HHS Public Access

Author manuscript

J Surg Oncol. Author manuscript; available in PMC 2023 November 01.

Published in final edited form as:

J Surg Oncol. 2022 November ; 126(6): 1003–1010. doi:10.1002/jso.27012.

Patient reported outcomes: Financial toxicity is a barrier to clinical trials and personalized therapy in cholangiocarcinoma

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Abstract

Purpose: Numerous experimental and targeted therapies are under investigation for patients with cholangiocarcinoma (CCA). Objective health-related quality of life (HRQoL) data for patients receiving these therapies are limited.

Methods: Patients engaged in the Cholangiocarcinoma Foundation completed two validated HRQoL surveys: Functional Assessment of Cancer Therapy (FACT)-Hepatobiliary and COmprehensive Score for financial Toxicity (COST).

Results: Two hundred eight patients were included. Seventy-five percent had intrahepatic CCA and 57% underwent resection, of which 48% had disease recurrence. Twenty-two percent enrolled in a clinical trial and 80% underwent molecular profiling, of which 29% received targeted therapy. While patients enrolled in a clinical trial or received targeted therapy reported similar HRQoL compared to those who did not, they reported higher financial toxicity ($p = 0.05$ and $p = 0.01$, respectively).

Conclusion: Enrollment in a clinical trial or receipt of targeted therapy do not affect a patient's physical, emotional, social, or functional well-being. However, patients report higher financial burden. These therapies are mainly offered in the advanced setting after significant financial strain has been endured and are often only available at large academic centers, creating a physical barrier to access. These findings underscore the need to increase availability and eliminate physical and financial barriers that threaten access and utilization of personalized and progressive therapies.

Keywords

advanced cholangiocarcinoma; clinical trials; financial toxicity; quality of life; targeted therapy

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

1 | INTRODUCTION

Cholangiocarcinoma (CCA) is a rare cancer of the biliary tract that accounts for approximately 3% of all gastrointestinal cancers, with an annual incidence of 1 per 100 000 persons in the United States. Resection represents the only chance for cure; however, few patients have resectable tumors at the time of diagnosis and recurrence rates after resection remain high.[1] Adjuvant capecitabine is the mainstay of treatment following resection,[2] and combination cisplatin and gemcitabine remains the first-line therapeutic option in the advanced setting.[3] Still, overall survival for resectable, locally advanced, and metastatic disease is poor, highlighting the need for novel therapies and clinical trials.

The current landscape of advanced therapeutic options focuses on clinical trials and targeted therapies usually offered in the second and third line. Phase 2 and 3 clinical trials evaluating FOLFIRINOX and FOLFOX, respectively, have demonstrated promising clinical activity for patients with advanced biliary tract cancers.[4,5] Treatment directed at molecular targets, including *FGFR2* fusions and *IDH-1* mutations, have shown significant promise as novel therapies for patients with advanced biliary tract cancers harboring these targetable genetic alterations.[6,7] The application of these therapies continues to evolve and expand into the first-line setting[8]; however, our understanding of the long-term patient-specific outcomes beyond toxicity and disease survival is limited.

Health-related quality of life (HRQoL) has been explored in numerous cancer states and has become an important component in clinical decision making.[9,10] Quality of life domains focusing on physical and functional well-being, emotional support, and financial burden provide critical insight into a patient's experience of disease, which can directly affect cancer outcomes. These psychosocial effects of a patient's care are often overlooked, particularly as they relate to a patient's decision to pursue advanced and investigational therapies.

In patients with CCA, particularly in those with advanced disease, the availability of objective data surrounding HRQoL are limited. Our aim was to evaluate patient-reported HRQoL associated with enrollment in clinical trials and receipt of targeted therapy for patients with advanced CCA.

2 | METHODS

2.1 | Study design and study population

Between March and June 2021, patients engaged in the Cholangiocarcinoma Foundation (CCF), a patient and caregiver advocacy group, were invited to participate via direct email communication and social media platforms. Patients received a study letter detailing the research objectives, procedures, risks and benefits of participation, and data confidentiality and monitoring measures. Individuals interested in participating were enrolled utilizing a signature-exempt consent process. Institutional Review Board approval was obtained before data collection.

Patients completed a 20-min online survey administered via a secure, internally-hosted Research Electronic Data Capture (REDCap) platform, which included relevant patient demographic data and two HRQoL instruments. Only patients who were validated as described below and completed the entire survey were included in the final analysis.

2.2 | HRQoL assessment

HRQoL was evaluated using the externally validated Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep), a 45-item questionnaire scored on a five-point Likert scale.[11] Subscale domains (physical well-being (PWB), score range 0–28; social/family well-being (SWB), score range 0–28; emotional well-being (EWB), score range 0–28; functional well-being (FWB), score range 0–28; and hepatobiliary cancer subscale (HCS), score range 0–72) and a FACT-Hep total score (score range 0–180; composite for PWB, SWB, EWB, FWB, and HCS) were calculated according to the FACIT-Manual, with higher values indicating improved HRQoL.

Financial toxicity was measured using the FACIT Comprehensive Score for financial Toxicity (COST) questionnaire, an externally validated 11-item instrument (score range 0–44) scored on a five-point Likert scale. A Financial Toxicity Score (FTS) subscale was calculated according to the FACIT manual,[12] where lower scores suggest greater financial toxicity.

2.3 | HRQoL questionnaire validation

One prior attempt was made to enroll patients in the study before the current study timeline. The survey platform was cyber hacked, resulting in the submission of over 3000 computer-based, fraudulent responses. To isolate a validated patient population and limit the potential for collection of automated, fraudulent responses, the study was re-launched using a fraud detection system incorporated into the REDCap platform. Participants who completed the survey were then cross-referenced in collaboration with the CCF and Ciitizen. Ciitizen is part of the Invitae data platform and leverages the HIPAA right of access on behalf of patients to collect medical records, extract relevant clinical information into a standardized and validated longitudinal data set, and enable research use of data with patient consent.

Participants were asked to share their email addresses as part of the survey. Email addresses were subsequently cross-referenced with a verified list of CCA patients who registered for the CCF Annual Conference in March 2021. Any email address that could not be verified was then cross-referenced with a list of CCA patients that had joined the Ciitizen platform as a CCA patient. This method of cross-referencing ensured only verified patients with CCA were included in the analysis set.

2.4 | Statistical analysis

Descriptive statistics for all variables were performed for the study population. For univariate analyses, a χ^2 test or analysis of variance was used for categorical variables and a student's *t*-test, or Mann–Whitney test, was used for continuous variables, where indicated. Standardized mean difference, or Cohen's *d*, was calculated and the FACIT effect size tables used for interpretation.[13] Statistical analyses were conducted using SPSS 26.0 software®

(IBM Inc.) and statistical significance was predefined as $p < 0.05$ using two-tailed tests for all analyses.

3 | RESULTS

3.1 | Study cohort characteristics

Of the 1080 participants who completed the survey, 208 were included in our analysis. Median age was 58 years (IQR 51–68) and 63% ($n = 130$) of patients were female. Most patients had private (59%, $n = 120$) or federally-funded (39%, $n = 80$) insurance, achieved a bachelor's degree or higher (60%, $n = 124$), were currently employed (41%, $n = 85$) or retired (39%, $n = 80$), and reported an annual income of greater than $75 000 (67%, $n = 124$).

Patients with intrahepatic CCA accounted for 75% of the study population ($n = 156$). Most patients underwent resection (57%, $n = 119$), of which 48% ($n = 57$) had disease recurrence. Twenty-two percent ($n = 45$) of patients were enrolled in a clinical trial. Eighty percent ($n = 167$) of patients completed molecular profiling, of which 29% ($n = 48$) received targeted therapy.

Compared to patients not enrolled in a clinical trial, those enrolled in a clinical trial reported a higher stage of disease [38% ($n = 17$) vs. 32% ($n = 53$) locally advanced and 33% ($n = 15$) vs. 17% ($n = 27$) metastatic disease; $p = 0.01$] (Table 1). Of those enrolled in a clinical trial, 51% ($n = 23$) previously underwent resection and most patients (70%, $n = 16$) had disease recurrence [compared to 43% ($n = 41$) among patients not enrolled in a clinical trial, $p = 0.04$]. Further, a greater proportion of patients enrolled in a clinical trial previously received targeted therapy [53% ($n = 21$) vs. 21% ($n = 27$), $p < 0.001$]. Elapsed time since diagnosis was greater among patients who were enrolled in a clinical trial [41 months (IQR 16–65) vs. 23 months (11–37)]; however, this was not statistically significant ($p = 0.06$).

A total of 167 patients (80%) underwent molecular profiling, of which 29% ($n = 48$) received targeted therapy (Table 2). Among those who received targeted therapies, the majority had either locally advanced (42%, $n = 20$) or metastatic disease (25%, $n = 12$), compared to 34% and 24%, respectively, among patients who did not receive targeted therapies. A greater proportion of patients who received targeted therapy were previously enrolled in a clinical trial (44% ($n = 21$) vs. 16% ($n = 19$), $p < 0.001$). Time since diagnosis was greater among those who received targeted therapy [34 months (IQR 22–67) vs. 20 months (11–36), $p = 0.04$].

Demographic and clinicopathologic data for patients enrolled and not enrolled in a clinical trial and patients who did and did not receive targeted therapy are listed in Tables 1 and 2, respectively.

3.2 | HRQoL assessment

Compared to patients not enrolled in a clinical trial, patients enrolled in a clinical trial had similar subscale scores for PWB (17.67 vs. 18.64), SWB (20.29 vs. 20.62), EWB (13.53 vs. 14.74), FWB (15.36 vs. 15.82), and HCS (48.38 vs. 50.29) (all $p > 0.1$) (Table 3).

Cohen's *d* effect size for all parameters was <0.5, suggesting a small effect size. FACT-Hep composite score was also similar between groups (115.23 and 120.12 for those enrolled and not enrolled in a clinical trial, respectively; effect size 0.17, $p = 0.31$). Patients who received targeted therapy had similar mean subscale domains (PWB 18.19 vs. 18.45, effect size 0.04; SWB 20.01 vs. 20.90, effect size 0.17; EWB 13.56 vs. 14.50, effect size 0.18; FWB 15.73 vs. 15.61, effect size 0.02; HCS 48.79 vs. 50.45, effect size 0.14) and composite scores (FACT-Hep 116.28 vs. 119.91, effect size 0.13) when compared to patients who did not receive targeted therapy (all $p > 0.28$).

3.3 | Financial toxicity

Patients enrolled in a clinical trial had a significantly lower mean FTS (24.96 compared to 28.25 among patients not enrolled in a clinical trial; effect size 0.33), suggesting higher financial toxicity ($p = 0.05$) (Table 3). Similarly, patients who received targeted therapy reported significantly higher financial toxicity compared to those that did not receive targeted therapy (FTS 24.67 and 28.89, respectively; effect size 0.43, $p = 0.01$).

4 | DISCUSSION

Patient-reported HRQoL data for patients with cholangiocarcinoma are scarce. This is expressly evident among patients with advanced disease. Here, we show that for patients with cholangiocarcinoma, enrollment in clinical trials or receipt of targeted therapy does not affect a patient's physical, emotional, social, or FWB; however, patients report significant financial toxicity associated with receipt of these advanced therapies. Thus, financial burden related to clinical trial enrollment or receipt of targeted therapies needs to be addressed on both an individual and systems level.

HRQoL encompasses numerous psychosocial domains, including physical and functional health, social relationships and support, and emotional well-being. Each component plays a distinct role in a patient's experience of disease and can inform a patient's ability to sustain advanced treatments, as well as cope with their diagnosis and treatments. Understanding the different facets of HRQoL is essential to provide comprehensive cancer care, particularly in the advanced disease setting where patients often experience protracted treatment courses and may seek advanced therapeutic options after initial therapies have failed.

Discussions with providers and their recommendation of cancer clinical trials are the primary drivers in patients' decisions to consider cancer clinical trial enrollment.[14] While structural barriers impact provider attitudes surrounding clinical trials, concern for detrimental side effects and potential damage to the physician–patient relationship also significantly influence whether providers advocate for clinical trial enrollment.[15] Consequently, as many as 76% of eligible patients are not being referred for clinical trial enrollment. In the setting of advanced cholangiocarcinoma, however, our data suggest that patients who enroll in clinical trials or receive 4targeted therapies report no worse HRQoL and thus should not factor into a provider's decision for recommending these advanced therapies.

Financial toxicity related to cancer care is a critical component of patient quality of life that is not routinely examined and thus often overlooked. Clinical trials and personalized therapy are mainly offered late in the advanced disease setting, at which point a significant financial toll has already been endured. It is estimated that as few as 3%–5% of patients enroll in cancer clinical trials and concerns about costs and logistics are often cited as significant barriers to enrollment.[14,16] While clinical trials are often paid for by participating institutions, the financial burden related to clinical trial enrollment spans a spectrum of actual and perceived costs: routine costs of care, including insurance copayments and deductibles, transportation, lodging, meals; potential expenses related to adverse effects of investigational drugs or therapies, including urgent care visits, hospitalizations, supportive care medications; and indirect costs, such as inability to work for significant periods of time, loss of employment and associated work-related benefits, and depleted family savings. With out-of-pocket expenses totaling thousands of dollars every year, the cost of cancer care, particularly for advanced disease when these therapies are often employed, continues to surpass the costs of other chronic conditions.[17]

Several factors impact perceived financial toxicity, including employment status, household income, and insurance status. Historically, patients with higher socioeconomic status enroll more frequently in cancer clinical trials, whereas low income, uninsured, or minority patients are less likely to participate in these trials and thus are underrepresented.[18] Racial or ethnic minorities are not only disproportionately affected by aggressive diseases, but also experience more substantial barriers to receiving appropriate care.[19] Interestingly, 88% of our study population self-reported as white, nearly all patients had either private or federally-funded insurance, and over 65% of patients reported an annual income of greater than $75 000. Still, our study found that enrollment in clinical trials or receipt of targeted therapy are significantly associated with financial toxicity among patients with cholangiocarcinoma. The financial toxicity associated with these advanced therapies may be even further amplified in populations with more limited healthcare support and lower socioeconomic status. Thus, these findings underscore the need to engage in conversations with patients about cost. At the level of individual providers, financial toxicity needs to be incorporated into patient counseling and treatment decision algorithms to identify the most appropriate next steps in care, not just from a disease perspective but from a patient-centered perspective.

Finally, clinical trials are often only available at large, academic centers, creating a physical barrier to access and further compounding the socioeconomic challenges that are often prohibitive to clinical trial enrollment. Indeed, clinical trials are beginning to move into the first-line setting as we attempt to mitigate treatment resistance and explore alternate treatment modalities, including new molecular and genetic targets for disease. Still, the physical barrier to trial enrollment persists. Historically, there have been limited resources to support clinical trials in community settings.[20] To bridge the gap between smaller community centers and the availability of clinical trial centers, partners such as the National Cancer Institute (NCI) and the Association of Community Cancer Centers (ACCC) have established programs, such as the Community Oncology Research Program and the Community Oncology Research Institute to facilitate access and delivery of more equitable care to patients.[21,22] Moving forward at the systems level, overcoming the physical

barrier to clinical trial enrollment will require stronger collaboration between academic and community partners.

There are several limitations to the current study. First, our study sample was drawn from a single registry through the CCF, which could introduce selection bias. Most patients in our population achieved a high level of education and reported high annual income. Further, through their involvement with the CCF, patients have greater exposure to ongoing research developments, new therapies, and availability of clinical trials, which may translate into higher rates of clinical trial enrollment and molecular profiling compared to the general population. While this creates a unique and highly selective study population, it also highlights the value of patient advocacy groups. Second, study participants were recruited via email and social media outlets, increasing susceptibility to cyber-attacks and fraudulent responses. This is a major challenge when collecting patient-reported HRQoL data outside the clinical setting. We incorporated fraud detection measures to limit capture of fraudulent responses and utilized a rigorous patient validation method of vetting patients by their email addresses against either the CCF or Ciitizen databases, to ensure that patients included in our analysis met inclusion criteria. As a result, our study population included a small sample size and subtle differences across groups may not be appreciated.

To our knowledge, this is the first study evaluating financial toxicity in this patient population.

5 | CONCLUSION

For patients with cholangiocarcinoma, clinical trials and targeted therapies offer the possibility of palliation for unresectable disease, or the option of novel treatment when first line therapies have been exhausted. Importantly, receipt of these advanced therapies does not compromise patient HRQoL. But these patients experience significantly higher financial toxicity. To limit deficits in comprehensive cancer care, it is vital to incorporate discussions of financial toxicity when counseling patients on goals of care. We also need to increase clinical trial availability and eliminate the physical and financial barriers that threaten access and utilization of personalized and progressive therapies, especially as these investigations move to the first-line setting.

ACKNOWLEDGMENTS

Assistance with participant communication, survey distribution, and patient validation was provided by Rick Pollock and Reham Abdelwahab from the CCF. Henry Hang, Conner O’Brien, and Katie Kang with Ciitizen, provided technical support necessary to implement fraud detection measures and assisted with patient validation. This study was supported, in part, by the Katz Foundation and the National Center for Advancing Translational Science, Grant/Award Number: TL1TR002382/UL1TR002378.

Funding information

National Center for Advancing Translational Sciences, Grant/Award Number: TL1TR002382 / UL1TR002378; Abraham J. and Phyllis Katz Foundation

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J Surg Oncol. Author manuscript; available in PMC 2023 November 01.

TABLE 1

Demographic and clinicopathologic factors for all patients, dichotomized by enrollment in a clinical trial.

	All patients (*n* = 208)	**No clinical trial (*n* = 163)**	**Clinical trial (*n* = 45)**	***p* Value**
Age (years), median (IQR)	58 (51–68)	60 (51–68)	55 (45–66)	0.04
Sex, *n* (%)				0.41
Female	130 (63)	99 (61)	31 (67)	
Male	78 (37)	64 (39)	14 (33)	
Race/ethnicity, *n* (%)				0.02
White	182 (88)	144 (89)	38 (84)	
Black	7 (3)	2 (1)	5 (11)	
Asian	12 (6)	10 (6)	2 (5)	
Other	6 (3)	6 (4)	0 (0)	
Insurance, *n* (%)				0.84
No insurance	3 (2)	2 (1)	1 (2)	
Private insurance	120 (59)	94 (59)	26 (61)	
Federally funded insurance	80 (39)	64 (40)	16 (37)	
Education, *n* (%)				0.23
Some high school or less	4 (2)	2 (1)	2 (5)	
Highschool graduate or equivalent	18 (9)	17 (10)	1 (2)	
Completed some college/technical school	42 (20)	35 (21)	7 (16)	
Associate’s degree	19 (9)	16 (10)	3 (7)	
Bachelor’s degree	54 (26)	42 (26)	12 (27)	
Completed some graduate school	10 (5)	7 (4)	3 (7)	
Graduate or professional degree	60 (29)	44 (27)	16 (36)	
Employment, *n* (%)				0.52
Unemployed	40 (20)	31 (19)	9 (20)	
Employed	85 (41)	64 (40)	21 (48)	
Retired	80 (39)	66 (41)	14 (32)	
Annual income, *n* (%)				0.32
Less than $75 000	60 (33)	44 (31)	16 (39)	
More than $75 000	124 (67)	99 (69)	25 (61)	
Site of disease, *n* (%)				0.50

	All patients (*n* = 208)	No clinical trial (*n* = 163)	Clinical trial (*n* = 45)	*p* Value
Intrahepatic	156 (75)	120 (74)	36 (80)	
Extrahepatic	52 (25)	42 (26)	9 (20)	
Stage, *n* (%)				0.01
Early stage	96 (46)	83 (51)	13 (29)	
Locally advanced	70 (34)	53 (32)	17 (38)	
Metastatic	42 (20)	27 (17)	15 (33)	
Time since diagnosis (months), median (IQR)	25 (12–48)	23 (11–37)	41 (16–65)	0.06
Resection, *n* (%)	119 (57)	96 (59)	23 (51)	0.45
Neoadjuvant chemotherapy, *n* (%)	42 (35)	32 (33)	10 (43)	0.50
Neoadjuvant radiation, *n* (%)	15 (13)	12 (13)	3 (13)	1.0
Adjuvant chemotherapy, *n* (%)	91 (77)	72 (76)	18 (78)	1.0
Adjuvant radiotherapy, *n* (%)	46 (39)	37 (39)	9 (39)	1.0
Recurrence, *n* (%)	57 (48)	41 (43)	16 (70)	0.04
Molecular profiling completed, *n* (%)	167 (80)	127 (78)	40 (89)	0.15
Received targeted therapy, *n* (%)	48 (29)	27 (21)	21 (53)	<0.001

Abbreviation: IQR, interquartile range.

J Surg Oncol. Author manuscript; available in PMC 2023 November 01.

TABLE 2

Demographic and clinicopathologic factors for all patients, dichotomized by receipt of targeted therapy.

	All patients (*n* = 167)	**No targeted therapy (*n* = 119)**	**Targeted therapy (*n* = 48)**	***p* Value**
Age (years), median (IQR)	57 (51–67)	59 (51–67)	54 (47–67)	0.05
Sex, *n* (%)				1.0
Female	105 (63)	75 (63)	30 (63)	
Male	62 (37)	44 (37)	18 (37)	
Race/ethnicity, *n* (%)				0.05
White	146 (88)	109 (92)	37 (77)	
Black	7 (4)	2 (2)	5 (10)	
Asian	10 (6)	5 (4)	5 (10)	
Other	3 (2)	2 (2)	1 (2)	
Insurance, *n* (%)				0.06
No insurance	2 (1)	1 (1)	1 (2)	
Private insurance	99 (60)	70 (59)	29 (64)	
Federally funded insurance	61 (37)	46 (39)	15 (33)	
Education, *n* (%)				0.30
Some high school or less	3 (2)	3 (3)	0 (0)	
Highschool graduate or equivalent	10 (6)	8 (7)	2 (4)	
Completed some college/technical school	32 (19)	24 (20)	8 (17)	
Associate’s degree	15 (9)	14 (12)	1 (2)	
Bachelor’s degree	43 (26)	29 (24)	14 (30)	
Completed some graduate school	10 (6)	7 (6)	3 (6)	
Graduate or professional degree	53 (32)	34 (28)	19 (40)	
Employment, *n* (%)				0.06
Unemployed	35 (21)	27 (23)	8 (17)	
Employed	69 (42)	43 (36)	26 (56)	
Retired	60 (37)	48 (41)	12 (26)	
Yearly income, *n* (%)				0.91
Less than $75 000	42 (29)	31 (30)	11 (27)	
More than $75 000	104 (71)	74 (70)	30 (73)	
Site of disease, *n* (%)				0.03

	All patients (*n* = 167)	No targeted therapy (*n* = 119)	Targeted therapy (*n* = 48)	*p* Value
Intrahepatic	129 (77)	86 (72)	43 (90)	
Extrahepatic	38 (23)	33 (28)	5 (10)	
Stage, *n* (%)				0.56
Early stage	66 (40)	50 (42)	16 (33)	
Locally advanced	61 (36)	41 (34)	20 (42)	
Metastatic	40 (24)	28 (24)	12 (25)	
Time since diagnosis (months), median (IQR)	24 (12–42)	20 (11–36)	34 (22–67)	0.04
Resection, *n* (%)	90 (54)	63 (53)	21 (44)	0.83
Neoadjuvant chemotherapy, *n* (%)	30 (33)	18 (29)	12 (57)	0.22
Neoadjuvant radiotherapy, *n* (%)	10 (11)	5 (8)	5 (24)	0.27
Adjuvant chemotherapy, *n* (%)	72 (80)	51 (81)	21 (100)	0.95
Adjuvant radiotherapy, *n* (%)	34 (38)	21 (33)	13 (62)	0.28
Recurrence, *n* (%)	50 (56)	30 (48)	20 (95)	0.04
Clinical trial, *n* (%)	40 (24)	19 (16)	21 (44)	<0.001

Abbreviation: IQR, interquartile range.

TABLE 3

FACT-hepatobiliary and COST subscales, composite scores, and effect sizes.

	Range	No clinical trial (*n* = 163)	Clinical trial (*n* = 45)	Effect size[a]	*p* Value	No targeted therapy (*n* = 119)	Targeted therapy (*n* = 48)	Effect size[a]	*p* Value
PWB	0–28	18.64	17.67	0.14	0.41	18.45	18.19	0.04	0.83
SWB	0–28	20.62	20.29	0.06	0.72	20.90	20.01	0.17	0.33
EWB	0–24	14.74	13.53	0.24	0.16	14.50	13.56	0.18	0.28
FWB	0–28	15.82	15.36	0.08	0.65	15.61	15.73	0.02	0.91
HCS	0–72	50.29	48.38	0.16	0.35	50.45	48.79	0.14	0.42
FACT-Hep[b]	0–180	120.12	115.23	0.17	0.31	119.91	116.28	0.13	0.46
FTS[c]	0–44	**28.25**	**24.96**	**0.33**	**0.05**	**28.89**	**24.67**	**0.43**	**0.01**

Note: Bold values are significant $p < 0.05$.

Abbreviations: COST, COmprehensive Score for financial Toxicity; EWB, emotional well-being; FACT, functional assessment of cancer therapy; FACT-G score (composite for PWB, SWB, EWB, and FWB); FACT-Hep total score (composite for PWB, SWB, EWB, FWB, and HCS); FTS, financial toxicity scale; FWB, functional well-being; HCS, hepatobiliary cancer subscale; HRQoL, health-related quality of life; PWB, physical well-being; SWB, social/family well-being; TOI, trial outcome index (composite for PWB, FWB, and HCS).

[a] Cohen's *d* effect size, $d = 0.2$ suggests small effect size, $d = 0.5$ medium effect size, $d = 0.8$ large effect size.

[b] FACT-Hep composite, high scores indicate improved HRQoL.

[c] FTS, lower scores indicate worse financial toxicity.

J Surg Oncol. Author manuscript; available in PMC 2023 November 01.