



Association between financial toxicity and health-related quality of life of patients with gynecologic cancer

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Abstract

Objectives Patients often struggle with their financial situation during cancer treatment due to treatment-related costs or loss of income. This resulting negative effect is called financial toxicity, which is a known as a side effect of cancer care. This study aimed to evaluate the association between financial toxicity and health-related quality of life among patients with gynecologic cancer using validated questionnaires.

Methods In this multicenter study, patients with gynecologic cancer receiving anti-cancer drug treatment for > 2 months were recruited. Patients answered the COmprehensive Score for Financial Toxicity (COST) tool, EORTC-QLQ-C30, disease-specific tools (EORTC-QLQ-OV28/CX24/EN24), and EQ-5D-5L. Spearman's rank correlation coefficient was used to determine associations.

Results Between April 2019 and July 2021, 109 cancer patients completed the COST questionnaire. The mean COST score was 19.82. Strong associations were observed between financial difficulty ($r = -0.616$) in the EORTC-QLQ-C30 and body image ($r = 0.738$) in the EORTC-QLQ-CX24, while weak associations were noted between the global health status/quality of life ($r = 0.207$), EQ-5D-5L index score ($r = 0.252$), and several function and symptom scale scores with the COST score.

Conclusions Greater financial toxicity was associated with worse health-related quality of life scores, such as financial difficulty in gynecologic cancer patients and body image in cervical cancer patients as strong associations, and weakly associated with general health-related quality of life scores and several function/symptom scales.

Keywords Financial toxicity · Health care costs · Gynecology · Patient-reported outcome measures · Quality of life

Introduction

Drugs used for patients with gynecologic cancer, such as molecular-targeted drugs, including anti-vascular endothelial growth factor (VEGF) antibody, anti-programmed death protein-1 (PD-1) antibody, and poly-(adenosine diphosphate-ribose) polymerase (PARP) inhibitors, are much more expensive than chemotherapy [1]. Patients often struggle with their financial situation during cancer treatment because of medical costs and loss of income [2, 3]. To avoid financial problems, patients reduce spending on food, clothing, and leisure activities and take fewer medicines than prescribed or spread out clinic appointments [4,

5]. This results in a decreasing health-related quality of life (HRQoL) [6–8]. This resulting negative effect is called financial toxicity, which is known as a side effect of cancer care. Even patients with little or no co-payment experience financial toxicity due to loss of income or non-medical costs [9, 10]. Multiple studies show that financial toxicity is associated with not only worse psychological scores of anxiety or depression but also worse physical, functional, or symptom scores on patient-reported outcomes [7, 8, 11, 12].

Among patients with gynecologic cancers in the USA, worse financial toxicity is related to worse general HRQoL due to non-adherence, delay, or avoidance of cancer care [13, 14]. A Society of Gynecologic Oncology clinical practice statement suggests screening for financial toxicity and discusses the cost of treatment as part of a shared decision-making model [15]. Evaluating the associations between financial toxicity and various HRQoL scales of general

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cancer and specific tools in gynecologic cancer is important to address financial toxicity for patients. The public health insurance system in the USA, including Medicaid and Medicare, covers low-income Americans, the elderly, and patients with long-term-disabilities [16]. Outside of public insurance, people utilize private insurance or remain uninsured. However, unlike in the USA, all Japanese citizens and foreigners with a residence card must be enrolled with Japanese public insurance [17]. Differences in the healthcare system may affect the impact of financial toxicity on patients.

Risk factors in the USA were age, race, employment, insurance, and household income [18, 19]. However, different health care systems may represent patients with other characteristics of financial toxicity and its risk factors. Although income-related factors were associated with financial toxicity in Japan, a Japanese study did not recruit patients with gynecologic cancer [5]. Gynecologic cancer patients are female and likely to be younger. Therefore, their socio-economic status is considered to be different from the others. Identifying risk factors in the population helps in screening high-risk patients. To alleviate financial toxicity, medical cost counseling is considered an option for intervention [20–22]. Many hospitals in Japan play a role in medical cost counseling, including medical social workers. It is important to understand how patients' experiences and expectations in terms of medical cost counseling are associated with financial toxicity.

This study was conducted to evaluate the association between financial toxicity and HRQoL, using validated questionnaires among patients with gynecologic cancer. In addition, the risk factors of patients with gynecologic cancer in Japan, where patients have limited co-payment by public insurance programs, and the need for medical cost counseling were evaluated.

Patients and methods

The study protocol and amendments were approved by the appropriate ethics committee of each institution. The study was conducted in accordance with the amendment protocol and Japanese Ethical Guidelines for Medical and Health Research Involving Human Subjects. Written informed consent was obtained from all the patients. This study was registered in the clinical trial registration of UMIN-CTR (UMIN000034953).

Patients

The inclusion criteria were age ≥ 20 years; stage I–IV or recurrence of ovarian cancer (including fallopian tube and peritoneal), stage III or IV or recurrence of cervical cancer, or stage I–IV or recurrence of endometrial cancer (including

carcinosarcoma) according to the International Federation of Gynecology and Obstetrics (FIGO) staging [23, 24]; and on systemic anti-cancer drug treatment for more than 2 months and scheduled to continue for more than 1 month. The exclusion criteria were diseases other than cancer that strongly influence the QoL determined by investigators, including debilitating neurological diseases that severely limited mobility or severe depression, difficulty in answering questionnaires, inability to appropriately provide consent, and no out-of-pocket direct medical costs. Patients without out-of-pocket costs were excluded because they have a different socioeconomic status from those with out-of-pocket medical costs.

Study design

This multicenter study was conducted at five cancer centers and university hospitals in Japan. Financial toxicity was quantified using the COMprehensive Score for financial toxicity (COST) tool, which consists of 11 items scored from 0 to 44, with 0 representing the worst financial toxicity. Its Japanese version has been developed and validated for patients with gynecologic cancer [9, 25]. The Japanese version of the COST tool, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core30 question (EORTC-QLQ-C30) (Japanese version 3), The 5-level EQ-5D version (EQ-5D-5L) (Japanese version for Japan, 2009), and a questionnaire regarding socioeconomic status and medical costs were answered by all participants. Additionally, the EORTC-QLQ-Ovarian Cancer Module (EORTC-QLQ-OV28) was answered by patients with ovarian cancer, EORTC-QLQ-Cervical Cancer Module (EORTC-QLQ-CX24) by patients with cervical cancer, and EORTC-QLQ-Endometrial Cancer Module (EORTC-QLQ-EN24) by patients with endometrial cancer. For scoring, the third edition of the EORTC-QLQ-C30 scoring manual, each scoring manual of EORTC-QLQ-OV28/CX24/EN24, and the Japanese value set for EQ-5D-5L were used [26]. Patients answered the paper-based questionnaires and sent the questionnaires to the data center themselves using the provided envelopes. Investigators and other staff at the hospital were blinded to the answers of individual patients to protect their privacy. Investigators reported patients' clinical status at the data center.

To evaluate the correlation between financial toxicity and HRQoL, we used the COST score to depict financial toxicity. For HRQoL scores, function scales, symptom scales, and global health status (GHS)/QoL of the EORTC-QLQ-C30/OV28/CX24/EN24 and EQ VAS scores and EQ-5D-5L index score of the EQ-5D-5L were used. Higher scores in these HRQoL scores, except symptom scales and EQ-5D-5L items (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), indicated better HRQoL. Lower

scores in the symptom scales and EQ-5D-5L items indicated better HRQoL.

We evaluated factors associated with financial toxicity using the COST score. The evaluated factors were age, cancer lesion, disease (FIGO) stage, Eastern Cooperative Oncology Group performance status, surgery, high-price drugs, inpatient during anti-cancer therapy, scheduled treatment completion date, duration from initial diagnosis to reporting, duration from starting anti-cancer drug to reporting, employment, annual household income, household saving, major income of the family, having a dependent child/children, having family members requiring nursing care, and private insurance.

Experience and expectations for medical cost counseling at the hospital were assessed using a patient-reported questionnaire. The question had four options as answers: “I received the explanation and could use the counseling,” “I received the explanation, but I wanted more counseling,” “I have not received the explanation, and I wanted the counseling,” and “I do not need the explanation and counseling.”

Statistical analysis

The between-item correlation was evaluated using Spearman’s rank correlation coefficients and partial correlation coefficients, using age as a control variable. The COST score was used as a continuous variable because the scores, in gynecologic cancer patients, showed normal distribution [9]. The sample size was considered to find weak associations for EORTC-QLQ-C30 and EQ-5D-5L, which require 97 patients, and moderate associations for EORTC-QLQ-OV28/CX24/EN24, which require 25 patients with ovarian, cervical, and endometrial cancer, respectively. To evaluate the factors associated with the COST score, the factors were tested using univariate analysis. Multivariable analysis was performed using factors that presented significant differences in the univariate analysis. Patients who did not answer an item were excluded for test in that item. Statistical comparisons were two-sided, and a p value < 0.05 was considered statistically significant for all statistical tests. Data analyses were performed using R version 3.5.2 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Between April 2019 and July 2021, 125 patients were selected as candidates for participation from five sites (Fig. 1). Three patients did not consent to participate in this study, and four patients were excluded because three patients received systemic anti-cancer drug treatment for less than 2 months and one patient had no out-of-pocket medical costs. Among the enrolled 118 patients, 9 did not complete

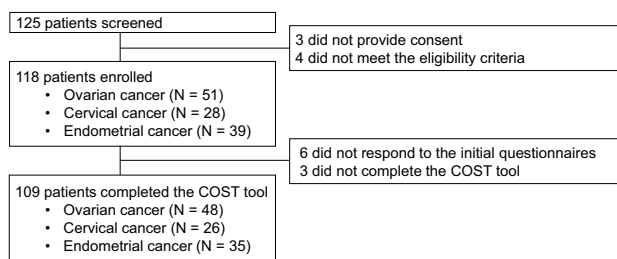


Fig. 1 Study profile. COST Comprehensive Score for financial toxicity

the COST tool. For the analysis, 109 patients who completed all items of the COST tool were included. The demographic and clinical characteristics of the cancer lesions (ovarian, cervical, and endometrial) are shown in Table 1. The median age of the patients was 58 years (range 28–78). Eighty-two percent of the patients had advanced disease (disease stage III/IV/recurrent). The mean COST scores and the standard deviations (SD) were as follows: 19.82 (SD 7.28) for all the patients; 18.34 (SD 6.72) for patients aged < 65 years; 23.90 (SD 7.31) for those aged ≥ 65 years; 19.10 (SD 8.34) for ovarian cancer patients; 20.50 (SD 7.45) for cervical cancer patients; 20.29 (SD 5.48) for endometrial cancer patients; 20.29 (SD 4.89) for full-time employees; 17.27 (SD 6.44) for part-time employees; 16.89 (SD 4.74) for those temporally leaving from work; and 18.90 (SD 8.64) for those that retired owing to cancer.

Correlations between COST and HRQoL scores

A summary of HRQoL scores is shown in Table 2. Strong significant correlations, which were defined as $0.600 < |r| \leq 0.800$, between COST score and financial difficulties ($r = -0.616$, $p < 0.001$) on the EORTC-QLQ-C30 and body image ($r = 0.738$, $p < 0.001$) on the EORTC-QLQ-CX24 were found (Fig. 2). Weak correlations, which were defined as $0.200 < |r| \leq 0.400$, were found for GHS/QoL ($r = 0.207$, $p = 0.036$), role functioning ($r = 0.215$, $p = 0.025$), emotional functioning ($r = 0.249$, $p = 0.012$), social functioning ($r = 0.250$, $p = 0.011$), fatigue ($r = -0.310$, $p = 0.001$), pain ($r = -0.253$, $p = 0.008$), and dyspnea ($r = -0.248$, $p = 0.009$) on the EORTC-QLQ-C30; hormonal/menopausal symptoms ($r = -0.345$, $p = 0.016$) on the EORTC-QLQ-OV28; poor body image ($r = -0.400$, $p = 0.017$) on the EORTC-QLQ-EN24; and usual activities ($r = -0.217$, $p = 0.030$), pain/discomfort ($r = -0.328$, $p < 0.001$) and EQ-5D-5L index score ($r = 0.252$, $p = 0.012$) on the EQ-5D-5L. These correlations were consistent with partial correlations using age as a control variable. Body image ($r = 0.288$, $p = 0.058$) and attitude to disease/treatment ($r = 0.235$, $p = 0.129$) on the EORTC-QLQ-OV28; sexual/vaginal functioning ($r = 0.205$, $p = 0.741$), symptom

Table 1 Clinical and socioeconomic characteristics of the patients

| Characteristic | Ovarian (n=48) | Cervical (n=26) | Endometrial (n=35) |
|---|-----------------|-----------------|--------------------|
| Clinical characteristic | | | |
| Median age, year (range) | 59 (41–76) | 49 (28–73) | 58 (40–78) |
| FIGO staging, no. (%) | | | |
| I | 2 (4%) | – | 15 (43%) |
| II | 1 (2%) | – | 2 (6%) |
| III | 14 (29%) | – | 9 (26%) |
| IV | 10 (21%) | 13 (50%) | 1 (3%) |
| Recurrence | 21 (44%) | 13 (50%) | 8 (23%) |
| ECOG performance status, no. (%) | | | |
| 0 | 38 (79%) | 20 (77%) | 31 (89%) |
| 1 | 10 (21%) | 5 (19%) | 4 (11%) |
| 2 | 0 (0%) | 1 (4%) | 0 (0%) |
| High-price drugs ^a , no. (%) | | | |
| Yes | 29 (60%) | 15 (58%) | 7 (20%) |
| No | 19 (40%) | 11 (42%) | 28 (80%) |
| Surgery | | | |
| Yes | 15 (31%) | 1 (4%) | 8 (23%) |
| No | 33 (69%) | 25 (96%) | 27 (77%) |
| Inpatient during anti-cancer therapy, no. (%) | | | |
| Yes | 32 (67%) | 15 (58%) | 23 (66%) |
| No | 16 (33%) | 11 (42%) | 12 (34%) |
| Median days from initial diagnosis to reporting (range) | 677 (93–5304) | 456.5 (75–2832) | 146 (82–1883) |
| Median days from starting anti-cancer drug to reporting (range) | 155.5 (62–1303) | 100.5 (63–2813) | 84 (61–313) |
| Scheduled treatment completion date | | | |
| Yes | 21 (44%) | 8 (31%) | 25 (71%) |
| No/Until PD | 27 (56%) | 18 (69%) | 10 (29%) |
| Socioeconomic characteristic | | | |
| Employment, no. (%) | | | |
| Full-time employee | 7 (15%) | 0 (0%) | 0 (0%) |

Table 1 (continued)

| Characteristic | Ovarian (n=48) | Cervical (n=26) | Endometrial (n=35) |
|--|----------------|-----------------|--------------------|
| Part-time employee | 5 (10%) | 4 (15%) | 2 (6%) |
| Executive/Self-employed | 3 (6%) | 3 (12%) | 4 (11%) |
| Temporarily leaving work | 6 (13%) | 4 (15%) | 9 (26%) |
| Retirement/resignation owing to cancer | 12 (25%) | 3 (12%) | 6 (17%) |
| Retirement/resignation not owing to cancer | 8 (17%) | 8 (31%) | 8 (23%) |
| No work experience | 4 (8%) | 1 (4%) | 3 (9%) |
| Not answered | 3 (6%) | 3 (12%) | 3 (9%) |
| Household annual income ^b , no. (%) | | | |
| <JPY 2,000,000 (USD 19,447) | 7 (15%) | 1 (4%) | 4 (11%) |
| JPY 2,000,000–4,000,000 (USD 19,447–38,895) | 13 (27%) | 4 (15%) | 11 (31%) |
| JPY 4,000,000–6,000,000 (USD 38,895–58,343) | 8 (17%) | 4 (15%) | 6 (17%) |
| JPY 6,000,000–8,000,000 (USD 58,343–77,791) | 8 (17%) | 8 (31%) | 8 (23%) |
| JPY 8,000,000–10,000,000 (USD 77,791–97,238) | 6 (13%) | 4 (15%) | 1 (3%) |
| ≥JPY 10,000,000 (USD 97,238) | 2 (4%) | 2 (8%) | 2 (6%) |
| Not answered | 4 (8%) | 3 (12%) | 3 (9%) |
| Household annual income ^b , no. (%) | | | |
| <JPY 2,000,000 (USD 19,447) | 7 (15%) | 1 (4%) | 4 (11%) |
| JPY 2,000,000–4,000,000 (USD 19,447–38,895) | 13 (27%) | 4 (15%) | 11 (31%) |
| JPY 4,000,000–6,000,000 (USD 38,895–58,343) | 8 (17%) | 4 (15%) | 6 (17%) |

Table 1 (continued)

| Characteristic | Ovarian (n=48) | Cervical (n=26) | Endometrial (n=35) |
|--|----------------|-----------------|--------------------|
| JPY 6,000,000–8,000,000 (USD 58,343–77,791) | 8 (17%) | 8 (31%) | 8 (23%) |
| JPY 8,000,000–10,000,000 (USD 77,791–97,238) | 6 (13%) | 4 (15%) | 1 (3%) |
| ≥JPY 10,000,000 (USD 97,238) | 2 (4%) | 2 (8%) | 2 (6%) |
| Not answered | 4 (8%) | 3 (12%) | 3 (9%) |
| Household saving ^b , no. (%) | | | |
| <JPY 2,000,000 (USD 19,447) | 7 (15%) | 8 (31%) | 5 (14%) |
| JPY 2,000,000–4,000,000 (USD 19,447–38,895) | 11 (23%) | 1 (4%) | 4 (11%) |
| JPY 4,000,000–6,000,000 (USD 38,895–58,343) | 4 (8%) | 2 (8%) | 1 (3%) |
| JPY 6,000,000–8,000,000 (USD 58,343–77,791) | 0 (0%) | 2 (8%) | 3 (9%) |
| JPY 8,000,000–10,000,000 (USD 77,791–97,238) | 5 (10%) | 3 (12%) | 5 (14%) |
| JPY 10,000,000–15,000,000 (USD 97,238–145,858) | 4 (8%) | 3 (12%) | 6 (17%) |
| ≥JPY 15,000,000 (USD 145,858) | 12 (25%) | 4 (15%) | 5 (14%) |
| Not answered | 5 (10%) | 3 (12%) | 6 (17%) |
| Major income of the family | | | |
| Yes | 7 (15%) | 3 (12%) | 6 (17%) |
| No (other family) | 39 (81%) | 20 (77%) | 26 (74%) |
| Not answered | 2 (4%) | 3 (12%) | 3 (9%) |
| Having a dependent child/children | | | |
| Yes | 7 (15%) | 6 (23%) | 4 (11%) |
| No | 39 (81%) | 17 (65%) | 28 (80%) |
| Not answered | 2 (4%) | 3 (12%) | 3 (9%) |

Table 1 (continued)

| Characteristic | Ovarian (n=48) | Cervical (n=26) | Endometrial (n=35) |
|---|----------------|-----------------|--------------------|
| Having family member requiring nursing care | | | |
| Yes | 9 (19%) | 3 (12%) | 4 (11%) |
| No | 37 (77%) | 20 (77%) | 29 (83%) |
| Not answered | 2 (4%) | 3 (12%) | 2 (6%) |
| Private insurance | | | |
| Yes | 36 (75%) | 20 (77%) | 28 (80%) |
| No | 10 (21%) | 3 (12%) | 5 (14%) |
| Not answered | 2 (4%) | 3 (12%) | 2 (6%) |

ECOG Eastern Cooperative Oncology Group performance status; scores ranged from 0 to 5, with higher scores indicating greater disability, FIGO International Federation of Gynecology and Obstetrics staging [23, 24]

^aHigh-priced drugs include bevacizumab, olaparib, and pembrolizumab

^bUSD 1 =JPY 102.84, Purchasing Power Parities in 2020

Table 2 Summary of health-related quality of life scores

| Tool/Domain | N | Range | Mean | SD |
|---|-----|-----------|------|------|
| COST score | 109 | 3–43 | 19.8 | 7.3 |
| EORTC-QLQ-C30 | | | | |
| Global health status/QoL | 102 | 16.7–100 | 58.6 | 19.2 |
| Physical functioning | 109 | 6.7–100 | 74.9 | 18.4 |
| Role functioning | 109 | 0–100 | 67.1 | 27.5 |
| Emotional functioning | 101 | 25.0–100 | 77.7 | 17.9 |
| Cognitive functioning | 102 | 0–100 | 75.0 | 23.3 |
| Social functioning | 102 | 0–100 | 72.2 | 23.5 |
| Fatigue ^a | 109 | 0–100 | 41.7 | 20.4 |
| Nausea and vomiting ^a | 109 | 0–100 | 9.0 | 16.7 |
| Pain ^a | 109 | 0–100 | 22.5 | 23.4 |
| Dyspnea ^a | 109 | 0–100 | 22.0 | 22.3 |
| Insomnia ^a | 108 | 0–100 | 27.5 | 27.3 |
| Appetite loss ^a | 108 | 0–100 | 19.4 | 25.0 |
| Constipation ^a | 109 | 0–100 | 25.7 | 26.7 |
| Diarrhea ^a | 102 | 0–100 | 12.1 | 18.0 |
| Financial difficulties ^a | 102 | 0–100 | 35.6 | 29.8 |
| EORTC-QLQ-OV28 | | | | |
| Body image | 44 | 0–100 | 52.7 | 29.4 |
| Sexuality | 42 | 0–50.0 | 3.4 | 10.6 |
| Attitude to disease/treatment | 43 | 0–88.9 | 38.2 | 23.5 |
| Abdominal/GI symptoms ^a | 48 | 0–90.5 | 21.7 | 18.5 |
| Peripheral neuropathy ^a | 48 | 0–100 | 27.9 | 23.0 |
| Hormonal/menopausal symptoms ^a | 48 | 0–66.7 | 19.1 | 19.1 |
| Taste change ^a | 48 | 0–100 | 17.4 | 23.8 |
| Muscle aches/pains ^a | 48 | 0–66.7 | 22.2 | 26.0 |
| Hearing problem ^a | 48 | 0–100 | 6.3 | 17.7 |
| Urinary frequency ^a | 45 | 0–100 | 23.0 | 25.4 |
| Skin problem ^a | 48 | 0–100 | 29.9 | 25.9 |
| Hair loss ^a | 48 | 0–100 | 30.2 | 34.8 |
| EORTC-QLQ-CX24 | | | | |
| Body image | 26 | 0–100 | 58.6 | 29.7 |
| Sexual activity | 25 | 0–66.7 | 8.0 | 17.4 |
| Sexual enjoyment | 5 | 33.3–66.7 | 40.0 | 14.9 |
| Sexual/vaginal functioning | 5 | 33.3–75.0 | 60.0 | 18.1 |
| Symptom experience ^a | 26 | 0–33.3 | 14.7 | 9.9 |
| Lymphedema ^a | 26 | 0–100 | 15.4 | 25.4 |
| Peripheral neuropathy ^a | 26 | 0–100 | 41.0 | 33.1 |
| Menopausal symptoms ^a | 26 | 0–100 | 21.8 | 32.6 |
| Sexual worry ^a | 24 | 0–66.7 | 15.3 | 24.0 |
| EORTC-QLQ-EN24 | | | | |
| Sexual interest | 35 | 0–33.3 | 1.0 | 5.6 |
| Sexual activity | 35 | 0 | 0.0 | 0.0 |
| Sexual enjoyment | 0 | NA | NA | NA |
| Lymphedema ^a | 35 | 0–66.7 | 19.1 | 18.6 |
| Urological symptoms ^a | 35 | 0–58.3 | 10.5 | 14.6 |
| Gastrointestinal symptoms ^a | 35 | 0–26.7 | 8.6 | 8.3 |
| Poor body image ^a | 35 | 0–100 | 52.4 | 33.4 |
| Sexual/vaginal problems ^a | 0 | NA | NA | NA |
| Pain in back and pelvis ^a | 35 | 0–66.7 | 16.2 | 20.4 |

Table 2 (continued)

| Tool/Domain | N | Range | Mean | SD |
|---------------------------------|-----|---------|-------|------|
| Tingling/numbness ^a | 34 | 0–100 | 41.2 | 29.7 |
| Muscular pain ^a | 34 | 0–66.7 | 18.6 | 23.5 |
| Hair loss ^a | 34 | 0–100 | 42.2 | 37.9 |
| Taste change ^a | 35 | 0–100 | 18.1 | 29.5 |
| EQ-5D-5L | | | | |
| EQ-5D-5L index score | 100 | 0.332–1 | 0.773 | 0.15 |
| EQ Visual analogue scale | 104 | 10–100 | 68.1 | 18.8 |
| Mobility ^a | 100 | 1–5 | 1.74 | 0.91 |
| Self-care ^a | 100 | 1–3 | 1.13 | 0.37 |
| Usual activities ^a | 100 | 1–5 | 1.83 | 0.96 |
| Pain/Discomfort ^a | 100 | 2–4 | 1.87 | 0.80 |
| Anxiety/depression ^a | 100 | 2–5 | 1.72 | 0.81 |

COST Comprehensive Score for financial toxicity, CX24 Cervical Cancer Module, C30 Core30 question (Japanese version 3), EN24 Endometrial cancer Module, EORTC-QLQ European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, EQ-5D-5L The 5-level EQ-5D version (Japanese version for Japan, 2009), OV28 Ovarian Cancer Module, SD standard deviation, QoL quality of life

^aHigher scores represent worse symptom or response level for symptom scales of the EORTC-QLQ, and EQ-5D-5L items (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Higher scores represent a better status in terms of other scales or items

experience ($r = -0.225$, $p = 0.269$), and menopausal symptoms ($r = -0.310$, $p = 0.123$), and sexual worry ($r = -0.224$, $p = 0.293$) on the EORTC-QLQ-CX24; sexual interest ($r = -0.247$, $p = 0.152$) and muscular pain ($r = -0.211$, $p = 0.231$) on the EORTC-QLQ-EN24 showed a weak correlation with the COST score, but these were not significant.

Factors associated with financial toxicity

Factors such as a younger age, the absence of scheduled treatment completion date, lower annual household income, and lower household savings were associated with significantly worse COST scores in the univariate analyses (Table 3). Cancer lesion, FIGO staging, ECOG performance status, surgery, use of high-price drugs (bevacizumab, olaparib, pembrolizumab), inpatient admission, duration from initial diagnosis, duration of anti-cancer drug treatment, employment, major income of the family, having a dependent child or children, having family members requiring nursing care, and private insurance were not statistically significant. Among the factors that were statistically significant, younger age ($\beta = 0.115$, $p = 0.003$), absence of scheduled treatment completion date ($\beta = -3.615$, $p = 0.010$), and lower household savings ($\beta = 0.053$, $p = 0.014$) were also significant in the multivariable analysis. Income ($\beta = 0.035$,

$p = 0.105$) was not statistically significant in the multivariable analysis.

Experience and expectation for medical cost counseling at hospital

At least 27.5% of the patients did not receive an explanation for the medical costs (Table 4). By combining answers “I received the explanation, but I wanted more counseling” and “I have not received the explanation, and I wanted counseling,” 56.9% of patients hoped to have more counseling for medical costs at the hospital. A higher percentage of patients receiving an explanation regarding the medical cost, such as the answer “I received the explanation and could use the counseling” or “I received the explanation, but I wanted more counseling”, were the patients with household annual income \geq JPY 8,000,000 (76.5%, 13/17), followed by those with no work experience (75.0%, 6/8), those with a family member requiring nursing care (75.0%, 12/16), or those with household savings $<$ JPY 2,000,000 (75.0%, 15/20).

Discussion

Our study demonstrated that worse financial toxicity correlated with worse HRQoL scores in financial difficulties of the EORTC-QLQ-C30 and body image of the EORTC-QLQ-CX24 as strong associations and with GHS/QoL, EQ-5D-5L index score, and several function or symptom scales as weak associations. As expected, a strong correlation between the COST score and financial difficulties is reasonable because both scores measure the financial situation of the patients. The COST tool measures financial toxicity from several perspectives using 11 questions. On the other hand, EORTC-QLQ-C30 employs one question for scoring financial difficulties. The difference would be based on the strong association or not very strong association. In addition to a strong correlation with body image on the EORTC-QLQ-CX24, body image on the EORTC-QLQ-OV28 and poor body image on the EORTC-QLQ-EN24 showed a comparably higher correlation than most other items. A large proportion of patients reduce their spending on clothing or leisure activities to cope with cancer care expenses [5, 27]. Patients with higher financial toxicity may stop buying clothes or cosmetics to save money on cancer care and other necessities. Appearance-related symptoms are associated with greater distress, especially in female patients [28]. The relationship between body image and financial toxicity is an important finding in the QoL of patients with gynecologic cancer. Previous studies in the USA and South Korea have shown similar results regarding GHS/QoL [8, 29].

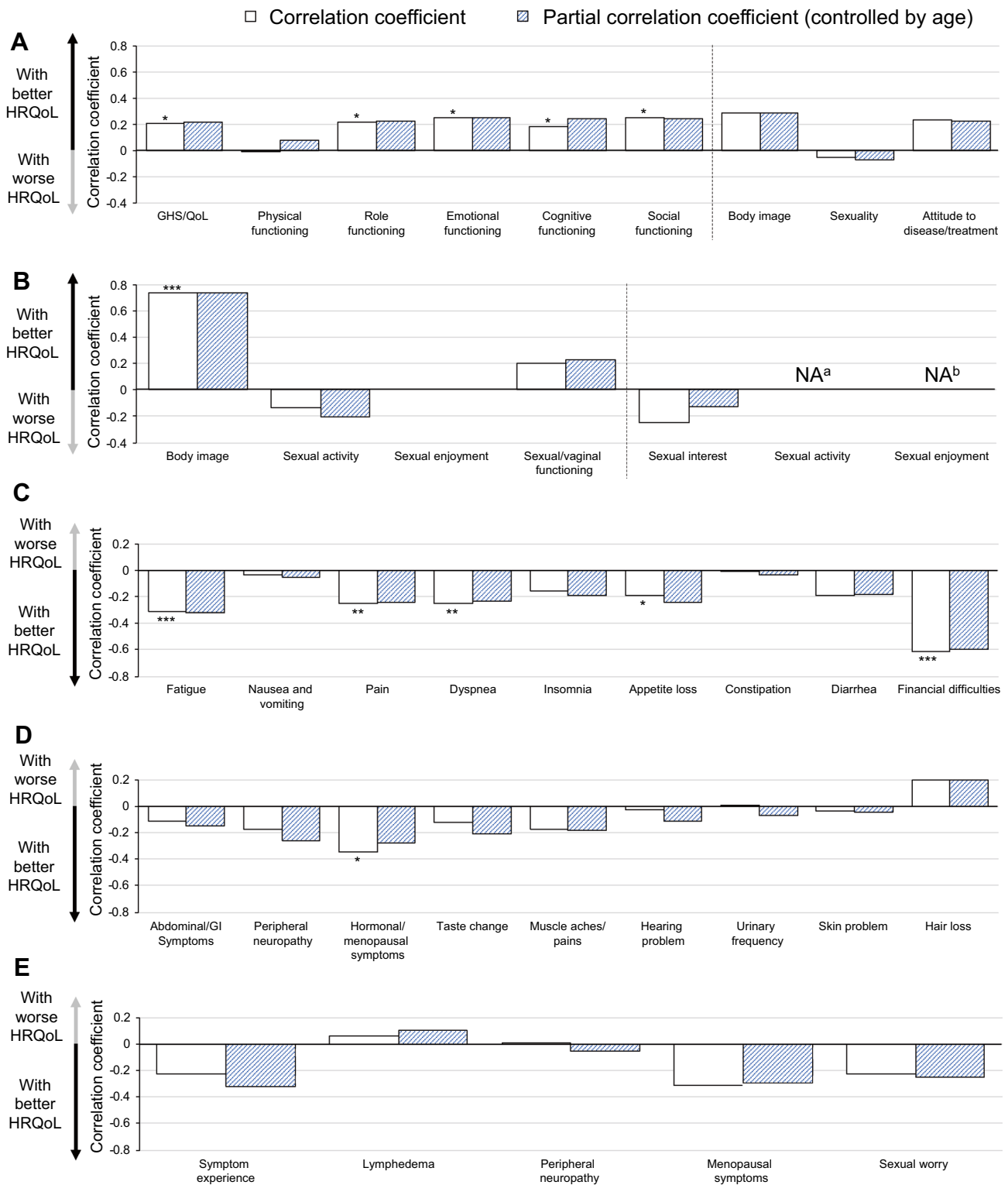


Fig. 2 Correlation between COST and HRQoL scores. **A** Function scales of EORTC-QLQ-C30 (Left) and EORTC-QLQ-OV28 (Right); **B** Function scales of EORTC-QLQ-CX24 (Left) and EORTC-QLQ-EN24 (Right); **C** Symptom scales of EORTC-QLQ-C30; **D** Symptom scales of EORTC-QLQ-OV28; **E** Symptom scales of EORTC-QLQ-CX24; **F** Symptom scales of EORTC-QLQ-EN24; **G** EQ-5D-5L. *COST* Comprehensive Score for financial toxicity; CX24, Cervical Cancer Module,

C30 Core30 question (Japanese version 3), *EN24* Endometrial cancer Module, *EORTC-QLQ* European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, *EQ-5D-5L* The 5-level EQ-5D version (Japanese version for Japan, 2009), *GHS* Global Health Status, *OV28* Ovarian Cancer Module, *QoL* Quality of Life. * $p < 0.05$; ** $p < 0.01$, *** $p < 0.001$; a, all patients had 0 score; b, no patient answered. Partial correlations controlled by age are not tested

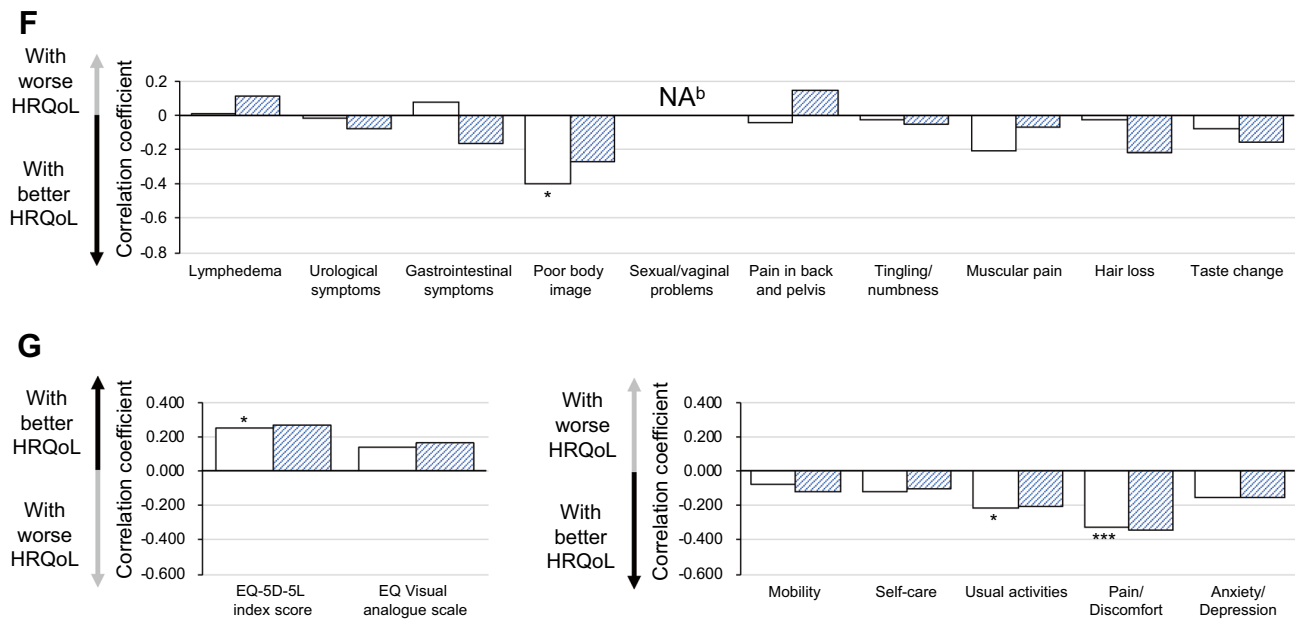


Fig. 2 (continued)

This consistency supports the notion that financial toxicity is associated with the general HRQoL in various healthcare systems and cancer types. The correlation coefficients of function and symptom scales also showed results similar to those of a study on breast cancer survivors in South Korea [8]. From the results of the correlations, the financial toxicity of cancer care is a global issue, and alleviating financial toxicity may improve the HRQoL of cancer patients. Regardless of the small number of patients in Japan who withdrew or changed their cancer treatment recommended by their physicians compared to that in the USA, GHS/QoL and several HRQoL scores were related with the COST score in our study [27]. HRQoL declines not only because of withdrawal from or change of cancer treatment but also the physical or psychological burden caused by financial difficulties. The results of the partial correlation coefficient indicate that financial toxicity has an impact on HRQoL regardless of age.

The independent risk factors for financial toxicity were younger age, lower household savings, and absence of a scheduled treatment completion date. Identifying risk factors is important when screening high-risk patients for financial toxicity. Our results reveal lower household savings as a risk factor. However, many patients hesitate to share their savings or income in the usual clinical setting. Younger age was also an independent factor, whereas age was strongly associated with savings [30]. Age is considered a useful factor for identifying high-risk patients. The results of several studies identifying younger age as a risk factor also support this finding [5, 8, 14]. Receiving treatment without a completion

date, such as maintenance therapy until progressive disease (PD), was another risk factor. For such patients, the duration of treatment and medical costs of cancer care are unknown. Financial uncertainty results in patient anxiety and burden [31]. This leads to poor financial toxicity. By contrast, private insurance was not a risk factor in our study, but this was a prominent risk factor in North America [4, 18, 32]. Public health insurance in Japan covers all Japanese citizens and works well to alleviate financial toxicity, even if the patient uses high-priced drugs. Healthcare professionals need to be vigilant of financial toxicity in patients who are younger or receiving treatment until PD in the clinical setting.

Regarding experience and expectations for medical cost counseling, at least 56.9% of patients had received medical cost explanations, but 53.2% still hoped to receive medical cost counseling, with a tendency toward worse COST scores. This implies that medical cost counseling is a potential intervention for more than half of patients who hope to receive medical counseling. Research in the USA showed that knowledge of healthcare costs upfront was preferred to minimize financial toxicity [33]. Clarifying the expected medical costs as far as possible and discussing how to cope with them through continuous counseling play important roles in shared decision-making. Although several interventions for financial toxicity have been implemented, their feasibility and effectiveness in different healthcare systems, cultures, and clinical settings are unknown [20–22]. Although patients with low household savings were likely to receive medical cost consultations, these patients experienced worse

Table 3 Univariate and multivariable analysis for factors associated with COST scores

| Factor | Mean COST score (SD) | Univariate analysis | Multivariable analysis | |
|--|----------------------|---------------------|------------------------|----------------|
| | | <i>P</i> value | Regression coefficient | <i>P</i> value |
| Age | NA* | < 0.001 | 0.115 | 0.003 |
| Cancer lesion | | | | |
| Ovarian | 19.10 (8.34) | Reference | | |
| Cervix | 20.50 (7.45) | 0.464 | | |
| Endometrial | 20.29 (5.48) | 0.439 | | |
| FIGO staging | | | | |
| I, II | 22.50 (7.00) | Reference | | |
| III, IV, Recurrent | 19.21 (7.25) | 0.068 | | |
| ECOG performance status | | | | |
| 0 | 20.01 (6.92) | Reference | | |
| ≥ 1 | 18.95 (8.87) | 0.558 | | |
| Surgery | | | | |
| Yes | 18.52 (7.85) | Reference | | |
| No | 20.12 (7.15) | 0.368 | | |
| High-price drugs ^a | | | | |
| Yes | 19.44 (7.49) | Reference | | |
| No | 20.14 (7.15) | 0.622 | | |
| Inpatient during anti-cancer therapy | | | | |
| Yes | 19.24 (6.88) | Reference | | |
| No | 20.85 (7.95) | 0.273 | | |
| Scheduled treatment completion date | | | | |
| Yes | 21.26 (7.97) | Reference | Reference | |
| Not scheduled/until PD | 18.40 (6.29) | 0.040 | – 3.615 | 0.010 |
| Duration from initial diagnosis to reporting | NA ^b | 0.103 | | |
| Duration from starting anti-cancer drug to reporting | NA ^b | 0.630 | | |
| Employment | | | | |
| Full-time employee | 20.29 (4.89) | Reference | | |
| Part-time employee | 17.27 (6.44) | 0.307 | | |
| Executive/Self-employed | 22.20 (5.02) | 0.447 | | |
| Temporarily leaving from work | 16.89 (4.74) | 0.121 | | |
| Retirement/resignation due to cancer | 18.90 (8.64) | 0.693 | | |
| Retirement/resignation due to not cancer | 20.83 (7.08) | 0.850 | | |
| No work experience | 24.88 (8.72) | 0.241 | | |
| Household annual income ^c | NA ^b | 0.034 | 0.035 | 0.105 |
| Household saving ^c | NA ^b | < 0.001 | 0.053 | 0.014 |
| Major income of the family | | | | |
| Yes | 20.19 (7.17) | Reference | | |
| No | 19.79 (7.25) | 0.840 | | |
| Having a dependent child/children | | | | |
| Yes | 19.65 (8.90) | Reference | | |
| No | 19.89 (6.88) | 0.899 | | |
| Having family members requiring nursing care | | | | |
| Yes | 17.00 (6.27) | Reference | | |
| No | 20.42 (7.24) | 0.080 | | |
| Private insurance | | | | |
| Yes | 20.04 (6.83) | Reference | | |
| No | 19.17 (8.80) | 0.643 | | |

Statistical comparisons were two-sided, and a *p* value < 0.05 was considered statistically significant for all statistical tests (in bold)

Patients who did not answer were excluded from the analysis

COST COMprehensive Score for financial Toxicity, *ECOG* Eastern Cooperative Oncology Group performance status, *FIGO* International Federation of Gynecology and Obstetrics staging, *PD* progressive disease, *SD* standard deviation

^aHigh-price drugs include bevacizumab, olaparib, and pembrolizumab

Table 3 (continued)

^bNot available because age was tested via parametric analysis, duration from the initial diagnosis to reporting, duration from the initiation of anti-cancer drugs to reporting, annual household income, and household savings were tested by non-parametric analysis

^cUSD 1 = JPY 102.84, Purchasing Power Parities in 2020

Table 4 Experience and expectation for medical cost counseling at hospital

| Patients' answer | n (%) | COST score, mean (SD) |
|--|-----------|-----------------------|
| I received the explanation and could use the counseling | 34 (31.2) | 20.74 (7.16) |
| I received the explanation, but I wanted more counseling | 28 (25.7) | 18.07 (7.21) |
| I have not received the explanation, and I wanted counseling | 30 (27.5) | 18.93 (6.81) |
| I do not need the explanation and counseling | 4 (3.7) | 27.00 (6.93) |
| Not answered | 13 (11.9) | 21.00 (8.70) |

COST Comprehensive Score for financial Toxicity, SD standard deviation

financial toxicity. Other interventions including financial support for medical care may be needed to alleviate such financial toxicity. More intervention trials and understanding these differences are necessary to address financial toxicity.

The strength of this study was the use of multiple general and disease-specific HRQoL questionnaires to evaluate associations with financial toxicity. We could show multidimensional findings of financial toxicity, focusing on patients undergoing anti-cancer treatment. However, our study had some limitations. First, the sample size was insufficient for disease-specific questionnaires to determine weak associations. Several items on the questionnaire showed weak correlations but were not significant. Despite this limitation, the data showed a tendency towards correlation without significance, which may be informative. Second, there was a multiplicity issue of the correlation tests resulting from using 5 questionnaires with the COST score. For confirmation of the associations, a prospective study would be helpful. We plan to follow-up the study participants until the end of treatment for a maximum of 1 year if the treatment exceeds 1 year. Findings changes in financial toxicity with each scale or domain will be informative. Third, confounding factors should be considered to understand our results because this was a cross-sectional study. Age may be a major confounding factor. Therefore, age-controlled partial correlation coefficient analysis was performed.

In conclusion, greater financial toxicity was associated with worse HRQoL scores, such as financial difficulty in gynecologic cancer patients and body image in cervical cancer patients as strong associations, and weakly associated with general HRQoL scores and several function/symptom scales. Our study also revealed younger age, lower household savings, and receiving treatment scheduled until PD as independent risk factors for financial toxicity.

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Data availability Individual participant data that underlie the results reported in this article after deidentification and study materials are available upon reasonable request.

Declarations

Conflict of interest Yusuke Kajimoto is an employee of the MSD K.K. Ataru Igarashi received a consultant fee, grants, and other from Pfizer Japan Inc. and Terumo Corporation; a consultant fee and grants from Beckton Dickinson and Company, Milliman Inc., and Taiho Pharmaceutical Co. Ltd.; a consultant fee and others from Abbvie GK, Ayumi Pharmaceutical Inc., Chugai Pharmaceuticals Inc., Eisai Inc., GSK., Nippon Boehringer Ingelheim Inc., Novartis Pharma K.K., Novo Nordisk Japan Inc., Ono Pharmaceutical Inc., Sumitomo Dainippon Pharma Inc., and Takeda Pharmaceutical Inc.; consultant fees from Otsuka Pharmaceutical Co., Ltd. and Sanofi Japan Inc.; grants and others from Gilead Sciences K.K.; grants from Boston Scientific Japan Inc. and Intuitive Surgical GK.; others from Astellas Pharma Inc., CSL Behring Japan Inc., Fuji Film Inc. and Medilead Inc. The other authors have no conflicts of interest to declare.

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