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ORIGINAL ARTICLE

The psychological impact of COVID-19 pandemic on patients with neuroendocrine tumors: Between resilience and vulnerability

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Abstract

The COVID-19 pandemic has added another layer of complexity to the fears of patients with neuroendocrine tumors (NETs). Little is known regarding the psychological impact of the COVID-19 outbreak on patients with gastroenteropancreatic or bronchopulmonary (BP) NETs. We longitudinally surveyed the mental symptoms and concerns of NET patients during the plateau phase of the first (W1) and second epidemic waves (W2) in Italy. Seven specific constructs (depression, anxiety, stress, health-related quality of life, NET-related quality of life, patient–physician relationship, psychological distress) were investigated using validated screening instruments, including DASS-21, EORTC QLQ-C30, EORTC QLQ GI.NET21, PDRQ9 and IES-R. We enrolled 197 patients (98 males) with a median age of 62 years. The majority of the patients had G1/G2 neoplasms. Some 38% of the patients were on active treatment. At W1, the prevalence of depression, anxiety and stress was 32%, 36% and 26% respectively. The frequency of depression and anxiety increased to 38% and 41% at W2, whereas no modifications were recorded in the frequency of stress. Poor educational status was associated with higher levels of anxiety at both W1 (odds ratio [OR] = 1.33 ± 0.22; $p = .07$) and W2 (OR = 1.45 ± 0.26; $p = .03$). Notably, post-traumatic stress symptoms were observed in the 58% of the patients, and both single marital status (OR = 0.16, 95% confidence interval [CI] = 0.06–0.48; $p = .0009$) and low levels of formal education (OR = 0.47, 95% CI = 0.23–0.99; $p = .05$) predicted their occurrence. No significant deteriorations of health-related quality of life domains were observed from W1 to W2. High patient care satisfaction was documented despite the changes in health systems resource allocation. NET patients have an increased risk of developing post-traumatic stress symptoms as result of the COVID-19 pandemic. Specific screening measures and psychological interventions should be implemented in NET clinics to prevent, recognize and treat mental distress in this vulnerable population.

Eleonora Lauricella and Mauro Cives contributed equally to this work.

KEYWORDS
anxiety, carcinoid, depression, HRQoL, post-traumatic stress disorder

1 | INTRODUCTION

In early December 2019, the first cluster of pneumonia cases of unknown origin was identified in Wuhan, the capital city of the Hubei province in China.[1] The causative agent was subsequently identified as a novel enveloped RNA betacoronavirus that was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[2] Some 3 months after its first description, the SARS-CoV-2-associated disease (COVID-19) spread globally, and the World Health Organization (WHO) declared pandemic status on March 11, 2020.[3]

The COVID-19 pandemic poses unprecedented medical, economic and social challenges. The need for social distancing, the isolation induced by lockdowns and quarantine orders enforced by national governments, the fear of infection and death from the virus, and the financial problems caused by the epidemic (i.e., job loss, income cuts, etc.) have been described as major threats for mental health.[4] In this context, multiple studies have already shown rising levels of psychological distress and mental illness in the general population as result of the pandemic surge.[5-7]

Patients with cancer are at higher risk of morbidity and mortality from COVID-19 compared to the general population, probably as consequence of advanced age, coexisting chronic comorbidities, and cancer-related and drug-related immunosuppression.[8] Moreover, the COVID-19 pandemic has transformed every aspect of cancer care, including deferring screening procedures and diagnosis, postponing elective surgeries and follow-up visits, and adopting less-intensive care regimens. Delays and changes in cancer diagnosis, treatment and follow-up, in combination with concerns about the viral threat per se, have the potential to impair patients' mental and emotional well-being, thus negatively impacting on their quality of life.

Neuroendocrine tumors (NETs) are a heterogeneous group of malignancies arising from the diffuse neuroendocrine system.[9] Although NETs may develop in almost any organs, they predominate in the gastroenteropancreatic (GEP) tract and bronchopulmonary (BP) system. Well-differentiated NETs are characterized by a relatively indolent growth, and survival outcomes in the metastatic setting often span years. The rarity of the disease and the requirement of expertise available only in specialized centers, the long survival durations and the need of multiple therapy lines throughout the treatment journey, and the possible occurrence of clinical syndromes related to the ectopic secretion of peptide hormones or biogenic amines all render NET patients particularly vulnerable to the psychological distress induced by the COVID-19 pandemic. In the present study, we aimed to investigate the impact of the COVID-19 crisis on the mental health and quality of life of a heterogeneous, real-world cohort of 197 patients with well-differentiated GEP-NET or BP-NET.

2 | MATERIALS AND METHODS

2.1 | Study setting and design

The present study was carried out in two tertiary hospitals in Italy (Policlinico di Bari, Bari; National Cancer Institute Foundation "G. Pascale", Naples). Both centers have a specific expertise in managing patients with NETs, and represent the two main institutions specialized in treatment of NETs in South Italy. As of the last day of data collection (November 14, 2020), 1,144,552 confirmed COVID-19 infections and 44,683 deaths were recorded in Italy. To manage the pandemic, the Italian government instituted a full lockdown from March 11, 2020 to May 4, 2020, as well as a partial lockdown from October 13, 2020. During this period, we longitudinally surveyed the demographics, mental symptoms and concerns of NET patients twice, namely during the plateau phase of the first (W1) and second epidemic waves (W2) in Italy (Figure 1). In both occurrences, information was collected over 2 weeks via phone interviews by medical oncology fellows or research assistants. The study was approved by the Ethics Committee of both participating institutions. Enrolled patients provided their written informed consent to participate in the study.

2.2 | Patients

We searched a prospective database of patients with GEP or BP NETs managed at our institutions. Within this group, we identified adult patients (age ≥ 18 years) with advanced, inoperable disease or who underwent R0/R1 surgical resection up to 5 years prior to enrollment. Patients with stage IV disease could receive any type of treatments. Patients with an Eastern Cooperative Oncology Group performance status ≥ 2, subjects on active therapy with psychotropic agents and subjects with a history of infection by SARS-CoV-2 before enrollment were excluded from the study. Patients with mixed adenoneuroendocrine tumors were also excluded.

The following information was collected by review of patient medical records: demographics, marital status, level of education, date of initial diagnosis, location of primary tumor, stage at diagnosis and at study entry according to the American Joint Committee on Cancer classification,[10-12] presence of a functional hormonal syndrome, presence of a prior diagnosis of psychic illness needing active, chronic treatment with psychotropic agents. The tumor grade by WHO criteria[13,14] was obtained by review of surgical pathology reports.

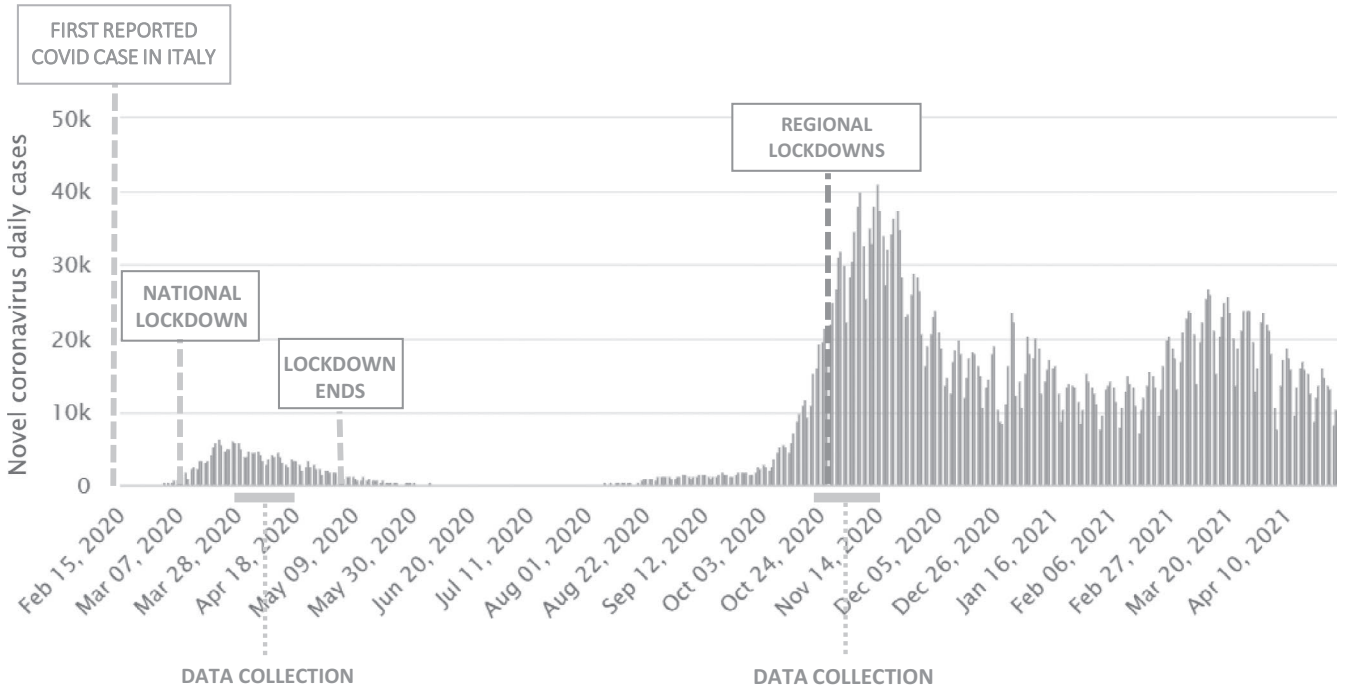

FIGURE 1 Timeline of events and data collection during the first and second waves of COVID-19 in Italy

2.3 | Questionnaire instruments

Seven specific constructs (depression, anxiety, stress, quality of life, NET-related quality of life, patient–physician relationship, psychological distress) were investigated using validated screening instruments, including the Depression anxiety stress scale-21 (DASS-21),[15] the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (EORTC QLQ)-C30,[16] the EORTC QLQ gastrointestinal NET 21 (GI.NET21),[17] the patient doctor relationship questionnaire 9 (PDRQ9)[18] and the Impact of event scale-revised (IES-R).[19] For each instrument, the overall score and the scores of the relative subscales were calculated as detailed in the Supporting information (Methods S1). All patients were asked to answer questions from the Italian version of DASS-21, EORTC QLQ-C30, EORTC QLQ-GI.NET21 and PDRQ9 during the first and second waves of the pandemic outbreak in Italy. The IES-R instrument was administered only during the second wave, given its ability in capturing features suggestive of post-traumatic stress disorder (PTSD), a condition usually arising several months after a traumatic event.

2.4 | Statistical analysis

Descriptive statistics were used for patient demographics and the results of questionnaire instruments. The association between ordinal classes obtained from individual questionnaire scores (i.e., normal vs non-normal or normal vs mild depression vs moderate depression vs severe depression vs extremely severe depression) and patient clinicopathological features was evaluated by Fisher's test or one-way ANOVA, as appropriate. Factors showing $p \leq .2$ at univariate analysis were introduced in a multivariable logistic regression model or an ordinal regression model, as appropriate, in which variables were selected using backward stepwise elimination with $p \leq .05$ being considered statistically significant. The assumption of proportionality was verified by likelihood ratio test. When this assumption was violated, the generalized ordered logit model was used. Exact 95% confidence intervals (CIs) were calculated for each proportion of interest. All tests were two-sided, and statistical significance was declared at $p \leq .05$. Statistical analysis was conducted using MedCalc, version 12.7 (MedCalc Software bvba) and STATA, version 16 (StataCorp. 2019: StataCorp LLC).

A potential confounding factor in an analysis of the psychological impact of COVID-19 pandemic is the occurrence of the infection in patients themselves or their first-degree relatives during the study. To mitigate this bias, we carried out separate analyses for patients with and without personal or family history of confirmed SARS-CoV-2 infection.

3 | RESULTS

3.1 | Demographics and tumor characteristics

Demographic variables and clinicopathological characteristics of the 197 patients included in the study are provided in Table 1. The number of male and female patients was similar, and the median age at NET diagnosis was 62 years (range 19–84 years). All patients were Caucasian. The majority of subjects (129/197; 65%) were married and approximately one quarter of the cohort received prior therapy with psychotropic agents, particularly benzodiazepines. The level of

TABLE 1 Patient demographics and clinical characteristics

Characteristics	Number of patients ($n = 197$)
Age (years)	
Median	62
Range	19–84
Gender	
Male	98 (50%)
Female	99 (50%)
Marital status	
Married	129 (65%)
Single	36 (18%)
Widow/widower	32 (17%)
Level of instruction	
Bachelor's degree	50 (25%)
High school	54 (27%)
Middle school	61 (31%)
Elementary school	32 (17%)
Prior therapy for anxiety	
Yes	51 (25%)
No	146 (75%)
Date of diagnosis	
< 1 year	28 (14%)
1–2 years	102 (52%)
> 3 years	67 (34%)
Primary site	
Pancreas	58 (29%)
Small intestine	48 (25%)
Stomach	37 (19%)
Colon–rectum	26 (13%)
Appendix	16 (8%)
Duodenum	6 (3%)
Lung	6 (3%)
Grade	
G1	83 (42%)
G2	107 (54%)
G3	5 (3%)
Unknown	2 (1%)
Stage at diagnosis	
I	62 (32%)
II	43 (22%)
III	29 (15%)
IV	50 (25%)
Unknown	13 (6%)
Hormone secretion	
Yes	31 (16%)
No	166 (84%)
Management	
Active surveillance	122 (62%)
Active therapy	75 (38%)

education was heterogeneous, with 52% of patients (104/197) harboring at least a high school degree. The majority of patients had pancreatic (29%) or small bowel (25%) primaries, and G1/G2 tumors were diagnosed in the 96% of cases (190/197). Seven patients harbored G3 NETs. The diagnosis of NET occurred within 2 years from enrollment in two-thirds of patients (130/197). Presence of clinical syndromes associated with hormone secretion was documented in 31 patients (16%). At study entry, 75 patients (38%) were on treatment with anti-cancer agents, 16 patients were on active surveillance for panNETs < 2 cm and 106 patients were on follow-up after surgery. Nine patients were diagnosed with COVID-19 when on study, and one of them died. Two non-COVID-19-related deaths were also recorded before W2.

3.2 | Depression, anxiety and stress

At W1, the prevalence of depression, anxiety and stress by DASS-21 questionnaire was 32%, 36% and 26%, respectively (Figure 2). The frequency of depression and anxiety increased to 38% and 41% at W2, in the absence of modifications in the frequency of stress. Although the levels of depression and anxiety (mild, moderate, severe and extremely severe[15]) appeared to be similarly distributed at W1, moderate depression and anxiety tended to prevail at W2. No substantial modifications in the rate of depression, anxiety and stress at W2 were observed after removing patients who were diagnosed with COVID-19 (see Supporting information, Figure S1). At W1, patients with hormonal syndromes showed a significantly higher frequency of depression ($p = .001$) and anxiety ($p = .04$). Moreover, subjects with education lower than secondary level displayed higher rates of depression ($p = .02$), whereas the prevalence of stress was significantly higher among females ($p = .01$). At W2, depression was documented more frequently in patients older than 65 years ($p = .01$), with poor education ($p = .01$) and in those who were previously treated with psychotropic agents ($p = .007$). Low-level education ($p = .009$) and advanced age ($p = .03$) were also significantly associated with the occurrence of anxiety (Table 2). When patients with a personal or family history of COVID-19 were removed from analysis, low tumor grade showed a significant association with depression at W2 ($p = .04$). After adjusting for variables that showed a $p \leq .2$ in univariate analysis at W1, the presence of functioning tumors and the female sex remained associated with anxiety (odds ratio [OR] = 2.21, 95%

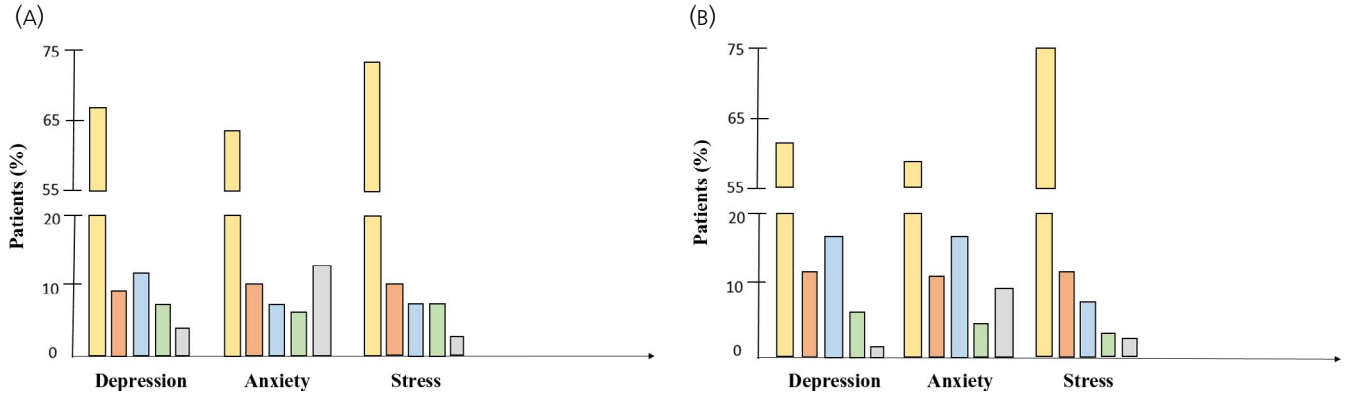

FIGURE 2 Prevalence of depression, anxiety and stress in the overall cohort. The frequency of depression and anxiety, but not stress, increased from (A) the first (W1) to (B) the second (W2) epidemic wave

CI = 1–4.8; p = .04) and stress (OR = 0.44, 95% CI = 0.22–0.84; p = .01), respectively. At W2, advanced age and poor education remained significantly associated with depression (OR = 2.31, 95% CI = 1.24–4.31; p = .009) and anxiety (OR = 1.47, 95% CI = 1.1–1.96; p = .009), respectively. By ordinal logistic regression analysis, female patients tended to show more severe forms of stress at W1 (OR = 0.45 ± 0.14; p = .01), whereas educational status was associated with the levels of anxiety at both W1 (OR = 1.33 ± 0.22; p = .07) and W2 (OR = 1.45 ± 0.26; p = .03).

3.3 | Health-related quality of life (HRQoL)

Mean and median HRQoL scores are detailed in Table 3. Overall, the global health status of study participants did not change between W1 and W2. Intriguingly, a significant improvement of the physical (p = .03) and emotional functioning domains (p = .001) was observed over time. Moreover, both nausea/vomiting (p = .0002) and appetite (p = .02) improved significantly between W1 and W2. Treatment-related symptoms (p = .005) and disease-related worries (p = .0006) were reported less commonly at W2 compared to W1, and an improvement of sexual function was also noted between W1 and W2 (p = .02). We then analyzed separately HRQoL changes in patients under surveillance (n = 122) and in those receiving active treatment (n = 75). No significant modifications of HRQoL domains were documented in actively treated patients, whereas an improvement of the physical functioning domain (p = .04), emotional functioning domain (p = .002), nausea/vomiting (p = .004), appetite (p = .009) and disease-related worries (p = .001) was observed in patients on follow-up. No changes were seen after excluding patients with a personal or family history of COVID-19 from analysis.

A 10-point change in each EORTC-QLQ-C30 or EORTC-QLQ-GINET.21 domain score is frequently considered a minimal clinically important difference.[20,21] Figure 3 illustrates the clinically important changes that occurred in each HRQoL domain from W1 to W2. To identify those patients most likely to undergo HRQoL deterioration during the COVID-19 pandemic, we evaluated the association between score modifications and selected clinical-pathological features. By univariate analysis, advanced age, poor education and hormonal secretion were associated with a substantial deterioration of multiple HRQoL domains (Table 4). By multivariable analysis, advanced age remained significantly associated with a worsening in the physical functioning, cognitive functioning, fatigue, constipation and financial difficulties domains.

3.4 | Patient–physician relationship

A drastic reduction in the number of outpatient visits for NET patients has been recorded in our country during the COVID-19 pandemic.[22] We therefore investigated possible changes in the patient–physician relationship between W1 and W2. The mean (± SD) score of the PDRQ9 questionnaire was 4.36/5 (±0.76) at W1 and 4.35/5 (±0.56) at W2.

3.5 | Psychological distress

In the evaluable population (n = 195; two patients died before W2), the mean (± SD) total score of the IES-R was 34.7 (±17). A score ≥ 33, suggestive of a higher risk of PTSD diagnosis,[19] was documented in 114 (58.4%) patients. The mean scoreds of the intrusion, avoidance and hyperarousal subscales were 1.8, 1.4 and 1.6, respectively. After excluding patients with a personal or family history of COVID-19, 110/186 (59.1%) patients displayed a total score ≥ 33. Among patients with personal or family experience of the COVID-19 disease, a score ≥ 33 was observed in 3/9 cases (33%). In the global population, IES-R scores consistent with PTSD diagnosis were seen more frequently in patients that were single/widow (p = .0007) or in those with poor education (p = .002). By multivariable analysis, both the single marital status (OR = 0.16, 95% CI = 0.06–0.48; p = .0009) and the low level of education (OR = 0.47, 95% CI = 0.23–0.99; p = .05) remained significantly associated with IES-R scores ≥ 33.

TABLE 2 Univariate analysis of potential predictors of depression, anxiety and stress

	First wave						Second wave					
Characteristics	**Depression rate**	***p***	**Anxiety rate**	***p***	**Stress rate**	***p***	**Depression rate**	***p***	**Anxiety rate**	***p***	**Stress rate**	***p***
Sex												
Male	27.5%	.18	31.6%	.25	18.4%	**.01**	33.3%	.2	40.6%	.93	19.8%	.14
Female	36.4%		39.4%		34.3%		42.3%		41.2%		28.9%	
Age at diagnosis (years)												
≤ 65	30.9%	.67	34.7%	.74	27.6%	.61	30.8%	**.01**	35%	**.03**	22.3%	.39
> 65	33.8%		37%		24.3%		49.3%		50.7%		27.8%	
Marital status												
Married	33.1%	.66	35.2%	.88	25%	.54	38.9%	.68	38.9%	.43	23%	.55
Single/widow	30%		36.2%		29%		35.8%		44.8%		26.9%	
Level of instruction												
Bachelor degree	40%	**.02**	38%	.09	42.9%	.27	37.5%	**.01**	35.4%	**.009**	29.2%	.35
High school	25.9%		27.8%		24.1%		24.5%		31.5%		17%	
Middle school	21.3%		31.1%		19.7%		37.7%		39.3%		22.9%	
Elementary	50%		53.1%		37.5%		61.3%		67.8%		32.3%	
Prior therapy for anxiety												
Yes	27.4%	.42	33.3%	.7	29.1%	.59	51.6%	**.007**	45.1%	.48	21.6%	.59
No	33.6%		36.3%		25.3%		31.3%		39.4%		25.3%	
Stage												
I	30.7%	.75	30.6%	.47	25.8%	.88	38.7%	.3	35.5%	.63	21%	.84
II	27.9%		37.2%		25.6%		28.6%		45.2%		23.8%	
III	31%		31%		33.3%		41.4%		41.4%		27.6%	
IV	38%		44%		28%		48%		46.8%		27.7%	
Hormonal syndrome												
Yes	52.4%	**.001**	51.6%	**.04**	29%	.72	50%	.13	53.3%	.13	33.3%	.21
No	26.5%		32.5%		25.9%		35.6%		38.6%		22.7%	
Active treatment												
Yes	32.5%	.97	36.8%	.73	25%	.77	41.7%	.38	45.8%	.23	23.6%	.9
No	32.2%		34.5%		26.9%		35.3%		37%		24.4%	
Time from diagnosis												

(Continues)

TABLE 2 (Continued)

Characteristics	First wave					Second wave				
	Depression rate	p	Anxiety rate	p	Stress rate	Depression rate	p	Anxiety rate	p	Stress rate	p
≤ 12 months	28.6%	.71	42.9%	.36	25%	32.1%	.53	42.9%	.68	21.4%	.73
> 12 months	32.1%		33.9%		26.8%	38.4%		38.8%		24.4%	
Grading											
G1	34.9%	.5	38.5%	.35	31.3%	44.6%	.08	42.2%	.65	27.7%	.38
G2–G3	30.4%		32.1%		23.2%	32.4%		38.9%		22.2%	
Primary site											
Pancreas	25.9%	.59	27.6%	.53	20.7%	33.3%	.65	35.1%	.34	21.1%	.56
Stomach/small bowel	35.2%		38.5%		29.1%	41.1%		46.7%		26.7%	
Colon	35.7%		42.9%		31%	39%		41.5%		26.8%	
Lung	16.7%		16.7%		16.7%	20%		0%		0%	

Bold values are statistically significant ($p < 0.05$)

4 | DISCUSSION

To our knowledge, this is the first study to evaluate the psychological impact of the COVID-19 outbreak in patients with NET. Yet accurate information on mental health and QoL during the COVID-19 pandemic is critically important: psychological interventions might be implemented in NET clinics if needed, COVID-19-influenced HRQoL levels can be assessed for future interpretation of QoL measures of ongoing clinical trials, and recommendations on health policy measures specifically concerning the NET patient population can be drawn upon our findings to improve the quality of care.

Several studies have already documented high rates of neuropsychiatric symptoms in patients with NETs. In particular, depression, anxiety and difficulty in impulse control have been described in 20%–50%, 35% and 75% of NET patients, respectively.[23-28] Moreover, NET patients have been shown to score considerably worse than healthy subjects in terms of HRQoL.[29]

The COVID-19 pandemic has added another layer of complexity to the fears of NET patients. Inability to travel, difficult access to hospitals and NET clinics, delayed imaging studies, and deferred surgeries or interventional procedures[22,30] are only a few factors potentially contributing to an enhanced psychological distress in NET patients. We longitudinally surveyed a bi-institutional cohort of 197 patients with NET under active treatment or surveillance. Given the fluctuant nature of mental symptoms and the rapidly evolving pandemic scenario, patients were interviewed during the plateau phase of both the first and second waves of the epidemic in Italy. At W1, the frequency of depression, anxiety and stress was 32%, 36% and 26%, respectively, which is in line with prior reports preceding the onset of the COVID-19 pandemic. Notably, the rate of depression (38%) and anxiety (41%) increased substantially at W2, possibly as a consequence of chronic exposure of patients to fears related to COVID-19. By multivariable analysis, advanced age and poor education were found to be significantly associated with depression and anxiety at W2. This is in line with prior studies focusing on the mental impact of COVID-19 in patients with cancer.[31,32] Tailored psycho-oncological interventions should be offered, if possible, particularly to older patients with a low level of formal education, aiming to recognize, prevent or treat mental distress during the COVID-19 pandemic.

According to a study carried out in the pre-COVID-19 era,[33] the prevalence of PTSD among patients with NET is approximately 15%, and patients with emotional distress caused by their cancer appear to be at higher risk for this condition. In the present study, we found a frequency of PTSD of approximately 60%, with single marital status and low level of education significantly predicting the occurrence of the disorder. Post-traumatic stress symptoms are well characterized psychological effects of quarantine, particularly in subjects with poor education levels.[34,35] Nevertheless, a lower rate of PTSD (9%–36%) has been described in response to the COVID-19 pandemic in patients with non-neuroendocrine cancers,[36-38] thus suggesting that NET patients might be particularly vulnerable to this condition. Systematic screening of PTSD occurrence is advised for

TABLE 3 Health-related quality of life (HRQoL) scores in the first and second epidemic waves

	First wave			Second wave			
HRQoL domain	Mean (SD)	Median	Q1-Q3	Mean (SD)	Median	Q1-Q3	p^a
Global health status	67.5 (20.3)	66	50–83	67.2 (21.5)	66	50–83	.67
Physical functioning	81.5 (18.4)	87	67–100	82.9 (18.3)	87	67–100	**.03**
Role functioning	79.5 (21.6)	84	67–100	81.4 (20)	84	67–100	.13
Emotional functioning	68.7 (22.7)	67	59–84	72 (21.4)	67	67–92	**.001**
Cognitive functioning	84.3 (18.5)	84	67–100	84 (18.1)	84	67–100	.44
Social functioning	79.1 (23.3)	84	67–100	78.3 (24)	84	67–100	.32
Fatigue	23.7 (20)	20	0–33	22.6 (19.5)	20	0–33	.47
Nausea/vomiting	12 (18.6)	0	0–20.2	8.2 (15)	0	0–16	**.0002**
Pain	18.6 (20)	16	0–33	20.6 (24)	16	0–33	.33
Dyspnea	18 (22)	0	0–33	16.2 (21)	0	0–33	.17
Insomnia	24.2 (24.6)	33	0–33	21.9 (25.6)	33	0–33	.12
Appetite loss	16 (22)	0	0–33	12.8 (20)	0	0–33	**.02**
Constipation	13.2 (20.2)	0	0–33	12.1 (18.6)	0	0–33	.4
Diarrhea	12.6 (20.4)	0	0–33	12.2 (20)	0	0–33	.9
Financial difficulties	20.2 (24.8)	0	0–33	20.9 (25.4)	0	0–33	.54
Endocrine scale	11.1 (17.3)	0	0–20	12 (16.3)	0	0–20	.37
Gastrointestinal scale	16.7 (16.3)	13	0–26	16.9 (15.6)	13	0–26	.49
Treatment scale	17.3 (20.3)	13	0–26	11.2 (16.7)	0	0–16	**.005**
Disease-related worries scale	38.5 (25.7)	33	20–53	33.8 (25.2)	33	13–46	**.0006**
Social functioning scale	27.3 (22.4)	20	10–43	25.7 (21.3)	20	10–43	.19
Muscle/bone pain symptom	17.6 (25)	0	0–33	17.1 (25.1)	0	0–33	.65
Sexual function	24.4 (30)	33	0–33	13.6 (24.8)	0	0–33	**.02**
Information/communication function	53.9 (31.4)	66	33–66	53.9 (32)	66	33–66	.44
Weight loss	10.9 (20.8)	0	0–33	10.6 (19.4)	0	0–33	.76
Weight gain	10.2 (21.4)	0	0–0	8 (18.1)	0	0–0	.05

Abbreviation: Q, quartile.

[a]Wilcoxon matched-pairs signed rank test.

Bold values are statistically significant ($p < 0.05$)

all NET patients and the bio-psychological basis of such an elevated PTSD frequency should be investigated further.

HRQoL is increasingly recognized as a crucial endpoint in clinical trials for cancer patients, and contrasting data have been reported so far regarding the effects of the COVID-19 pandemic on the QoL of patients with cancer.[39-42] In the present study, we longitudinally assessed intraindividual changes between W1 and W2 in patients with NETs. By contrast to our expectations, only a minority of patients underwent a clinically significant HRQoL deterioration throughout the pandemic, thus suggesting that NET patients were able to cope with the traumatic events associated with the epidemic outbreak. Several reasons might explain this phenomenon, at least theoretically. First, patients who are already accustomed to restrictions in everyday life might cope better with the additional restrictions imposed in response to the COVID-19 pandemic. Second, the increase of intrafamilial proximity (especially for family members living in the same household) might potentially alleviate the physical and emotional distress suffered by NET patients. Not surprisingly, healthy subjects have reported loneliness as a result of the COVID-19 pandemic more frequently than cancer patients.[43] Third, because NET patients have already re-prioritized their life upon receiving a diagnosis of a rare, poorly understood form of cancer, they might be particularly resilient when exposed to a new, obscure, potentially life-threatening situation. In our cohort, old patients appeared to be at higher risk of developing HRQoL deterioration, and particular attention should be paid to the worsening of physical and cognitive functioning areas in this frail subject category.

The relationship between patients and doctors is an essential component of patient care. Evidence demonstrates that HRQoL is positively associated with all aspects of care among cancer patients in general,[44] and also that care satisfaction is strictly related to better HRQoL and psychosocial function of NET patients in particular.[45-47] In the present study, the confidence in NET specialists was very high, and no longitudinal changes were noted despite the

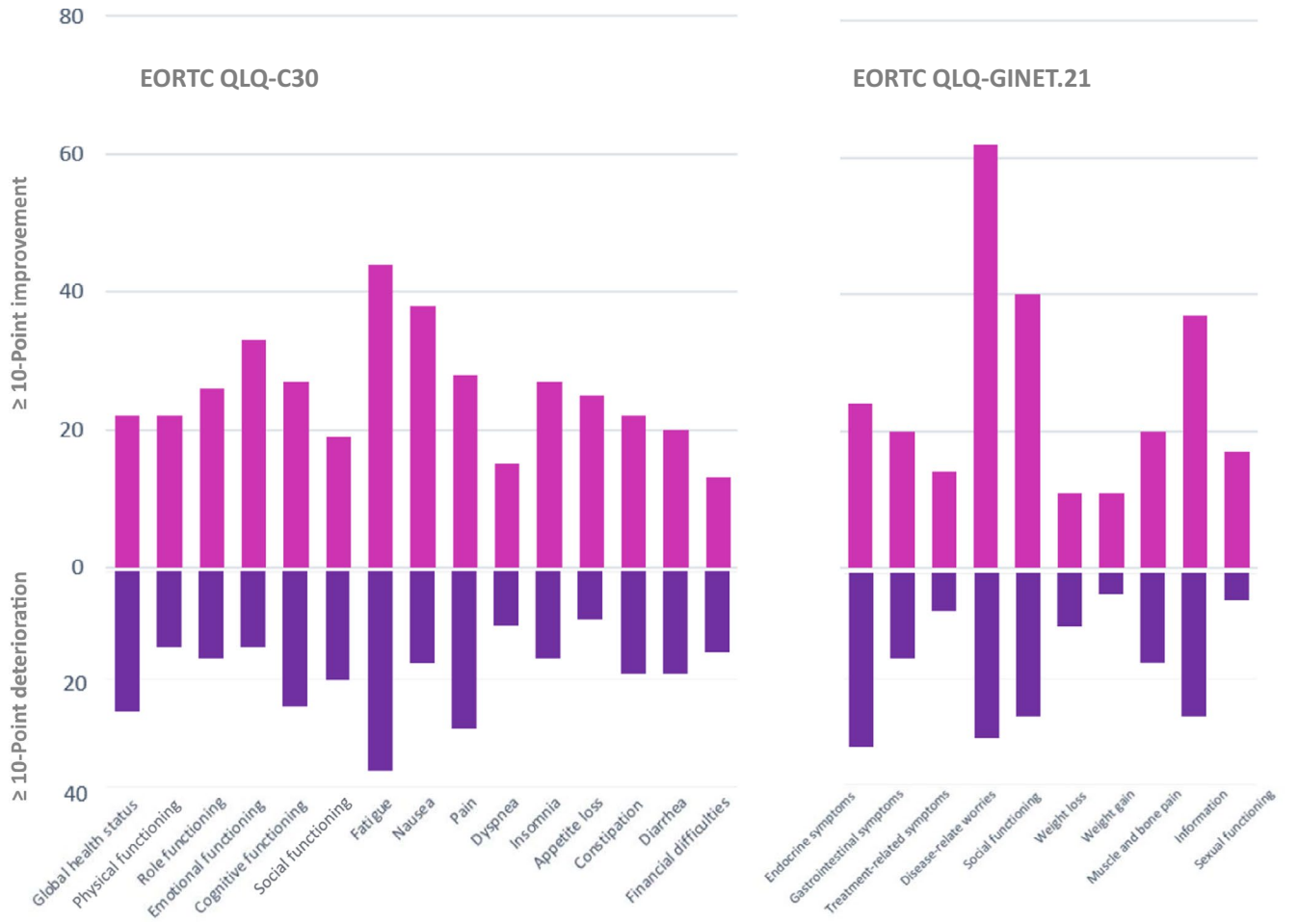

FIGURE 3 Effects of COVID-19 pandemic on clinically significant health-related quality of life changes between the first (W1) and second (W2) epidemic waves. EORTC, European Organization for Research and Treatment of Cancer; QLQ, quality of life questionnaire

persistence of the pandemic threat. Although we acknowledge that the level of patient satisfaction could be overestimated in our study because the responses to questionnaires were not anonymized, it is also possible that the degree of confidence in physicians might be the consequence of patient management in two large-volume institutions highly specialized in the treatment of NETs. A potential impact of elevated patient satisfaction on psychometric measures and HRQoL therefore cannot be excluded in our cohort.

The present study has several limitations. First, the study was conducted in two tertiary centers in South Italy, and our findings might thus have limited geographic generalizability. Nevertheless, although psychosocial regional differences should be always taken into account, we consider that the experiences and perceptions faced by study participants are similar to those experienced by NET patients internationally, or at least where lockdown measures were adopted. Second, fears and hopes related to the COVID-19 pandemic have changed rapidly in recent months, and will likely continue to fluctuate over the next few months. Despite its longitudinal design, the present study only allows for an understanding of patient perceptions during the exact time frame of data collection. In this context, we are unable, for example, to evaluate the impact of anti-SARS-CoV-2 vaccine development and mass vaccination campaigns on psychometric evaluations and HRQoL measures. Lastly, despite the sample size of this study being relatively large, a very heterogeneous population of patients was included. Although subanalysis exploring defined subclasses of patients have been carried out, reliable conclusions are hindered in several cases by small numbers.

Several lessons can be learnt from the current pandemic crisis with respect to minimizing the psychological impact of future pandemic outbreaks on NET patients. Although reallocation of health care resources can be necessary during a pandemic, pathways dedicated to patients with cancer (and in particular to those with rare cancers) should always remain active. Technology has undoubtedly facilitated uninterrupted cancer patient care during the COVID-19 pandemic but, although being key in connecting patients with their physicians, telemedicine can also increase the disparity between low-income and high-income or old and young patients, providing suboptimal support to patient categories at high risk of psychological distress. Dedicated pathways should therefore be provided to high-risk patients, and psychological consultations should be part of these pathways. Simplified access to anti-cancer agents (ideally with door-to-door delivery of oral drugs), as well as rationalization of clinical trial procedures (i.e., shipment of investigational oral drugs to patients' homes, possibility of performing lab work in local facilities,

TABLE 4 Predictors of health-related quality of life (HRQoL) deterioration during the COVID pandemic

HRQoL domain deterioration	Univariate analysis	Multivariable analysis
Global health status	Prior therapy for anxiety: $p = .04$ Poor instruction: $p = .0002$	–
Physical functioning	Age > 65 years: $p = .002$ Hormone secretion: $p = .05$	Age > 65 years: $p = .005$ (OR = 6.66; 95% CI = 1.77–24.97)
Role functioning	–	–
Emotional functioning	–	–
Cognitive functioning	Age > 65 years: $p = .01$	Age > 65 years: $p = .01$ (OR = 2.95; 95% CI = 1.25–6.97)
Social functioning	–	–
Fatigue	Age > 65 years: $p = .0009$ Active therapy: $p = .04$ Poor instruction: $p < .0001$	Age > 65 years: $p = .0007$ (OR = 3.9; 95% CI = 1.77–8.63)
Nausea/vomiting	–	–
Pain	Age > 65 years: $p = .03$ Poor instruction: $p = .02$	–
Dyspnea	Single marital status: $p = .02$ Poor instruction: $p = .02$	Single marital status: $p = .003$ (OR = 9.08; 95% CI = 2.13–38.80)
Insomnia	–	–
Appetite loss	–	–
Constipation	Age > 65 years: $p = .01$ Poor instruction: $p = .001$	Age > 65 years: $p = .03$ (OR = 2.96; 95% CI = 1.08–8.11)
Diarrhea	Hormone secretion: $p = .008$ Poor instruction: $p = .01$	Hormone secretion: $p = .01$ (OR = 5; 95% CI = 1.39–18) Poor instruction: $p = .03$ (OR = 0.15; 95% CI = 0.03–0.82)
Financial difficulties	Age > 65 years: $p = .01$ Married marital status: $p = .005$	Age > 65 years: $p = .02$ (OR = 8.31; 95% CI = 2.15–32.15) Married marital status: $p = .04$ (OR = 5.03; 95% CI = 1.09–23.30)
Endocrine scale	Age > 65 years: $p = .007$ Prior therapy for anxiety: $p = .02$ Poor instruction: $p < .0001$ Diagnosis > 1 year: $p = .04$	–
Gastrointestinal scale	–	–
Treatment scale	–	–
Disease-related worries scale	Hormone secretion: $p = .05$	Hormone secretion: $p = .002$ (OR = 4.01; 95% CI = 1.68–9.6)
Social functioning scale	–	–
Muscle/bone pain	–	–
Sexual function	–	–
Information/communication	–	–
Weight loss	–	–
Weight gain	–	–

Abbreviations: CI, confidence interval; OR, odds ratio.

and the use of telehealth services for follow-up visits) are other important aspects that might reduce the psychological burden of future pandemics.

In conclusion, despite heightened vulnerability in terms of PTSD occurrence, NET patients show an elevated psychological resilience in response to the COVID-19 pandemic. The high level of care

satisfaction might contribute to explain the absence of significant HRQoL deterioration and the relatively small increase in depressive symptoms and anxiety from W1 to W2. We advise a systematic screening of post-traumatic stress symptoms for all NET patients until the end of the pandemic. Specific psychological interventions should be developed to treat this vulnerable population.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

Eleonora Lauricella: Conceptualization; Data curation; Investigation; Methodology; Project administration; Writing – original draft. **Mauro Cives:** Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Supervision; Writing – original draft. **Alessandra Bracigliano:** Data curation; Writing – review & editing. **Ottavia Clemente:** Data curation; Writing – review & editing. **Valentina Felici:** Conceptualization; Data curation; Methodology; Writing – review & editing. **Rossella Lippolis:** Conceptualization; Methodology; Writing – review & editing. **Brunella Amoruso:** Data curation; Writing – review & editing. **Eleonora Pelle':** Data curation; Writing – review & editing. **Barbara Mandriani:** Data curation; Writing – review & editing. **Chiara Esposto:** Data curation; Writing – review & editing. **Cira Forte:** Data curation; Writing – review & editing. **Francesco Perri:** Data curation; Writing – review & editing. **Camillo Porta:** Supervision; Writing – review & editing. **Salvatore Tafuto:** Conceptualization; Methodology; Writing – review & editing.

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DATA AVAILABILITY STATEMENT

Data are available from the corresponding author upon reasonable request.

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