COVID-19 Content

Stress and Symptom Burden in Oncology Patients During the COVID-19 Pandemic

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Abstract

Context. No information is available on oncology patients' level of stress and symptom burden during the coronavirus disease 2019 (COVID-19) pandemic.

Objectives. To evaluate for differences in demographic and clinical characteristics, levels of social isolation and loneliness, and the occurrence and severity of common symptoms between oncology patients with low vs. high levels of COVID-19 and cancer-related stress. In addition, to determine which of these characteristics were associated with membership in the high-stressed group.

Methods. Patients were 18 years and older; had a diagnosis of cancer; and were able to complete an online survey.

Results. Of the 187 patients in this study, 31.6% were categorized in the stressed group (Impact of Event Scale—Revised [score of ≥24]). Stressed group's Impact of Event Scale—Revised score exceeds previous benchmarks in oncology patients and equates with probable post-traumatic stress disorder. In this stressed group, patients reported occurrence rates for depression (71.2%), anxiety (78.0%), sleep disturbance (78.0%), evening fatigue (55.9%), cognitive impairment (91.5%), and pain (75.9%). Symptom severity scores equate with clinically meaningful levels for each symptom.

Conclusion. We identified alarmingly high rates of stress and an extraordinarily high symptom burden among patients with cancer, exceeding those previously benchmarked in this population and on par with noncancer patients with post-traumatic stress disorder. Given that the COVID-19 pandemic will likely impact cancer care for an indefinite period, clinicians must exhibit increased vigilance in their assessments of patients' level of stress and symptom burden. Moreover, an increase in referrals to appropriate supportive care resources must be prioritized for high-risk patients. J Pain Symptom Manage 2020;60:e25—e34.

Key Words

Symptoms, stress, cancer, loneliness, social isolation, COVID-19

Introduction

A cancer diagnosis and its treatments are stressful experiences for most patients.[1,2] The coronavirus disease 2019 (COVID-19) pandemic and associated mitigation procedures have imposed additional stress. Emerging evidence suggests that fear of infection, concerns regarding the efficacy of COVID-19 treatments, the negative impact of various mitigation procedures (e.g., social isolation), and economic

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uncertainty are associated with higher levels of perceived stress in the general population.[3–8] In addition, oncology patients may experience higher levels of stress if they perceive themselves to be at increased risk for contracting the disease[9,10] and for serious adverse events if they become infected with COVID-19.[10–12] Furthermore, the social distancing procedures and restrictions in access to care may increase patients' fears and concerns about receiving cancer treatments and disease recurrence.[13–15]

Although the types and duration of stressors can vary, a significant amount of variability exists in individuals' cognitive, emotional, and neurobiological responses to stress.[16] A growing body of evidence from the general population suggests that these interindividual differences in responses to stress contribute to higher rates and severity of both psychological and physical symptoms. Surprisingly, research on the association between stress and symptom burden in oncology patients is limited.

In terms of psychological symptoms, in a meta-analysis of studies that focused on the prevalence of COVID-19-related stress and anxiety in the general population,[7] 29.6% of individuals surveyed reported high levels of stress, 31.9% reported anxiety, and 33.7% reported depression. Although often studied together as psychological distress,[17,18] depression occurs in 15%–30% of oncology patients and anxiety in 30%–50%.[19,20] In three recent studies that evaluated psychological symptoms in oncology patients during the COVID-19 pandemic,[21–23] occurrence rates for depression and anxiety ranged from 9.3%[21] to 31.0%[23] and from 8.9%[21] to 36.0%,[23] respectively. The wide range in occurrence rates may be related to the instruments and clinically meaningful cutoff scores that were used to dichotomize the samples.

Less is known about the impact of the COVID-19 pandemic on physical symptoms. Although fatigue occurs in 60%–90% of oncology patients,[24] recent evidence suggests that higher levels of stress correlated with increased fatigue in oncology patients undergoing chemotherapy.[25] Sleep disturbance is reported by 30%–88% of oncology patients.[26,27] Although findings from preclinical and clinical studies suggest that stress has a negative impact on the sleep-wake cycle,[28,29] no data are available on the relationship between stress and sleep disturbance in oncology patients. Similarly although increased stress can exacerbate chronic pain,[30,31] less is known about this relationship in patients with cancer. Our study was the first to report significant levels of stress in patients with chemotherapy-induced peripheral neuropathy.[32] In another study that assessed both combat and cancer-related post-traumatic stress disorder (PTSD) in veterans with oral-digestive cancers,[33] patients with both types of stress had an 8.49 times higher odds of experiencing chronic pain. Finally, cancer-related cognitive impairment occurs in 75% of oncology patients[34] and has been associated with increased levels of stress.[35,36] In terms of the relationships between physical symptoms and COVID-19, in one study of patients with breast cancer,[21] 12.9% of women reported moderate and 4.0% reported severe insomnia. In another study of patients with heterogeneous cancer diagnoses,[22] higher levels of fatigue and pain were associated with higher risk for mental disorders.

The loneliness and social isolation imposed by COVID-19 stay-at-home orders are additional sources of stress.[37,38] Although not extensively studied in oncology patients,[39] loneliness and social isolation are associated with a higher symptom burden,[40] poorer health, and higher all-cause mortality in older adults.[41]

Given the paucity of research on the associations between COVID-19 and cancer-related stress and the severity of common symptoms in oncology patients, we evaluated for differences in demographic and clinical characteristics, levels of social isolation and loneliness, and the occurrence and severity of common symptoms between oncology patients with low vs. high levels of COVID-19 and cancer-related stress. In addition, we determined which demographic, clinical, symptom, and stress characteristics were associated with membership in the high-stressed group. We hypothesized that patients in the high-stressed group would have a higher symptom burden and higher levels of social isolation and loneliness.

Methods

Sample and Settings

Patients were recruited from a registry of individuals who participated in our previous National Cancer Institute-funded studies (CA187160, CA212064, and CA151692). Potential participants received an electronic mail (e-mail) with a brief explanation of the study and a link that directed them to the study's enrollment page. This study was exempt from requiring written informed consent by the Institutional Review Board at the University of California, San Francisco. Patients were included if they were 18 years and older; were able to read, write, and understand English; had a diagnosis of cancer; and were able to complete the survey online.

Survey Administration

E-mails were sent to potential participants beginning May 27, 2020. Patients who received the survey link were asked to complete the survey within two weeks. One e-mail reminder was sent 14 days after the initial request. Patients were asked to answer all

the survey questions in relationship to their experiences in the past 14 days. The entire survey took approximately 60 minutes to complete. All the instruments were completed online using the Research Electronic Data Capture system.[42,43] Responses as of July 10, 2020 are presented in this article.

Instruments

Demographic and Clinical Characteristics. Patients completed demographic and clinical questionnaires, Karnofsky Performance Status scale,[44] and Self-Administered Comorbidity Questionnaire (SCQ).[45]

Stress Measure. The 22-item Impact of Event Scale—Revised (IES-R) was used to measure COVID-19 and cancer-related stress.[46] Patients rated each item based on how distressing each potential difficulty was for them during the past 14 days with respect to their cancer and its treatment and the COVID-19 pandemic. Each item was rated on a 0−4 Likert scale. Three mean subscale scores were created that evaluated levels of perceived intrusion, avoidance, and hyperarousal. A total IES-R score was created by summing the responses to the 22 items and can range from 0 to 88. A total IES-R score of ≥24[47] indicates clinically meaningful post-traumatic symptomatology, and scores of ≥33 indicate probable PTSD.[48,49] The IES-R has been used to assess COVID-19-specific stress in the general population in China,[50] the Chinese workforce,[51] health care workers,[52] psychiatric patients,[53] and oncology patients.[21−23]

Additional measures of stress included the Perceived Stress Scale (PSS, general stress),[54,55] Connor Davidson Resilience Scale (resilience),[56] and Comprehensive Score for Financial Toxicity (financial stress).[57]

Loneliness and Social Isolation. The University of California, Los Angeles Loneliness Scale assesses an individual's subjective feelings of loneliness and social isolation.[58−60] A score of 36.0 represents a normative value for the general population.[61] Social Isolation Scale evaluates an individual's perceptions of connectedness and belongingness.[62] A score of between 10 and 15 suggests that an individual is at risk for social isolation, and a score of ≤9 indicates social isolation.

Symptom Measures. To assess the occurrence and severity of the most common symptoms associated with cancer and its treatment, patients completed Center for Epidemiological Studies-Depression scale (CES-D),[63] Spielberger State-Trait Anxiety Inventories,[64] General Sleep Disturbance Scale (GSDS),[65] Lee Fatigue Scale (which assessed levels of morning and evening fatigue and morning and evening energy),[66] Attentional Function Index,[67] and Brief Pain Inventory.[68]

Data Analysis

Data were downloaded from Research Electronic Data Capture system[42,43] into the Statistical Package for the Social Sciences, Version 27 (IBM Corporation, Armonk, NY). Descriptive statistics were generated for sample characteristics and study measures. Using the IES-R total score, patients were dichotomized into the stressed (i.e., ≥24) and nonstressed (i.e., <24) groups.[48,49] To determine symptom occurrence rates, symptoms were dichotomized based on clinically meaningful cutoff scores for each of the symptom measures. Between-group differences were evaluated using independent-sample t-tests, Chi-squared analyses, and Mann-Whitney *U* tests. Multiple logistic regression analysis was used to evaluate for predictors of stress group membership. A *P*-value of <0.05 was considered statistically significant.

Results

A total of 627 e-mails were sent, 250 patients began the survey (39.9% response rate), and 187 provided complete information (29.8% completion rate). The characteristics of the total sample and the two stress groups are presented in Table 1.

Demographic and Clinical Characteristics

Of these 187 patients, 31.6% ($n = 59$) were categorized in the stressed group. Compared with the nonstressed group, the stressed group had a higher number of comorbidities, a higher comorbidity burden, were fewer years from their cancer diagnosis, were more likely to report a diagnosis of depression, and had a lower functional status score (all $P < 0.05$; Table 1).

Stress, Social Isolation, and Loneliness Scores

Compared with the nonstressed group, the stressed group had significantly higher scores for general stress, intrusion, avoidance, hyperarousal, and loneliness. In addition, they had lower scores (indicating worse outcomes) for resilience, social isolation, and financial toxicity (Table 2).

Symptom Scores

As shown in Table 3, compared with the nonstressed group, the stressed group had significantly higher occurrence rates for all the symptoms except decrements in evening energy. In addition, compared with the nonstressed group, the stressed group had significantly higher scores for depressive symptoms, trait and state anxiety, sleep disturbance, and morning and

Table 1
Differences in Demographic, Clinical, and Behavioral Characteristics Between the Stress Groups

	Total Sample	Nonstressed Group	Stressed Group	
	($n = 187$)	68.4% ($n = 128$)	31.6% ($n = 59$)	
Characteristic	Mean (SD)	Mean (SD)	Mean (SD)	Statistics
Demographic and clinical characteristics				
Age (yrs)	63.3 (10.9)	63.0 (12.4)	62.8 (10.5)	t = 0.41; $P = 0.680$
Number of people in your household including yourself	1.9 (0.9)	2.0 (0.9)	1.9 (0.9)	t = 0.49; $P = 0.624$
Body mass index (kg/m^2)	26.3 (5.4)	26.5 (5.8)	25.9 (4.4)	t = 0.71; $P = 0.476$
KPS score	92.8 (9.1)	93.7 (9.1)	90.7 (8.9)	t = 2.14; $P = 0.033$
Number of comorbidities	1.6 (1.4)	1.4 (1.4)	2.0 (1.4)	t = −2.53; $P = 0.012$
SCQ score	3.2 (3.0)	2.7 (2.8)	4.1 (3.1)	t = −3.06: $P = 0.003$
Time since cancer diagnosis (yrs)	9.7 (6.9)	10.9 (7.4)	7.2 (4.6)	$U = 0.001$
Time since cancer diagnosis—median	8.1	8.7	6.4	
Number of previous cancer treatments	3.0 (1.0)	3.1 (1.0)	2.9 (0.9)	t = 1.64; $P = 0.103$
Number of current cancer treatments	0.3 (0.5)	0.3 (0.5)	0.3 (0.5)	t = −0.19; $P = 0.851$
	n (%)	*n* (%)	*n* (%)	
Female (% yes)	183 (97.9)	125 (97.7)	58 (98.3)	FE, $P = 1.000$
Living arrangements				
Private home or apartment	186 (99.5)	127 (99.2)	59 (100.0)	$\chi^2 = 0.46$; $P = 0.496$
Assisted living facility	0 (0.0)	0 (0.0)	0 (0.0)	
Other	1 (0.5)	1 (0.8)	0 (0.0)	
Lives alone (% yes)	56 (29.9)	39 (30.5)	17 (28.8)	FE, $P = 0.865$
Married/partnered (% yes)	115 (61.5)	77 (60.2)	38 (64.4)	FE, $P = 0.630$
Race/ethnicity				FE, $P = 0.838$
White	154 (82.4)	106 (82.8)	48 (81.4)	
Nonwhite	33 (17.6)	22 (17.2)	11 (18.6)	
Highest level of education				
High school	5 (2.7)	4 (3.1)	1 (1.7)	*U*, $P = 0.107$
Some college	37 (19.9)	28 (22.0)	9 (15.3)	
College graduate	48 (25.8)	35 (27.6)	13 (22.0)	
Some graduate school	28 (15.1)	17 (13.4)	11 (18.6)	
Advanced degree	68 (36.5)	43 (33.9)	25 (42.4)	
Currently employed (% yes)	75 (40.3)	53 (41.7)	22 (37.3)	FE, $P = 0.631$
Annual household income				
<$20,000	8 (5.0)	5 (4.7)	3 (5.8)	*U*, $P = 0.957$
$20,000–$59,000	39 (24.5)	26 (24.3)	13 (25.0)	
$60,000–$100,000	35 (22.0)	25 (23.4)	10 (19.2)	
>$100,000	77 (48.5)	51 (47.6)	26 (50.0)	
Chronic conditions (% yes)				
Heart disease	15 (8.2)	9 (7.1)	6 (10.5)	FE, $P = 0.561$
High blood pressure	52 (28.1)	31 (24.2)	21 (36.8)	FE, $P = 0.110$
Lung disease	10 (5.5)	6 (4.8)	4 (7.0)	FE, $P = 0.505$
Diabetes	8 (4.3)	7 (5.5)	1 (1.8)	FE, $P = 0.438$
Ulcer or stomach disease	6 (3.3)	5 (4.0)	1 (1.7)	FE, $P = 0.667$
Kidney disease	3 (1.6)	2 (1.6)	1 (1.8)	FE, $P = 1.000$
Liver disease	3 (1.7)	3 (2.4)	0 (0.0)	—
Anemia or blood disease	4 (2.2)	3 (2.4)	1 (1.8)	FE, $P = 1.000$
Depression	47 (25.7)	19 (15.0)	28 (50.0)	FE, $P < 0.001$
Osteoarthritis, degenerative arthritis	53 (28.8)	35 (27.8)	18 (31.0)	FE, $P = 0.727$
Back pain	59 (32.6)	37 (29.8)	22 (38.6)	FE, $P = 0.306$
Rheumatoid arthritis	7 (4.0)	6 (5.0)	1 (1.8)	FE, $P = 0.437$
Cancer diagnosis				
Breast cancer	149 (80.6)	102 (80.3)	47 (81.0)	$\chi^2 = 6.60$; $P = 0.360$
Gastrointestinal	6 (3.2)	3 (2.4)	3 (5.2)	
Lung	1 (0.5)	1 (0.8)	0 (0.0)	
Malignant melanoma	1 (0.5)	1 (0.8)	0 (0.0)	
Gynecological	9 (4.9)	4 (3.1)	5 (8.6)	
Prostate	1 (0.5)	1 (0.8)	0 (0.0)	
Multiple cancer types or other	18 (9.8)	15 (11.8)	3 (5.2)	

(*Continued*)

Table 1
Continued

Characteristic	Total Sample ($n = 187$) Mean (SD)	Nonstressed Group 68.4% ($n = 128$) Mean (SD)	Stressed Group 31.6% ($n = 59$) Mean (SD)	Statistics
The presence of metastatic disease (% yes)	45 (24.7)	29 (23.2)	16 (28.1)	FE, $P = 0.579$
Currently receiving cancer treatment (% yes)	49 (26.2)	33 (25.8)	16 (27.1)	FE, $P = 0.859$

KPS = Karnofsky Performance Status; SCQ = Self-Administered Comorbidity Questionnaire; FE = Fischer's exact test; U = Mann-Whitney U test.

evening fatigue. In addition, they had lower scores (indicating a higher level of symptom severity) for morning and evening energy and attentional function (Table 2).

Factors Associated With Stressed Group Membership

In the logistic regression analysis, clinical characteristics (i.e., time since cancer diagnosis, SCQ score, Karnofsky Performance Status score), stress scores (i.e., PSS, University of California, Los Angeles Loneliness Scale, Social Isolation Scale, the Connor Davidson Resilience Scale, Comprehensive Score for Financial Toxicity), and symptom severity scores (i.e., CES-D, Spielberger Trait Anxiety Inventory, Spielberger State Anxiety Inventory, GSDS, morning and evening fatigue, morning energy, Attentional Function Index, the presence of pain) that were significantly different between the two stress groups in the bivariate analyses

Table 2
Differences in Stress and Symptom Scores Between the Stress Groups

Characteristic[a]	Total Sample $n = 187$ Mean (SD)	Nonstressed Group 68.4% ($n = 128$) Mean (SD)	Stressed Group 31.6% ($n = 59$) Mean (SD)	Statistics
Stress scores				
IES-R—total score (≥24)	18.6 (14.8)	10.2 (6.9)	36.9 (10.1)	$t = -18.43$; $P < 0.001$
IES-R—intrusion subscale	0.9 (0.8)	0.4 (0.4)	1.8 (0.6)	$t = -15.56$; $P < 0.001$
IES-R—avoidance subscale	0.8 (0.7)	0.5 (0.5)	1.5 (0.5)	$t = -13.22$; $P < 0.001$
IES-R—hyperarousal subscale	0.8 (0.8)	0.4 (0.4)	1.7 (0.7)	$t = -13.92$; $P < 0.001$
Perceived Stress Scale (≥14.0)	14.6 (7.3)	12.0 (6.1)	20.2 (6.7)	$t = -8.20$; $P < 0.001$
CDRS	29.9 (6.4)	31.4 (5.8)	26.6 (6.5)	$t = 5.07$; $P < 0.001$
SIS (≤9 is social isolation; 10–15 at risk for social isolation)	23.3 (4.1)	24.0 (3.7)	21.8 (4.7)	$t = 3.15$; $P = 0.002$
UCLA Loneliness Scale (≥36)	37.5 (10.8)	35.0 (9.3)	42.8 (11.9)	$t = -4.82$; $P < 0.001$
COST	31.3 (10.1)	32.4 (9.8)	29.1 (10.7)	$t = 2.04$; $P = 0.043$
Symptom scores				
CES-D (≥16)	14.5 (10.0)	10.8 (7.7)	22.4 (9.8)	$t = -8.02$; $P < 0.001$
Trait anxiety (≥31.8)	36.0 (10.7)	32.5 (8.5)	43.4 (11.3)	$t = -6.60$; $P < 0.001$
State anxiety (≥32.2)	34.5 (12.6)	30.6 (10.3)	42.7 (13.2)	$t = -6.22$; $P < 0.001$
GSDS (≥43.0)	50.2 (21.4)	45.6 (19.7)	60.1 (21.8)	$t = -4.54$; $P < 0.001$
Morning fatigue (≥3.2)	3.4 (2.5)	2.8 (2.3)	4.8 (2.4)	$t = -5.5$; $P < 0.001$
Evening fatigue (≥5.6)	5.0 (2.2)	4.6 (2.1)	5.7 (2.2)	$t = -3.09$; $P = 0.002$
Morning energy (≤6.2)	5.0 (2.4)	5.4 (2.4)	4.1 (2.2)	$t = 3.65$; $P < 0.001$
Evening energy (≤3.5)	2.8 (2.1)	2.9 (2.2)	2.6 (1.9)	$t = 0.77$; $P = 0.441$
Attentional Function Index (<5 = low cognitive function; 5–7.5 = moderate cognitive function; and >7.5 = high cognitive function)	6.7 (1.7)	7.2 (1.6)	5.6 (1.6)	$t = 6.29$; $P < 0.001$
Types of pain				$\chi^2 = 10.61$; $P = 0.014$ 0 > 1
None	38.8 (71)	45.6 (57)	24.1 (14)	
Only noncancer pain	14.8 (27)	10.4 (13)	24.1 (14)	
Only cancer pain	25.1 (46)	24.8 (31)	25.9 (15)	
Both noncancer and cancer pain	21.3 (39)	19.2 (24)	25.9 (15)	
Worst pain intensity score	6.6 (2.2)	6.8 (2.0)	6.3 (2.5)	$t = 1.17$; $P = 0.245$
Mean pain interference score	3.2 (2.2)	2.9 (2.1)	3.6 (2.2)	$t = -1.63$; $P = 0.105$

IES-R = Impact of Event Scale—Revised; CDRS = Connor Davidson Resilience Scale; SIS = Social Isolation Scale; UCLA = The University of California, Los Angeles; COST = Comprehensive Score for Financial Toxicity; CES-D = Center for Epidemiological Studies-Depression scale; GSDS = General Sleep Disturbance Scale.
[a]Clinically meaningful cutoff scores are provided in parentheses.

Table 3
Differences in Symptom Occurrence Rates Between the Stress Groups

	Total Sample	Nonstressed Group	Stressed Group	Statistics
Symptom Occurrence	($n = 187$)	68.4% ($n = 128$)	31.6% ($n = 59$)	
Depression	39.8	25.4	71.2	FE, $P < 0.001$
Trait anxiety	59.1	48.8	81.4	FE, $P < 0.001$
State anxiety	48.4	34.6	78.0	FE, $P < 0.001$
Sleep disturbance	59.7	51.2	78.0	FE, $P < 0.001$
Morning fatigue	45.9	38.6	72.9	FE, $P < 0.001$
Evening fatigue	40.5	33.3	55.9	FE, $P = 0.004$
Decrements in morning energy	69.2	62.7	83.1	FE, $P = 0.006$
Decrements in evening energy	67.7	66.9	69.5	FE, $P = 0.866$
Decrements in cognitive function	68.3	57.5	91.5	FE, $P < 0.001$
Pain	61.2	54.4	75.9	FE, $P = 0.006$

FE = Fischer's exact test.

were included in the model. Although the number of comorbidities and proportion of patients with a diagnosis of depression were significantly different between the two stress groups, they were not included in the analysis because the total SCQ and CES-D scores were used in the logistic regression.

As shown in Table 4, the overall model was significant ($\chi^2 = 85.20$; $P < 0.001$). Three variables were significant in the final model (i.e., length of time since cancer diagnosis, PSS score, and occurrence of pain). Patients who were a shorter time from their cancer diagnosis; had a higher level of general stress; and who reported the occurrence of pain were more likely to be in the stressed group.

Table 4
Multiple Logistic Regression Analysis Predicting Stress Group Membership ($n = 169$)

Predictor	Odds Ratio (95% CI)	*P*
KPS score	1.06 (1.00−1.13)	0.072
SCQ score	1.15 (0.97−1.35)	0.102
Time since cancer diagnosis in years	0.92 (0.85−0.99)	0.028
Perceived Stress Scale score	1.13 (1.01−1.27)	0.033
CDRS score	0.97 (0.87−1.09)	0.646
SIS score	0.95 (0.80−1.12)	0.518
UCLA Loneliness Scale score	0.96 (0.90−1.04)	0.329
COST	1.04 (0.98−1.10)	0.171
CES Scale score	1.11 (1.00−1.25)	0.062
Trait anxiety score	1.00 (0.90−1.11)	0.995
State anxiety score	0.99 (0.92−1.06)	0.737
GSDS score	0.98 (0.95−1.02)	0.294
LFS—morning fatigue score	1.34 (0.94−1.89)	0.102
LFS—evening fatigue score	0.94 (0.71−1.25)	0.686
LFS—morning energy score	1.22 (0.92−1.61)	0.172
Attentional Function Index score	0.72 (0.47−1.11)	0.140
Occurrence of pain	5.02 (1.64−15.4)	0.005
Overall model fit: degrees of freedom = 17; $\chi^2 = 85.2$; $P < 0.001$		

KPS = Karnofsky Performance Status; SCQ = Self-Administered Comorbidity Questionnaire; CDRS = Connor Davidson Resilience Scale; SIS = Social Isolation Scale; UCLA = The University of California, Los Angeles; COST = Comprehensive Score for Financial Toxicity; CES = Center for Epidemiological Studies; GSDS = General Sleep Disturbance Scale; LFS = Lee Fatigue Scale.

Discussion

Consistent with a prevalence rate of 29.6% for high levels of COVID-19-related stress in the general population,[7] 31.6% of our patients were categorized into the stressed group. Although the IES-R score of 18.6 for the total sample was below the clinically meaningful cut point, patients in our stressed group had a mean score of 36.9 (±10.1; range 24−60), which is alarmingly high and consistent with probable PTSD.[48] It should be noted that, although most patients in the present study were females, white, well educated, had an annual income of ≥$60,000, had completed their cancer treatment, and had a high functional status, the IES-R cutoff score used in this study was established with war veterans,[48] earthquake survivors,[47] and survivors of the Tokyo Metro sarin gas attack.[47] By way of comparison, in our study of patients receiving chemotherapy before COVID-19,[69] IES-R scores ranged from 15.4 (±12.1) to 27.9 (±13.8). In addition, in two recent studies of oncology patients during the COVID-19 pandemic, IES-R total scores ranged from 19.7[23] to 28.2.[21] Taken together, these findings indicate that during this COVID-19 pandemic, oncology patients are experiencing a clinically meaningful level of stress that exceeds previously reported benchmarks and equates with probable PTSD.

In addition to the COVID-19 and cancer-related stress measure, patients completed a measure of general stress (i.e., PSS). For the total sample, their PSS score slightly exceeded the clinically meaningful cut-point score of ≥14.0 (i.e., 14.6 [±7.3]) and was significantly higher in the stressed group (i.e., 20.2 [±6.7]). In the study mentioned previously of patients

receiving chemotherapy,[69] PSS scores ranged from 8.5 (±4.5) to 25.4 (±6.7). During these particularly stressful times, which include the stressors associated with the pandemic as well as societal and political challenges, the use of a general measure of stress captures additional information on patients' experiences.

Consistent with the known associations between COVID-19 mitigation procedures and heightened levels of loneliness in the general population,[70] it is not surprising that patients in our stressed group reported higher levels of social isolation and loneliness. Although our sample did not meet the clinically meaningful cut point for social isolation, the loneliness score for the total sample was above the clinically meaningful cut point. Finally, given the economic consequences of the COVID-19 pandemic[71] and the financial toxicity associated with cancer and its treatment,[72] it is not surprising that the stressed group reported more financial concerns. Given that most patients in this study had a relatively high annual income, additional research is needed on the added stress of the COVID-19 pandemic on patients with fewer economic and health care resources.

The population-based studies that evaluated for associations between COVID-19-related stress and symptoms assessed anxiety and depression. As noted in a recent systematic review of these studies,[7] the prevalence rates for COVID-19-related anxiety and depression were 31.9% and 33.7%, respectively.[7] In addition, in studies of oncology patients during COVID-19, occurrence rates for depression and anxiety ranged from 9.3%[21] to 31.0%[23] and from 8.9%[21] to 36.0%,[23] respectively. Although for our total sample, the rate of depression was comparable (i.e., 39.8%), our rates for trait (59.1%) and state (48.4%) were considerably higher.[7] Reasons for these differences may include the measures used to evaluate the symptoms; differences in sample characteristics; and/or various additional stressors not evaluated in the questionnaires (e.g., access to care, sociopolitical stress). However, it is notable that in studies of oncology patients before the COVID-19 pandemic, rates of depression and anxiety ranged from 15% to 30% and from 30% to 50%, respectively.[19,20] In addition, in the current sample, between-group differences in the severity of both anxiety and depression represent not only statistically significant but also clinically meaningful differences ($d = 1.07$ for state anxiety to $d = 1.38$ for depression). In addition, the CES-D scores of the patients in the stressed group (i.e., 22.4 [±9.8]) suggest the need for a clinical evaluation of depression.

The results of this study extend the findings of previous studies of COVID-19 stress,[7] by evaluating the impact of this added stress on the occurrence and severity of physical symptoms in oncology patients. In the previous study of patients with breast cancer who were evaluated during COVID-19,[21] only 12.9% of women reported moderate and 4.0% reported severe insomnia. In contrast, nearly 60% of the total sample and 78% of the stressed group reported clinically meaningful levels of sleep disturbance. The severity of sleep disturbance reported by the stressed group (i.e., GSDS score of 60.1) is comparable to that of permanent shift workers[65] or parents of newborn infants.[73] Consistent with the very high level of sleep disturbance in these patients, the occurrence rates for and severity of morning fatigue as well as decrements in morning and evening energy represent clinically meaningful levels of all three symptoms. Previous work from our research team demonstrated that although morning and evening fatigue as well as morning and evening energy are associated with depression, they are distinct symptoms.[74–76] Although cancer-related cognitive impairment occurs in 75% of oncology patients,[34] 91.5% of the patients in the stressed class reported clinically meaningful decrements in cognitive function. Finally, although fewer patients in the nonstressed group (54.4%) compared with the stressed group (75.9%) reported pain, both groups reported pain severity scores in the moderate-to-severe range that had a moderate impact on their functional activities.[77] Taken together, these findings demonstrate an extremely strong relationship between COVID-19 and cancer-related stress and a significant symptom burden. Although this relationship was stronger in the stressed group, the occurrence rates and severity of symptoms in the nonstressed group are clinically meaningful, higher than normative data, and warrant immediate assessment and management.

In terms of the regression analysis, shorter time since the cancer diagnosis, higher levels of general stress (i.e., higher PSS scores), and the occurrence of pain were significant predictors of membership in the stressed group. Although in a recent systematic review,[78] no association was found between time since cancer diagnosis and PTSD, this nonmodifiable characteristic may be used to identify high-risk patients. It is interesting to note that patients with higher scores on our measure of general stress were more likely to be in the stressed group. This finding suggests that stressors other than those related to COVID-19 and cancer (e.g., social unrest, family stress) can contribute to the overwhelming stress reported by the patients in our sample.

Of note, pain was the only symptom associated with membership in the stressed group. Consistent with previous reports,[32,33] patients with pain were 5.02 times more likely to be in the stressed group. Sixty-one percent of the total sample and 75.9% of the stressed group reported this symptom. The most

common causes of noncancer pain were low back pain (20.7%) and arthritis (24.5%). In terms of cancer pain, 16.0% reported chronic postsurgical pain and 19.7% reported chemotherapy-induced peripheral neuropathy. Given that the severity of and level of interference from pain were relatively high in both groups, effective management of this symptom (e.g., cognitive behavioral therapy[79]) is warranted.

Although this study provides new information on the significant impact of COVID-19 and cancer-related stress on oncology patients,[80] several limitations warrant consideration. Given that most patients were well-educated women with breast cancer, the generalizability of our findings to men or patients with other cancer diagnoses warrant confirmation in future studies. Given that most of our patients were white, had health insurance (97.7%), and reported annual incomes of >$60,000, we may be significantly underestimating the impact of the stress associated with this pandemic, particularly among individuals who are socioeconomically disadvantaged. Expansion of this research to underserved populations is needed to inform planning and implementation of appropriate interventions to decrease stress and symptom burden. Longitudinal studies are needed to assess the relationships among changes over time in stress and symptom burden as the COVID-19 pandemic evolves.

In conclusion, we identified alarmingly high rates of stress and an extraordinarily high symptom burden among patients with cancer in the COVID-19 pandemic, exceeding those previously benchmarked in this patient population and on par with noncancer patients with PTSD. Given that the COVID-19 pandemic and the ensuing economic downturn will likely impact cancer care for an indefinite period, clinicians must exhibit increased vigilance in their assessments of oncology patients' level of stress and symptom burden. In addition, clinicians need to educate patients on the benefits of using simple strategies (e.g., relaxation exercises, stress reduction techniques) to manage stress and decrease symptoms.[15] Equally important, an increase in referrals to appropriate supportive care resources (e.g., online peer support groups, exercise therapy, psycho-oncology, symptom management services) must be prioritized for high-risk patients. At the institutional level, we recommend that supportive care services increase; patients have increased access to these services using telehealth approaches; and concerted efforts be made to provide these services to our most vulnerable and underserved patients. Future research should identify additional factors that contribute to heightened stress levels and increased symptom burden among patients with cancer and how these factors may vary with race, socioeconomic status, and other important social determinants of health.

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References

1. Cordova MJ, Riba MB, Spiegel D. Post-traumatic stress disorder and cancer. Lancet Psychiatry 2017;4:330–338.

2. Weber D, O'Brien K. Cancer and cancer-related fatigue and the interrelationships with depression, stress, and inflammation. J Evid Based Complement Altern Med 2017; 22:502–512.

3. Picaza Gorrochategi M, Eiguren Munitis A, Dosil Santamaria M, Ozamiz Etxebarria N. Stress, anxiety, and depression in people aged over 60 in the COVID-19 outbreak in a sample collected in Northern Spain. Am J Geriatr Psychiatry 2020;28:993–998.

4. Cortes-Alvarez NY, Pineiro-Lamas R, Vuelvas-Olmos CR. Psychological effects and associated factors of COVID-19 in a Mexican sample. Disaster Med Public Health Prep 2020: 1–12.

5. Serafini G, Parmigiani B, Amerio A, et al. The psychological impact of COVID-19 on the mental health in the general population. QJM 2020;113:531–537.

6. Taylor S, Landry CA, Paluszek MM, et al. COVID stress syndrome: concept, structure, and correlates. Depress Anxiety 2020;37:706–714.

7. Salari N, Hosseinian-Far A, Jalali R, et al. Prevalence of stress, anxiety, depression among the general population during the COVID-19 pandemic: a systematic review and meta-analysis. Glob Health 2020;16:57.

8. Wang C, Pan R, Wan X, et al. Immediate psychological responses and associated factors during the initial stage of the 2019 coronavirus disease (COVID-19) epidemic among the general population in China. Int J Environ Res Public Health 2020;17:1729.

9. Liang W, Guan W, Chen R, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol 2020;21:335–337.

10. Fung M, Babik JM. COVID-19 in immunocompromised hosts: what we know so far. Clin Infect Dis 2020 https://doi.org/10.1093/cid/ciaa863. [Epub ahead of print].

11. Kuderer NM, Choueiri TK, Shah DP, et al. Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study. Lancet 2020;395:1907–1918.

12. Lee LYW, Cazier JB, Starkey T, et al. COVID-19 mortality in patients with cancer on chemotherapy or other anticancer treatments: a prospective cohort study. Lancet 2020;395: 1919–1926.

13. Al-Shamsi HO, Alhazzani W, Alhuraiji A, et al. A practical approach to the management of cancer patients during the novel coronavirus disease 2019 (COVID-19) pandemic: an International Collaborative Group. Oncologist 2020;25:e936–e945.

14. van de Haar J, Hoes LR, Coles CE, et al. Caring for patients with cancer in the COVID-19 era. Nat Med 2020;26:665–671.

15. Gregucci F, Caliandro M, Surgo A, et al. Cancer patients in Covid-19 era: swimming against the tide. Radiother Oncol 2020;149:109–110.

16. Kalmbach DA, Cuamatzi-Castelan AS, Tonnu CV, et al. Hyperarousal and sleep reactivity in insomnia: current insights. Nat Sci Sleep 2018;10:193–201.

17. Jacobsen PB. Screening for psychological distress in cancer patients: challenges and opportunities. J Clin Oncol 2007;25:4526–4527.

18. Brintzenhofe-Szoc KM, Levin TT, Li Y, Kissane DW, Zabora JR. Mixed anxiety/depression symptoms in a large cancer cohort: prevalence by cancer type. Psychosomatics 2009;50:383–391.

19. Stiegelis HE, Ranchor AV, Sanderman R. Psychological functioning in cancer patients treated with radiotherapy. Patient Educ Couns 2004;52:131–141.

20. Linden W, Vodermaier A, Mackenzie R, Greig D. Anxiety and depression after cancer diagnosis: prevalence rates by cancer type, gender, and age. J Affect Disord 2012;141:343–351.

21. Juanjuan L, Santa-Maria CA, Hongfang F, et al. Patient-reported outcomes of patients with breast cancer during the COVID-19 outbreak in the epicenter of China: a cross-sectional survey study. Clin Breast Cancer 2020 https://doi.org/10.1016/j.clbc.2020.06.003. [Epub ahead of print].

22. Wang Y, Duan Z, Ma Z, et al. Epidemiology of mental health problems among patients with cancer during COVID-19 pandemic. Transl Psychiatry 2020;10:263.

23. Romito F, Dellino M, Loseto G, et al. Psychological distress in outpatients with lymphoma during the COVID-19 pandemic. Front Oncol 2020;10:1270.

24. Thong MSY, van Noorden CJF, Steindorf K, Arndt V. Cancer-related fatigue: causes and current treatment options. Curr Treat Options Oncol 2020;21:17.

25. Wright F, Kober KM, Cooper BA, et al. Higher levels of stress and different coping strategies are associated with greater morning and evening fatigue severity in oncology patients receiving chemotherapy. Support Care Cancer 2020;28:4697–4706.

26. Chen D, Yin Z, Fang B. Measurements and status of sleep quality in patients with cancers. Support Care Cancer 2018;26:405–414.

27. Walker WH 2nd, Borniger JC. Molecular mechanisms of cancer-induced sleep disruption. Int J Mol Sci 2019;20:2780.

28. Lo Martire V, Caruso D, Palagini L, Zoccoli G, Bastianini S. Stress & sleep: a relationship lasting a lifetime. Neurosci Biobehav Rev 2019 https://doi.org/10.1016/j.neubiorev.2019.08.024. [Epub ahead of print].

29. Dolsen MR, Crosswell AD, Prather AA. Links between stress, sleep, and inflammation: are there sex differences? Curr Psychiatry Rep 2019;21:8.

30. Woda A, Picard P, Dutheil F. Dysfunctional stress responses in chronic pain. Psychoneuroendocrinology 2016;71:127–135.

31. Thieme K, Turk DC, Gracely RH, Maixner W, Flor H. The relationship among psychological and psychophysiological characteristics of fibromyalgia patients. J Pain 2015;16:186–196.

32. Miaskowski C, Paul SM, Mastick J, et al. Associations between perceived stress and chemotherapy-induced peripheral neuropathy and toxicity in adult cancer survivors. J Pain Symptom Manage 2018;56:88–97.

33. Sager ZS, Wachen JS, Naik AD, Moye J. Post-traumatic stress disorder symptoms from multiple stressors predict chronic pain in cancer survivors. J Palliat Med 2020;23:1191–1197.

34. Janelsins MC, Kesler SR, Ahles TA, Morrow GR. Prevalence, mechanisms, and management of cancer-related cognitive impairment. Int Rev Psychiatry 2014;26:102–113.

35. Henneghan A. Modifiable factors and cognitive dysfunction in breast cancer survivors: a mixed-method systematic review. Support Care Cancer 2016;24:481–497.

36. Atallah M, Cooper B, Muñoz RF, et al. Psychological symptoms and stress are associated with decrements in attentional function in cancer patients undergoing chemotherapy. Cancer Nurs 2020;43:402–410.

37. Freedman A, Nicolle J. Social isolation and loneliness: the new geriatric giants: approach for primary care. Can Fam Physician 2020;66:176–182.

38. Smith KJ, Gavey S, Riddell NE, Kontari P, Victor C. The association between loneliness, social isolation and inflammation: a systematic review and meta-analysis. Neurosci Biobehav Rev 2020;112:519–541.

39. Leigh-Hunt N, Bagguley D, Bash K, et al. An overview of systematic reviews on the public health consequences of social isolation and loneliness. Public Health 2017;152:157–171.

40. Adams RN, Mosher CE, Winger JG, Abonour R, Kroenke K. Cancer-related loneliness mediates the relationships between social constraints and symptoms among cancer patients. J Behav Med 2018;41:243–252.

41. Steptoe A, Shankar A, Demakakos P, Wardle J. Social isolation, loneliness, and all-cause mortality in older men and women. Proc Natl Acad Sci U S A 2013;110:5797–5801.

42. Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: building an international community of software platform partners. J Biomed Inform 2019;95:103208.

43. Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42:377–381.

44. Karnofsky D. Performance scale. New York: Plenum Press, 1977.

45. Sangha O, Stucki G, Liang MH, Fossel AH, Katz JN. The Self-Administered Comorbidity Questionnaire: a new method to assess comorbidity for clinical and health services research. Arthritis Rheum 2003;49:156–163.

46. Weiss DS, Marmar CR. The Impact of Event Scale—Revised. New York: Guilford Press, 1997.

47. Asukai N, Kato H, Kawamura N, et al. Reliability and validity of the Japanese-language version of the impact of event scale-revised (IES-R-J): four studies of different traumatic events. J Nerv Ment Dis 2002;190:175–182.

48. Creamer M, Bell R, Failla S. Psychometric properties of the impact of event scale—revised. Behav Res Ther 2003;41:1489–1496.

49. Morina N, Ehring T, Priebe S. Diagnostic utility of the impact of event scale-revised in two samples of survivors of war. PLoS One 2013;8:e83916.

50. Wang C, Pan R, Wan X, et al. A longitudinal study on the mental health of general population during the COVID-19 epidemic in China. Brain Behav Immun 2020;87:40–48.

51. Tan W, Hao F, McIntyre RS, et al. Is returning to work during the COVID-19 pandemic stressful? A study on immediate mental health status and psychoneuroimmunity prevention measures of Chinese workforce. Brain Behav Immun 2020;87:84–92.

52. Chew NWS, Lee GKH, Tan BYQ, et al. A multinational, multicentre study on the psychological outcomes and associated physical symptoms amongst healthcare workers during COVID-19 outbreak. Brain Behav Immun 2020;88:559–565.

53. Hao F, Tan W, Jiang L, et al. Do psychiatric patients experience more psychiatric symptoms during COVID-19 pandemic and lockdown? A case-control study with service and research implications for immunopsychiatry. Brain Behav Immun 2020;87:100–106.

54. Hewitt PL, Flett GL, Mosher SW. The Perceived Stress Scale—factor structure and relation to depression symptoms in a psychiatric sample. J Psychopathol Behav Assess 1992;14:247–257.

55. Perera MJ, Brintz CE, Birnbaum-Weitzman O, et al. Factor structure of the Perceived Stress Scale-10 (PSS) across English and Spanish language responders in the HCHS/SOL Sociocultural Ancillary Study. Psychol Assess 2017;29:320–328.

56. Connor KM, Davidson JR. Development of a new resilience scale: the Connor-Davidson Resilience Scale (CD-RISC). Depress Anxiety 2003;18:76–82.

57. de Souza JA, Yap BJ, Wroblewski K, et al. Measuring financial toxicity as a clinically relevant patient-reported outcome: the validation of the COmprehensive Score for financial Toxicity (COST). Cancer 2017;123:476–484.

58. Russell D, Peplau LA, Cutrona CE. The revised UCLA Loneliness Scale: concurrent and discriminant validity evidence. J Pers Soc Psychol 1980;39:472–480.

59. Russell D, Peplau LA, Ferguson ML. Developing a measure of loneliness. J Pers Assess 1978;42:290–294.

60. Russell DW. UCLA Loneliness Scale (Version 3): reliability, validity, and factor structure. J Pers Assess 1996;66:20–40.

61. Knight RG, Chisholm BJ, Marsh NV, Godfrey HP. Some normative, reliability, and factor analytic data for the revised UCLA Loneliness Scale. J Clin Psychol 1988;44:203–206.

62. Nicholson NR, Feinn R, Casey EA, Dixon J. Psychometric evaluation of the social isolation scale in older adults. Gerontologist 2020;60:e491–e501.

63. Radloff LS. The CES-D Scale: a self-report depression scale for research in the general population. Appl Psychol Meas 1977;1:385–401.

64. Spielberger CG, Gorsuch RL, Suchene R, Vagg PR, Jacobs GA. Manual for the State-Anxiety (Form Y): Self Evaluation Questionnaire. Palo Alto, CA: Consulting Psychologists Press, 1983.

65. Lee KA. Self-reported sleep disturbances in employed women. Sleep 1992;15:493–498.

66. Lee KA, Hicks G, Nino-Murcia G. Validity and reliability of a scale to assess fatigue. Psychiatry Res 1991;36:291–298.

67. Cimprich B, Visovatti M, Ronis DL. The Attentional Function Index—a self-report cognitive measure. Psychooncology 2011;20:194–202.

68. Daut RL, Cleeland CS, Flanery RC. Development of the Wisconsin Brief Pain Questionnaire to assess pain in cancer and other diseases. Pain 1983;17:197–210.

69. Langford DJ, Cooper B, Paul S, et al. Distinct stress profiles among oncology patients undergoing chemotherapy. J Pain Symptom Manage 2020;59:646–657.

70. Banerjee D, Rai M. Social isolation in Covid-19: the impact of loneliness. Int J Soc Psychiatry 2020;66:525–527.

71. Congressional Research Service. Global economic effects of COVID-19. Available from https://fas.org/sgp/crs/row/R46270.pdf. Accessed July 28, 2020.

72. Chan RJ, Gordon LG, Tan CJ, et al. Relationships between financial toxicity and symptom burden in cancer survivors: a systematic review. J Pain Symptom Manage 2019;57:646–660.

73. Gay CL, Lee KA, Lee SY. Sleep patterns and fatigue in new mothers and fathers. Biol Res Nurs 2004;5:311–318.

74. Abid H, Kober KM, Smoot B, et al. Common and distinct characteristics associated with trajectories of morning and evening energy in oncology patients receiving chemotherapy. J Pain Symptom Manage 2017;53:887–900.

75. Lerdal A, Kottorp A, Gay CL, Lee KA. Lee fatigue and energy scales: exploring aspects of validity in a sample of women with HIV using an application of a Rasch model. Psychiatry Res 2013;205:241–246.

76. Wright F, Hammer M, Paul SM, et al. Inflammatory pathway genes associated with inter-individual variability in the trajectories of morning and evening fatigue in patients receiving chemotherapy. Cytokine 2017;91:187–210.

77. Paul SM, Zelman DC, Smith M, Miaskowski C. Categorizing the severity of cancer pain: further exploration of the establishment of cutpoints. Pain 2005;113:37–44.

78. Marziliano A, Tuman M, Moyer A. The relationship between post-traumatic stress and post-traumatic growth in cancer patients and survivors: a systematic review and meta-analysis. Psychooncology 2020;29:604–616.

79. Ho CS, Chee CY, Ho RC. Mental health strategies to combat the psychological impact of COVID-19 beyond paranoia and panic. Ann Acad Med Singapore 2020;49:155–160.

80. Tran BX, Ha GH, Nguyen LH, et al. Studies of novel coronavirus disease 19 (COVID-19) pandemic: a global analysis of literature. Int J Environ Res Public Health 2020;17:4095.