relatively lower FT observed. Marriage was independently associated with a lower FT in the multivariable analysis. This finding is consistent with those of previous studies indicating that relationship status and social support may influence patients' ability to cope with the financial consequences of cancer care [31, 34–36]. Marriage may reflect access to shared household income, practical caregiving assistance, and emotional support [37]. In contrast, patients without spousal support may have fewer financial and practical resources to cope with treatment-related expenses, transportation needs, and disruptions in daily life [31]. Nevertheless, the finding that more than one-third of the participants experienced FT indicates that the financial burden remains relevant despite the broad public coverage of routine cancer care. The independent association between marriage and lower FT further highlights the importance of considering family and social support systems when assessing FT risk.

Although several irAE variables were associated with FT in the bivariate analysis (Table 4), none remained independently associated with FT in the multivariable model. This finding differs from previous evidence suggesting that adverse events and symptom burden may increase financial hardship through additional healthcare utilization, medication costs, and work disruption [6–8]. One possible explanation is that the overall reported irAE burden in this study was relatively lower compared with the possible score range (10.9 ± 8.6 ; range, 0–42) and may, therefore, not have required intensive or costly management. The most frequently reported irAE-related symptom categories were GI symptoms ($n = 75$, 77.3%), systemic symptoms ($n = 72$, 74.2%), and pain-related symptoms ($n = 53$, 54.6%). Additionally, many direct medical costs associated with irAE monitoring and management may have been covered by Taiwan's NHI, thereby limiting the proportion directly borne by the patients. Although medical expenditures were not separated into treatment-related and symptom management costs, 38 of the 81 participants who reported expenditure data (46.9%) had out-of-pocket medical expenditures below NT\$10,000 in the previous month. Nevertheless, these explanations should be cautiously interpreted, because irAE-specific healthcare utilization, out-of-pocket expenses, and indirect costs were not directly assessed in this study.

To the best of our knowledge, this is among the first studies to examine whether histories of targeted therapy and radiotherapy are associated with FT during subsequent immunotherapies. In the multivariable analysis, histories of targeted therapy and radiotherapy were independently associated with greater FT during immunotherapy. To explore possible explanations for this association, we conducted a post hoc descriptive examination and found that more than half of the participants with a history of targeted therapy received targeted therapy concurrently with immunotherapy ($n = 13/20$, 65%), and their

current immunotherapy was largely not reimbursed by the NHI ($n = 19/20$, 95%). These findings suggest that the higher FT in this subgroup may be due to prolonged exposure to high-cost therapies, combination treatment, and reimbursement gaps. Similar financial difficulties have been reported among patients receiving long-term targeted therapy, even in healthcare systems that cover most of the treatment costs [38, 39]. Prolonged treatment may lead to cumulative medical and nonmedical expenses, thereby increasing financial vulnerability over time [40]. Among the participants with a history of radiotherapy in our study, a lower proportion had private health insurance ($n = 9/17$, 52.9%) than those without a history of radiotherapy ($n = 61/80$, 76.3%), suggesting that some may have had less supplemental financial protection. Moreover, radiotherapy may also increase direct and indirect costs through frequent hospital visits, transportation expenses, time away from work, and income loss [41, 42]. Therefore, a history of radiotherapy may serve as a characteristic of previous exposure to a time-intensive treatment trajectory that may have depleted the patients' financial reserves before immunotherapy. However, as prior treatment-related expenses and changes in household finances were not directly measured, this interpretation should be considered exploratory.

This study has some limitations. First, because of the cross-sectional design, causal and temporal relationships between treatment history and FT could not be determined. Second, this was a single-center study, and participants were recruited only from inpatient wards; therefore, the findings may not be generalizable to patients receiving immunotherapy in outpatient settings or other healthcare institutions. Third, the findings should be interpreted within the context of a universal healthcare system and may not be directly applicable to healthcare systems with different reimbursement arrangements. Fourth, the relatively small sample size may have limited the statistical power and precision of the estimates. Fifth, this study only included patients in whom immunotherapy was initiated. Patients who were delayed or unable to initiate treatment owing to financial barriers may have been underrepresented, potentially leading to an underestimation of FT. Finally, irAEs were assessed by patient self-report and may have been affected by recall or reporting bias. Actual treatment-related out-of-pocket expenses, indirect costs, and insurance reimbursements were not directly measured.

Conclusion and implications

FT remains an important concern among patients with DSCs receiving immunotherapy, even within the universal healthcare system. Although Taiwan's NHI may partially buffer the financial burden of routine cancer care, more than one-third of the participants experienced some degree of FT. Marriage was associated with lower FT, whereas histories of radiotherapy and targeted therapy were associated with greater FT. Patient-reported irAEs were not independently associated with FT. Overall, these findings highlight the need to identify FT and provide support for high-risk patients receiving immunotherapy.

In clinical practice, routine screening for FT should be considered a part of oncology care, particularly for patients without spousal support and those with a history of radiotherapy or targeted therapy. FT screening may facilitate timely referral to financial counseling, social work services, and supportive care resources [43]. Future studies should adopt multicenter and longitudinal designs to examine changes in

FT over the course of immunotherapy and across different treatment trajectories. Comparative studies across healthcare systems are also required to better understand how insurance coverage, reimbursement policies, and healthcare financing structures shape the development and severity of FT [19].

Declarations

Competing Interests:

The authors have no relevant financial or non-financial interests to disclose.

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Competing Interests:

The authors have no relevant financial or non-financial interests to disclose.

Ethics Approval:

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Institutional Review Board, Taipei Veterans General Hospital (Date: 2023.03.14 / IRB No. 2023-03-005BC). Written informed consent was obtained from all individual participants included in the study.

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Author Contribution

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Yu-Chen Kuo, Hui-Ying Yang, Pei-Chen Chuang, and Shao-An Shen. The first draft of the manuscript was written by Yu-Chen Kuo and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability:

The datasets generated and analyzed during the current study are not publicly available because they contain potentially sensitive patient information but may be available from the corresponding author upon reasonable request and with approval from the relevant institution.

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