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Clinical Research Article

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Quality of Life in Patients with Neuroendocrine Neoplasms: The Role of Severity, Clinical Heterogeneity, and Resilience

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Abstract

Context: Although health-related quality of life (HRQoL) is a fundamental outcome in oncological clinical trials, its evaluation in the neuroendocrine neoplasm (NEN) research field is still limited.

Objectives: This study assessed the role of clinical severity (ie, presence or absence of metastasis and lines of therapies) and heterogeneity (ie, primary site, types of therapy, biology, and surgery) of NEN in relation to HRQoL, as well as resilience as a moderator between clinical severity and HRQoL.

Design: Cross-sectional multicentric study.

Setting: Italian university hospitals.

Patients: A total of 99 Italian patients (53 men and 46 women) with NEN and ranged in age from 22–79 years old.

Main Outcome Measure: Severity and heterogeneity of NENs, HRQoL, and resilience.

Results: The presence of metastasis and a greater number of therapies affected the global health and some physical symptoms. Resilience was associated with global health, functional status, and some physical symptoms, and it moderated the impact of metastases on constipation and of the multiple therapies on diarrhea and financial problems. Patients with NEN in districts other than the gastroenteropancreatic system and those in follow-up perceived fewer physical symptoms than their counterparts. Patients with a sporadic NEN perceived their functional status, global health, and disease-related

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worries as better than those with a hereditary NEN. Patients who underwent surgery were lower in constipation than their counterparts.
Conclusion: These findings highlight the need to assess the relationships between the clinical severity and heterogeneity of NEN with HRQoL and the role of resilience in improving patients' HRQoL.

Freeform/Key Words: neuroendocrine tumor, quality of life, resilience, severity, heterogeneity, metastases

Neuroendocrine neoplasms (NEN) are a group of neoplasms characterized by a wide clinical heterogeneity and biological variability. Since NENs originate from the cells of the diffused neuroendocrine system, they can arise in all organs and tissues, even if the most frequently affected sites are the gastroenteropancreatic (GEP) and respiratory tracts (1). Neuroendocrine neoplasms represent 2% of all malignant tumors, and recent epidemiological data have shown a progressive increase in their incidence (6.98/100 000) (2). Nevertheless, NENs are usually sporadic and occur in adulthood or in elderly patients. In 10% to 30% of cases they are associated with genetic syndromes, such as multiple endocrine neoplasia (MEN 1 and MEN 2), von Hippel Lindau syndrome, neurofibromatosis type 1, familial paragangliomatosis, and sclerosis tuberose; in patients with genetic syndromes, NENs occur at an earlier age (2, 3).

The most recent classification of the World Health Organization differentiates between GEP NENs with a variable aggressiveness, based on the proliferative activity expressed by the Ki67 index or mitotic count, subdivided into 3 well-differentiated forms (G1, G2, and G3), all associated with a good to moderate survival, and poorly differentiated NENs (G3) with a high Ki67 index, having a more unfavorable prognosis (4). More often, NENs are not associated with any endocrine syndrome, but cause nonspecific symptoms. In these cases, the diagnosis may be delayed for years and the condition may already be associated with metastases (5, 6). Furthermore, NENs generally have an indolent course and a high prevalence. Indeed, patient survival rates are higher than those of patients suffering from adenocarcinomas of the same anatomical origin, and an overall survival of 9.3 years has been estimated (2).

The heterogeneity of NENs, as well as their long natural history, combined with the necessity of long-lasting and stepwise therapies, can have a negative impact on the patients' health-related quality of life (HRQoL). Indeed, previous studies have highlighted that the uncertainty of the diagnostic and therapeutic course of the disease may have a negative role on HRQoL (7), producing anxiety disorders or depressive symptoms, which, in turn, may profoundly and negatively affect the emotional experiences associated with the therapy (8). Although HRQoL represents a fundamental outcome in oncological clinical trials, its evaluation in the NEN research field has not been deeply explored and scientific knowledge is still limited (9–11). Evidence suggests that NEN patients perceive their HRQoL as relatively good, although both physical and psychosocial complaints are often reported, such as poor emotional, mental, physical, and social functioning, sleep problems, and fatigue (10, 12–16). However, it is not clear from the literature how the severity of the clinical status and the clinical heterogeneity of the NEN may impact on HRQoL. Furthermore, surprisingly, no previous studies have assessed the role of resilience, ie, a dynamic psychological process promoting a positive adaptation within contexts of significant adversity helping people to overcome difficulties and stressful situations (17), in its association with the HRQoL of patients with NEN, although high levels of resilience help people with tumors to buffer the negative effects that diagnosis and treatment may have on HRQoL (18).

Based on these premises, the current study aims to assess the role of the clinical severity and heterogeneity of NENs on HRQoL in a sample of Italian patients with NEN, as well as the role of resilience as an individual-level protective factor against the negative effects of NEN on HRQoL. The main hypotheses of this study were: (1) the severity of the NEN (ie, metastatic NEN and multiple-line therapies) would be associated with a worse HRQoL, and (2) resilience would moderate the relationship between the severity of the NEN and HRQoL. Furthermore, the following additional hypotheses concerning the clinical heterogeneity of NENs were advanced: (1) the HRQoL of patients with GEP NENs would be lower than that of patients with a NEN in other districts (ie, the thyroid, lungs, oropharynx, paraganglia, or adrenals); (2) the HRQoL of patients undergoing follow-up without therapy would be higher than that of patients, respectively, undergoing somatostatin analogues (SSA) and other therapies (eg, chemotherapy or loco-regional therapy); (3) the HRQoL of patients with a sporadic NEN would be higher than that of patients with a hereditary NEN, matched for tumor grade and stage; and (4) the HRQoL of patients who underwent surgery treatment would be lower than that of patients who did not.

Materials and Methods

Procedures and patients

The data analyzed in the current study are part of a larger data collection project entitled "A Multicentric Clinical Study on the Quality of Life in Patients with Neuroendocrine Neoplasms," an Italian multicentric longitudinal study aimed at assessing the HRQoL in patients with NENs at different times in the treatment. In the current study, we have analyzed preliminary data from the first assessment, thus using a cross-sectional study design in accordance with the Strobe Statement.

To collect the data, patients with a NEN, accessing the Unit of Neuroendocrine Neoplasms of the University of Naples Federico II and the NeuroEndocrine Tumor TAskforcE (NETTARE) Unit of "Sapienza" University of Rome, were asked to participate in the study, which started in September 2019. The eligibility criteria were: (1) patients with an age between 18 and 75 years; (2) patients with a histologically confirmed NEN diagnosis, with a gastrointestinal, lung, or other anatomical neoplasm, metastatic or locally advanced, unresectable and associated or not with endocrine syndromes and hereditary syndromes; (3) patients able to understand and sign the informed consent; and (4) patients able to complete the questionnaire independently.

Endocrinologists clearly explained the objectives and procedures of the study to the patients. Patients who agreed to be involved in the study were then accompanied to the waiting room of the ward, where it was possible for them to answer the questions independently. An informed written consent was obtained from the patients and their participation was entirely voluntary and with no obligation.

A total of 99 patients took part in the study, which continued until February 24, 2020. The patients ranged in age from 22–79 years old (mean [M] = 56.46; standard deviation [SD] = 13.71). In regard to gender identity, 53 were men and 46 were women. Furthermore, 82.3% of the sample had an educational level ≤ high school, while for 17.7% an educational level ≥ university college was reported.

The study was conducted in accordance with the EU General Data Protection Regulation. Furthermore, it was designed in respect of the principles of the Declaration of Helsinki and approved by the Ethical Committee of the University of Naples Federico II (project identification code: 156/2019; date of approval: July 25, 2019).

Measures

Severity of the NEN

To evaluate the severity of the patients' clinical status, we considered 2 dimensions, namely: (1) the presence or absence of metastasis, and (2) the number of therapies experienced. In regard to the 1st indicator, the presence of metastasis indicated a greater level of severity of the NEN. In regard to the number of therapies that patients had undergone by the time of the survey, we computed an indicator reporting the total number of therapies, ranging from 0 to 2, with higher levels indicating a greater severity.

Clinical heterogeneity of the NEN

Among different clinical data collected through a clinician report completed by an endocrinologist for each patient and aimed at detecting clinical heterogeneity, in the current study we have used: (1) the site of the NEN (ie, GEP, thyroid, lungs, oropharynx, paraganglia or adrenals); (2) the type of therapy currently experienced (ie, follow-up without therapy, SSA, targeted therapy, oral and intravenous chemotherapy, radiotherapy or locoregional therapy); (3) the nature of the NEN, sporadic or hereditary; and (4) having undergone the surgery or not. Specifically, in regard to the primary site of the NEN, due to the relatively low number of patients and to the higher rates of GEP NENs (see the results related to the clinical heterogeneity of the participants), we created a dichotomized variable in which "1 = GEP" and "2 = non-GEP" (ie, thyroid, lungs, oropharynx, paraganglia or adrenals). In regard to the type of therapy, we created a scalar variable ranging from less to more severe therapy, as follows: 1 = follow-up without therapy; 2 = SSA; and 3 = other (ie, targeted therapy, chemotherapy, radiotherapy, or locoregional therapy).

Health-related quality of life

We assessed the HRQoL through the Italian versions of the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-C30 (EORTC QLQ-C30, version 3.0) and the EORTC Quality of Life Questionnaire—Neuroendocrine Carcinoid Module (EORTC QLQ-GINET21). Permission was obtained for the use of both questionnaires from the EORTC Quality of Life Group. EORTC QLQ-C30 assesses the HRQoL of cancer patients over the past week through 5 functional status scales (ie, physical, role, emotional, cognitive, and social functioning), 9 symptoms measured through both scales and single items (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties), and a global health (GH)/QoL scale (19). The QLQ-GINET21 consists of an additional 21 items measuring NEN-specific parameters over the past week, as follows: muscle and/or bone pain, body image, information, sexual functioning, endocrine symptoms, gastrointestinal symptoms, treatment-related symptoms, social functioning of the new module, and disease-related worries (20). For

both questionnaires, the response options ranged from "not at all" to "very much" on a 4-point Likert scale. The scoring procedures suggested by the EORTC Quality of Life Group were followed (21), according to which both scales and single-item scores were linearly transformed to a 0–100 scale. Specifically, in regard to the EORTC QLQ-C30, higher scores on the functional scales and (GH)/QoL scale indicate a higher level of functional status and GH/QoL, while higher scores on the symptom scales and single items indicate higher levels of symptoms and problems. Scores ≤ 33 on the functional scales and GH/QoL scale and ≥ 66 on the symptoms scales indicate groups of patients with unmet health needs in terms of HRQoL (22–24). In regard to the EORTC QLQ-GINET21, higher scores indicate more severe symptoms.

Resilience

The Resilience Scale for Adults (25) is a 33-item scale measuring resilience, namely the individual's capacity to overcome adversity and stress while maintaining normal psychological and physical functioning. The participants were asked to answer questions on a 7-point semantic differential scale, where each item had a positive and a negative attribute at each side of the scale continuum. Higher scores indicate higher levels of resilience. The α coefficient for the current sample was 0.88.

Statistical analyses

Based on previous studies highlighting that the main difference in terms of HRQoL is related to the presence or absence of metastasis (26, 27), this difference was considered as the primary outcome in the current study for the performance of a power analysis. A sample size of 61 in the group without metastatic NEN and 35 in the group with metastatic NEN achieved 80% of power to detect an HRQoL mean difference equal to 15, which corresponds to a medium effect size (ie, the standardized mean difference obtained using the best estimates of the standard deviation) of 0.6, as reported in Table 4 of the study by Cocks et al (28). The 2-sided *t*-test for 2 independent samples was considered with a significance level of $\alpha = 0.05$.

The associations between HRQoL, severity of the NEN, and resilience were tested through a series of multiple linear regressions, differentiated for the dimensions of NEN severity (metastasis vs nonmetastasis or the number of current therapies). Specifically, in all models, the HRQoL dimensions and resilience were considered as dependent variables, while the severity of the NEN dimensions and resilience were considered as independent variables. We first tested for the interaction term between the specific severity of the NEN dimension and resilience. If the interaction term was not statistically significant, we tested the model with only the 2 main effects of the specific severity of the NEN dimension and resilience.

Finally, in order to assess the clinical heterogeneity of NEN, we tested for statistically significant differences among groups through the Student's *t*-test or analysis of variance (ANOVA), depending on the number of groups to compare (GEP vs other, sporadic vs hereditary, surgery vs no-surgery, and current therapies [follow-up, SSA, or other]).

All the statistical analyses were performed using the R statistical software. All the tests were 2-sided, with a significance level of $\alpha = 0.05$.

Results

Clinical status of participants

The average latency from NEN diagnosis was 7.26 years (SD = 6.42), ranging from a few months to 36 years. Most patients had a NEN in the gastrointestinal tract (n = 67; 67.67%), with the remaining 32.32% (n = 32) affected by NENs in other sites, namely the thyroid (ie, medullary thyroid cancer [MTC]; n = 11; 11.1%), lungs (n = 9; 9.1%), oropharynx (n = 2; 2.1%), paraganglia (n = 6; 6.1%), and adrenals (n = 4; 4%). The primary site in the GEP was as follows: stomach (n = 7; 4.7%), pancreas (n = 44; 29.5%), small intestine (n = 14; 9.4%), and rectum (n = 2; 1.34%). Instead, tumor grade for GEP was as follows: G1 (n = 40; 26.8%), G2 (n = 15; 10%), and G3 (n = 5; 3%), while 5 lung NEN were typical and 4 were atypical.

In regard to the types of therapy, most patients (n = 59; 59.6%) were undergoing SSA, 23.2% (n = 23) were in follow-up without therapy, and 17.2% (n = 17) were benefiting from other types of therapy, namely peptide receptor radionuclide therapy (n = 5; 5%), targeted therapy (n = 4; 4.1%), oral (n = 6; 6.1%) and intravenous (n = 3; 3.1%) chemotherapy, radiotherapy (n = 2; 2.1%), and locoregional therapy (n = 1; 1.1%). At the time of the survey, 23.2% (n = 23) had not yet undergone any therapy, 64.64% (n = 64) had undergone only 1 line of therapy, and 12.1% (n = 12) had undergone 2 lines of therapy. Furthermore, 61.6% (n = 61) of the participants had a sporadic NEN, while 35.4% (n = 35) had a metastatic tumor. All patients with a genetic syndrome were affected by MEN 1 and pancreatic NEN. Moreover, 49.5% (n = 50) of the participants underwent surgery in the past. All patients with MTC underwent thyroidectomy.

In regard to the HRQoL, only 5.1% (n = 5) of the sample met the clinical cutoff for physical, emotional, cognitive, and social functioning, while 10.1% (n = 10) met the

Table 1. Regressions of health-related quality of life on the presence or absence of metastases and resilience

	Metastasis (no)			Resilience				
	b	B(SE)	95% CI	b	B(SE)	95% CI	F	R^2
Physical functioning	-0.027	-1.27(4.46)	-10.13, 7.59	0.380***	17.62(4.46)	8.77, 26.47	7.98**	0.146
Role functioning	-0.113	-6.91(6.13)	-19.08, 5.27	0.242*	14.79(6.12)	2.63, 26.95	3.77*	0.075
Emotional functioning	-0.027	-1.27(4.46)	-10.13, 7.59	0.380***	17.62(4.46)	8.77, 26.47	7.98**	0.146
Cognitive functioning	-0.024	-1.11(4.46)	-9.96, 7.74	0.380***	17.64(4.45)	8.79, 26.48	7.99**	0.147
Social functioning	-0.027	-1.27(4.46)	-10.13, 7.59	0.380***	17.62(4.46)	8.77, 26.47	7.98**	0.146
Global health score	-0.211*	-9.82(4.63)	-19.02, -0.62	0.178	8.26(4.63)	-0.93, 17.45	4.14*	0.082
Fatigue	0.159	9.23(5.84)	-2.35, 20.82	-0.198*	-11.49(5.83)	-23.06, 0.08	3.44*	0.069
Nausea and vomiting	0.060	2.22(3.74)	-5.20, 9.65	-0.192	-7.04(3.73)	-14.45, 0.38	2.04	0.042
Pain	0.030	1.68(5.62)	-9.48, 12.84	-0.282**	-15.86(5.61)	-27.00, -4.71	4.12*	0.081
Dyspnea	0.077	4.11(5.44)	-6.70, 14.91	-0.161	-8.55(5.43)	-19.34, 2.24	1.62	0.034
Insomnia	0.034	2.11(6.10)	-10.01, 14.23	-0.311**	-19.24(6.09)	-31.34, -7.14	5.15**	0.100
Appetite loss	0.104	4.41(4.21)	-3.95, 12.78	-0.253*	-10.68(4.21)	-19.04, 2.33	3.98*	0.079
Constipation	1.86*	99.38(40.18)	19.57, 179.19	0.135	7.23(6.92)	-6.51, 20.97	2.36*	0.071
Diarrhea	0.239*	14.41(6.04)	2.42, 26.40	-0.121	-7.29(6.03)	-19.26, 4.69	3.81*	0.076
Financial difficulties	0.239*	14.41(6.04)	2.42, 26.40	-0.121	-7.29(6.03)	-19.26, 4.69	3.81*	0.076
Endocrine symptoms	-0.092	-4.30(4.89)	-14.02, 5.41	0.106	4.91(4.82)	-4.68, 14.49	0.98	0.021
Gastrointestinal symptoms	-0.102	-4.88(5.03)	-14.88, 5.11	0.034	1.59(4.92)	-8.18, 11.35	0.55	0.012
Treatment-related symptoms	-0.196	-9.68(5.88)	-21.41, 2.05	0.086	4.02(5.60)	-7.17, 15.20	1.66	0.047
Social functioning (SF21)	-0.185	-10.31(5.57)	-21.37, 0.74	0.249*	13.72(5.49)	2.81, 24.63	5.22**	0.103
Disease-related worries	-0.131	-7.87(6.21)	-20.21, 4.46	0.155	9.13(6.07)	-2.93, 21.19	2.09	0.044
Muscle and/or bone pain	0.049	3.69(7.83)	-11.86, 19.24	-0.164	-12.26(7.73)	-27.60, 3.09	1.43	0.031
Body image	0.116	5.28(4.75)	-4.16, 14.71	-0.162	-7.27(4.66)	-16.53, 1.98	1.98	0.043
Information	-0.057	-2.37(4.31)	-10.94, 6.19	-0.110	-4.48(4.26)	-12.94, 3.97	0.66	0.014
Sexual functioning	0.081	5.76(7.90)	-9.99, 21.50	-0.313**	-21.93(7.77)	-37.42, -6.45	4.41*	0.108

Abbreviations: b, standardized regression coefficient; B, unstandardized regression coefficient; CI, confidence interval; F, F-test; R^2, R-Square; SE, standard error; SF21, social functioning of the QLQ-GINET21.
*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

clinical cutoff for role functioning. Instead, more than half of the sample (n = 60; 60.6%) met the clinical cutoff for the GH/QoL score.

Associations between severity of NEN and HRQoL and the moderating role of resilience

The results for the regressions of HRQoL on the presence or absence of metastasis and resilience are presented in Table 1, while those on the number of current therapies and resilience are presented in Table 2. As very few interaction terms proved to be significant, we have reported the related coefficients in the text.

In regard to the 1st dimension of NEN severity, the absence of metastasis was associated with higher levels of the GH/QoL score, thus increasing the likelihood of having a better HRQoL. On the contrary, the presence of metastases was associated with higher levels of constipation, diarrhea, and financial difficulties. Instead, resilience proved to be associated with more HRQoL dimensions than the presence or absence of metastasis. Specifically, higher levels of resilience were associated with higher levels of physical, emotional, cognitive, and social (both general and NEN-specific) functioning, and with lower levels of fatigue, pain, insomnia, appetite loss, and sexual problems, thus resulting as a protective dimension. The only significant interaction between the presence or absence of metastases and resilience was on constipation, indicating that the association between the presence of metastases and constipation was significant for lower levels of resilience (b = -1.91, 95% confidence interval [CI; -49.81, -6.13], $P = 0.013$).

In regard to the 2nd dimension of NEN severity, a greater number of therapies proved to be associated with a lower GH/QoL score and treatment-related symptoms, and with higher levels of fatigue, diarrhea, financial difficulties, and body image problems. Similar to previously reported results, higher levels of resilience were associated with higher levels of physical, role, emotional, cognitive and social (both general and NEN-specific) functioning, and with lower levels of fatigue, pain, insomnia, appetite loss, and sexual problems. Only 2 significant interactions between the number of therapies and resilience were found, specifically on diarrhea (b = -1.86, 95% CI [-45.35, -5.08], $P = 0.015$) and financial difficulties (b = -1.86, 95% CI [-45.35, -5.08], $P = 0.015$), indicating that the associations between a higher number of therapies and both diarrhea and financial problems were significant for lower levels of resilience.

These results partially confirm hypotheses 1 and 2. However, the R2 was generally low, ranging from 0.069 to 0.146 for the metastasis vs nonmetastasis variable and from 0.062 to 0.173 for the variable related to the number of current therapies.

Clinical heterogeneity and HRQoL

Hypotheses 3, 4, 5, and 6 were partially confirmed, as some HRQoL-related differences between the site of the NEN (GEP vs non-GEP), sporadic vs hereditary NEN, surgery (yes vs no), and current therapies (follow-up vs SSA vs other) were detected, as reported in Tables 3 and 4. Specifically, participants with a GEP NEN proved to have a higher score than those with NENs in other sites only in relation to nausea/vomiting and constipation. Furthermore, participants in follow-up proved lower than those undergoing SSA or other therapies only in diarrhea and financial difficulties. Instead, participants with sporadic NENs proved lower than those with hereditary NENs in physical, role, emotional, cognitive and social (both general and NEN-specific) functioning, as well as in the GH/QoL score. Moreover, the participants with sporadic NENs showed lower levels of worries but higher fatigue, pain, insomnia, diarrhea, financial difficulties, muscle and/or bone pain, and body image problems than the participants with hereditary NENs. Finally, the only difference between patients who underwent surgery and those who did not undergo any surgery was on constipation, indicating that patients receiving a surgical treatment were lower in constipation than their counterparts.

Discussion

The current study has assessed the role of the clinical severity and heterogeneity of NENs in the HRQoL of a group of Italian patients with NENs. It has also evaluated the role of resilience as a buffering dimension protecting the patients from the potential negative effects of clinical severity on HRQoL. The results have partially confirmed our hypotheses, depicting a strong heterogeneous situation.

First, with regard to patients' HRQoL status, the percentage of participants meeting the cutoff for the functional status scales is very low, confirming previous studies, which have highlighted that the HRQoL of patients with NEN is relatively good (13, 29). However, this was not the case with respect to the GH/QoL score, as more than half of the patients (60.6%) met the clinical cutoff. This finding may indicate that patients with NEN perceive their general

Table 2. Regressions of health-related quality of life on the number of current therapies and resilience

	Number of Current Therapies			Resilience				
	b	B(SE)	95% CI	b	B(SE)	95% CI	F	R^2
Physical functioning	-0.181	-6.86(3.55)	-13.92, 0.19	0.378***	17.60(4.36)	8.93, 26.27	9.85***	0.173
Role functioning	-0.048	-2.38(4.99)	-12.29, 7.52	0.245*	15.04(6.13)	2.86, 27.21	3.10*	0.062
Emotional functioning	-0.181	-6.86(3.55)	-13.92, 0.19	0.378***	17.60(4.36)	8.93, 26.27	9.85***	0.173
Cognitive functioning	-0.182	-6.89(3.55)	-13.94, 0.15	0.379***	17.60(4.36)	8.95, 26.26	9.89***	0.174
Social functioning	-0.181	-6.86(3.55)	-13.92, 0.19	0.378***	17.60(4.36)	8.93, 26.27	9.85***	0.173
Global health score	-0.270**	-10.17(3.67)	-17.37, -2.88	0.198	9.17(4.51)	-0.20, 18.13	5.79**	0.110
Fatigue	0.241*	11.49(4.66)	2.24, 20.75	-0.205*	-11.99(5.73)	-23.37, 0.63	5.14**	0.099
Nausea and vomiting	0.183	5.48(2.97)	-0.42, 11.38	-0.196	-7.19(3.65)	-14.44, 0.05	3.57*	0.071
Pain	0.189	8.66(4.44)	-0.16, 17.49	-0.285**	-16.05(5.46)	-26.89, -5.21	6.11**	0.115
Dyspnea	-0.032	-1.37(4.41)	-10.12, 7.39	-0.161	-8.55(5.42)	-19.34, 2.17	1.31	0.027
Insomnia	0.028	1.41(4.95)	-8.41, 11.24	-0.308**	-19.06(6.08)	-31.13, -6.98	4.94**	0.095
Appetite loss	0.170	5.84(3.37)	-0.85, 12.54	-0.260*	-10.96(4.14)	-19.19, 2.74	4.92**	0.095
Constipation	0.043	1.92(4.55)	-7.11, 10.95	-0.079	4.30(5.59)	-15.39, 6.79	0.38	0.008
Diarrhea	2.04**	100.50(35.93)	29.16, 171.85	-0.217	-13.10(10.41)	-7.57, 33.77	4.80**	0.134
Financial difficulties	2.04**	100.50(35.93)	29.16, 171.85	-0.217	-13.10(10.41)	-7.57, 33.77	4.80**	0.134
Endocrine symptoms	-0.105	-4.05(3.97)	-11.93, 3.83	0.110	5.12(4.78)	-4.38, 14.63	1.08	0.023
Gastrointestinal symptoms	-0.187	-7.43(4.09)	-15.56, 0.70	0.039	1.81(4.84)	-7.79, 11.42	1.71	0.036
Treatment-related symptoms	-0.298*	-12.34(4.80)	-21.92, -2.76	0.060	2.81(5.45)	-8.07, 13.69	3.59*	0.096
Social functioning (SF21)	-0.120	-5.50(4.57)	-14.58, 3.57	0.261*	14.40(5.51)	3.46, 25.35	4.09*	0.082
Disease-related worries	-0.016	-0.80(5.15)	-11.04, 9.43	0.161	9.46(6.09)	-2.63, 21.56	1.22	0.026
Muscle and/or bone pain	0.172	10.68(6.29)	-1.83, 23.19	-0.164	-12.27(7.59)	-27.36, 2.81	2.70	0.056
Body image	0.258*	9.57(3.72)	2.17, 16.97	-0.172	-7.72(4.48)	-16.63, 1.20	4.71*	0.095
Information	0.090	3.03(3.49)	-3.90, 9.97	-0.104	-4.35(4.21)	-12.62, 4.11	0.87	0.019
Sexual functioning	0.103	6.32(6.82)	-7.26, 19.91	-0.298**	-20.91(7.78)	-36.41, -5.41	4.46*	0.108

Abbreviations: b, standardized regression coefficient; B, unstandardized regression coefficient; CI, confidence interval; F, F-test; R^2, R-Square; SE, standard error; SF21, social functioning of the QLQ-GINET21.
*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

Table 3. Health-related quality of life according to the site of the NEN and current therapies

	Site of the NEN			Current Therapies			
	GEP N = 66 M(SD)	Non-GEP N = 30 M(SD)	*P*-value	Follow-up N = 22 M(SD)	SSA N = 59 M(SD)	Other N = 16 M(SD)	*P*-value
Physical functioning	79.34(22.83)	78.55(24.14)	0.878	80.35(26.64)	79.77(22.21)	79.48(23.16)	0.992
Role functioning	77.05(26.71)	72.22(35.91)	0.464	38.69(8.25)	24.40(3.18)	68.75(30.96)	0.111
Emotional functioning	79.34(22.83)	78.55(24.14)	0.878	80.35(23.64)	79.77(22.22)	79.48(23.16)	0.992
Cognitive functioning	79.19(22.78)	78.55(24.14)	0.901	80.35(23.64)	79.61(22.18)	79.48(23.16)	0.990
Social functioning	79.34(22.83)	78.55(24.14)	0.878	80.35(23.64)	79.77(22.22)	79.48(23.16)	0.992
Global health score	64.24(22.73)	68.22(22.48)	0.427	68.56(22.99)	64.21(22.64)	66.56(21.52)	0.729
Fatigue	38.45(28.45)	30.00(28.76)	0.182	32.92(30.76)	34.35(27.08)	39.58(30.08)	0.755
Nausea and vomiting	12.87(20.77)	5.56(11.85)	0.032	7.81(15.86)	9.97(16.04)	12.50(25.46)	0.726
Pain	27.15(29.14)	20.84(26.51)	0.314	26.14(30.68)	24.86(27.31)	19.79(22.13)	0.757
Dyspnea	18.01(26.03)	18.89(25.79)	0.878	19.01(28.31)	16.19(23.16)	25.00(31.03)	0.476
Insomnia	28.13(28.17)	27.62(33.98)	0.938	27.05(30.20)	29.78(30.12)	20.83(29.50)	0.571
Appetite loss	14.05(21.72)	12.67(23.83)	0.781	9.71(18.26)	12.88(20.29)	15.43(23.94)	0.687
Constipation	20.22(30.17)	8.89(17.36)	0.032	20.48(29.96)	14.71(24.77)	16.67(27.22)	0.682
Diarrhea	19.66(27.82)	24.05(32.64)	0.500	11.58(18.91)	19.53(28.83)	39.58(34.89)	0.010
Financial difficulties	19.66(27.82)	24.05(32.64)	0.500	11.58(18.91)	19.53(28.83)	39.58(34.89)	0.010
Endocrine symptoms	87.15(20.01)	79.63(28.89)	0.146	88.38(15.89)	85.18(25.83)	82.64(18.58)	0.736
Gastrointestinal symptoms	72.13(23.77)	81.49(21.67)	0.074	75.45(23.13)	76.07(22.71)	75.42(25.49)	0.992
Treatment-related symptoms	80.55(23.90)	84.09(23.84)	0.567	90.28(16.60)	81.85(24.83)	75.00(24.24)	0.264
Social functioning (SF21)	63.28(28.01)	64.44(26.96)	0.850	67.68(25.87)	65.01(29.25)	56.94(18.09)	0.458
Disease-related worries	54.34(30.21)	56.89(27.52)	0.699	52.52(28.16)	58.83(30.53)	48.61(22.91)	0.393
Muscle and/or bone pain	41.67(37.09)	27.78(33.99)	0.086	31.81(36.34)	39.18(36.79)	35.42(37.45)	0.718
Body image	8.60(19.96)	12.22(28.34)	0.481	1.58(7.27)	8.93(22.46)	18.75(29.74)	0.062
Information	8.33(22.22)	6.67(13.56)	0.706	10.61(18.93)	8.19(22.07)	4.17(11.38)	0.618
Sexual functioning	21.79(33.58)	30.55(39.21)	0.320	26.67(38.21)	22.67(35.28)	22.22(25.95)	0.919

Abbreviations: GEP, gastroenteropancreatic; M, mean; NEN, neuroendocrine neoplasms; SD, standard deviation; SF21, social functioning of the QLQ-GINET21; SSA, somatostatin analogues.

Table 4. Health-related quality of life according to tumor biology and surgery

	Tumor Biology			Surgery		
	Sporadic N = 61 M(SD)	Hereditary N = 37 M(SD)	*P*-value	No N = 50 M(SD)	Yes N = 49 M(SD)	*P*-value
Physical functioning	73.07(24.88)	89.61(14.69)	<0.001	79.16(23.29)	80.53(21.83)	0.766
Role functioning	70.81(30.19)	84.04(26.95)	0.031	75.19(31.67)	76.91(27.75)	0.777
Emotional functioning	73.07(24.88)	89.61(14.69)	<0.001	79.16(23.29)	80.53(21.83)	0.776
Cognitive functioning	73.06(24.88)	89.35(14.79)	<0.001	78.96(23.24)	80.53(21.83)	0.733
Social functioning	73.07(24.88)	89.61(14.69)	<0.001	79.16(23.29)	80.53(21.83)	0.766
Global health score	59.88(21.91)	74.09(20.86)	0.002	62.29(22.79)	68.81(21.71)	0.153
Fatigue	43.78(28.44)	21.67(23.30)	<0.001	34.58(27.33)	35.19(29.34)	0.915
Nausea and vomiting	10.37(19.44)	10.66(17.19)	0.942	11.10(18.51)	8.73(17.01)	0.512
Pain	29.92(30.06)	17.12(22.65)	0.028	27.43(29.22)	21.26(24.88)	0.265
Dyspnea	20.27(27.23)	14.51(22.63)	0.282	18.13(26.37)	18.44(25.28)	0.953
Insomnia	33.57(31.94)	18.02(23.03)	0.006	31.15(30.29)	24.29(29.43)	0.261
Appetite loss	15.96(24.53)	9.37(16.88)	0.153	14.45(22.44)	10.76(18.15)	0.374
Constipation	16.41(26.09)	18.48(29.86)	0.719	22.24(31.57)	10.56(18.23)	0.027
Diarrhea	25.09(32.39)	13.77(21.16)	0.039	17.31(23.47)	24.68(33.66)	0.215
Financial difficulties	25.09(32.39)	13.77(21.16)	0.039	17.31(23.47)	24.68(33.66)	0.215
Endocrine symptoms	82.29(26.67)	89.19(15.38)	0.112	84.87(21.29)	86.11(24.09)	0.791
Gastrointestinal symptoms	72.87(24.09)	79.28(21.82)	0.193	73.56(22.91)	78.08(23.18)	0.342
Treatment-related symptoms	80.55(21.75)	83.91(26.53)	0.562	81.48(25.13)	82.38(22.48)	0.874
Social functioning (SF21)	57.44(27.62)	73.72(23.88)	0.004	63.00(25.44)	65.51(28.46)	0.652
Disease-related worries	47.98(29.79)	66.07(24.97)	0.003	58.63(26.51)	52.60(30.99)	0.314
Muscle and/or bone pain	45.73(36.57)	24.32(33.93)	0.005	36.17(38.59)	37.50(34.81)	0.860
Body image	12.99(26.99)	3.81(10.76)	0.023	7.41(19.96)	10.42(23.97)	0.514
Information	10.17(20.76)	4.50(17.85)	0.174	5.68(18.80)	10.42(20.81)	0.247
Sexual functioning	28.15(36.89)	19.19(32.31)	0.268	24.77(34.62)	22.22(34.27)	0.748

Abbreviations: GEP, gastroenteropancreatic; M, mean; NEN, neuroendocrine neoplasms; SD, standard deviation; SF21, social functioning of the QLQ-GINET21; SSA, somatostatin analogues.

HRQoL as prevalently low but, at the same time, they feel that their specific psychological, social, and physical functioning status is not particularly damaged by the NEN. These findings may inform psychological clinical practice addressed to patients with NEN, as they seem to suggest focusing the intervention on the patient's general health situation rather than on definite dimensions related to specific functioning areas. However, self-report questionnaires on QoL are subject to a scale perception bias (30) and a more objective evaluation based on a multi-informant methodological approach is needed to draw more accurate conclusions. Future research should consider matching information on patients' HRQoL coming from multiple sources, such as caregivers and physicians.

Regarding our first hypothesis (ie, an association between the severity of the clinical status and HRQoL), we have found further evidence for the abovementioned differentiation between functional status and the GH/QoL score. Indeed, both the presence of metastasis and the greater number of therapies seem not to affect the specific functioning areas but only the GH/QoL score as well as specific symptoms. Specifically, our findings seem to indicate that the most significant physical symptoms provoked by the severity of the clinical status are fatigue, diarrhea, and constipation, which are typically NEN-related physical symptoms. However, our data indicate that the severity of the clinical status (specifically, the presence of metastasis) impacted also on the financial resources of the participants. If we consider the most affected physical areas (ie, fatigue, diarrhea, and constipation), it seems plausible to hypothesize that such physical impairments could increase daily fatigue and decrease physical strength and, as a consequence, make the management of one's job more difficult or even unbearable. Future studies may consider assessing the relationships between the severity of NENs, HRQoL, physical symptoms, and job satisfaction or loss, making inferences about the causality and temporality of such relationships. Indeed, previous studies have provided evidence about the impact of physical symptoms on the performance of work tasks and about the diminished work productivity of people with tumors (as in the case of women with breast cancer) (31). However, to the best of our knowledge, no

previous studies have explored this topic in patients with NEN. Future studies should also consider assessing the role of socioeconomic status (SES; ie, income), as it is plausible to hypothesize that the severity of the clinical status would impact people with low SES more than those with high SES. Furthermore, our findings indicate that the severity of the clinical status, and specifically the greater number of therapies, affects also the patient's body image. Body image problems are emotional reactions to physical changes, in this case produced by cancer-related treatments. Cancer patients cannot control all the bodily changes produced by the necessary treatments, especially in terms of the extent of severity (32). Thus, it is plausible to hypothesize that the greater the number of therapies the patient experiences, the more likely it is that bodily changes negatively affecting the patient's body image will be caused. However, this topic also seems not to have been previously and specifically addressed in patients with NEN, indicating a potential new research area to explore in future studies.

In support of our second hypothesis (ie, an association between HRQoL and resilience), we found that resilience seems to have a positive effect on almost all HRQoL dimensions, in particular on the GH/QoL score, functional status scales, and some physical symptoms (ie, fatigue, pain, insomnia, appetite loss, and sexual problems). This is in line with studies exploring the role of resilience in other malignancies. For instance, resilience resulted in a positive association with GH/QoL score and functional scales and a negative association with physical symptoms in patients with breast cancer (33). Similarly, resilience resulted in an association with overall HRQoL and socioemotional functioning in patients treated for cancer of the head and neck (34). These findings indicate that resilience may be considered as a significant protective factor that both medical and clinical psychological interventions should promote. Indeed, resilience has been described as a dynamic process, helping adult cancer patients to face the adversity related to the cancer experience and expressed by biological (eg, brain structure and neurobiological systems), personal (eg, hope, optimism, and active coping), and environmental factors (eg, social support and community connectedness) (35). Thus, our findings confirm previous studies which have highlighted that cancer patients with a higher resilience experience less distress and a higher HRQoL (36). However, when the interaction between the severity of the clinical status dimensions and resilience was considered, resilience proved to buffer only the effects of the presence of metastasis on constipation and of the greater number of therapies on diarrhea and financial problems. These findings, which indicate that resilience moderates the effect of clinical severity on very few HRQoL dimensions, can be explained in light of the evidence that, in our sample, the severity of the clinical status did not affect the HRQoL significantly, confirming what Seiler and Jenewein have reported (18), or, rather, that disease severity is not closely associated with the resilience of cancer patients. This may indicate that resilience should be promoted in patients with a NEN beyond the severity of their clinical status.

Finally, in support of the hypotheses concerning the role of the NEN clinical heterogeneity (ie, the 3rd, 4th, 5th, and 6th hypotheses), we have found that patients with NEN in districts other than the GEP and those in follow-up without any therapy perceive only a few physical symptoms, fewer than their counterparts (ie, nausea/vomiting and constipation in the first group and diarrhea and financial difficulties in the second). However, the dimension of clinical heterogeneity, which seemed to impact most significantly on the HRQoL differences is that relating to the difference between sporadic and hereditary NENs. Specifically, patients with a sporadic NEN seemed to perceive their functional status and GH/QoL as better, and their disease-related worries as less severe, than those with a hereditary NEN, although their physical symptoms were perceived as worse than their counterparts. These findings may be due to the fact that, compared with sporadic NENs, hereditary NEN diagnoses generally occur at an earlier age and in a less advanced stage than those of sporadic NENs (2, 3), due to familial screenings, or rather in a stage where the physical symptoms are generally not yet present. However, patients with hereditary NENs, such as in MEN 1, have several associated endocrine or nonendocrine diseases, and this may negatively affect their HRQoL, as well as increasing their disease-related worries. On the contrary, patients with sporadic NENs may perceive their physical symptoms as worse than patients with hereditary NENs due to the often more advanced stage of the disease, although their general HRQoL and functional areas may be perceived as better because of their greater possibility of recovery.

This study has significant limitations, which must be considered in interpreting the results. First, we have reported preliminary data from an extensive longitudinal study, thus using a cross-sectional study design that has prevented us from exploring changes in the explored variables over time. Secondly, although the power analysis indicated that our sample size was sufficient to perform our analyses, the sample is still relatively small, and the results cannot be generalized to the whole population with NENs. Thirdly, due to the low number of patients benefiting from peptide receptor radionuclide therapy, we could not assess any potential differences on HRQoL between those using and not using this therapy. Similarly, due to the sample size, it was not possible to further differentiate the patients, for instance considering the role of chemotherapy, which has important systemic side effects; the peculiarity of intestinal NENs, which generally lead to more disease- and treatment-related symptoms; and the role of therapy with SSA related to different primary

and the presence of metastases. Thus, future research should replicate our study with expanded samples, assessing the role of further differences in relation to HRQoL.

Conclusions

The findings from this study deepen our understanding of the role of severity and clinical heterogeneity in influencing the HRQoL of patients with NENs. Overall, based on our preliminary results, it seems possible to argue that, in assessing the health status of patients with a NEN, endocrinologists should focus particular attention on the relationships that the presence of metastasis and multiple therapies have with HRQoL, as well as on the diverse effects that sporadic and hereditary NENs may have on HRQoL. Furthermore, our study highlights that resilience is a crucial dimension able to promote the HRQoL in patients with NEN and that it should be promoted by psychological clinical interventions and assessed by endocrinologists, even in patients with lower levels of clinical severity.

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