European Journal of Endocrinology, 2026, 194, 431–439
https://doi.org/10.1093/ejendo/lvag052
Published: 24 March 2026
Original Research

Quality of life questionnaire development and validation for adrenocortical carcinoma patients

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Abstract

ACC patients' quality of life may be impacted by symptoms related to cancer or treatments, as well as emotional, spiritual, existential, social, economic, and sexual aspects. The aim was the development and psychometric validation of a new instrument (QoLACC) for measuring Patient-Reported Outcome in patients with ACC. The study was conducted from October 2024 to January 2025 at the Oncology Unit of Brescia's ASST. Fifteen patients and 15 physicians graded the comprehensibility/difficulty and relevance of the items of QoLACC whereas 37 consecutive patients assessed psychometric validity. Comprehensibility, difficulty and clinical relevance of the items to include in the QoLACC questionnaire were assessed by selected ACC patients and clinicians. Validated scales were co-administered to the developed QoLACC questionnaire to assess physical and psychological symptoms, and the test-retest reliability and construct validity psychometric validation were performed. The QoLACC items showed excellent content validity [0.93-1.00] and acceptable to excellent comprehensibility [0.80-1.00] and difficulty [0.80-1.00], with minor exceptions. Item analysis showed good discriminant capability and response variability. The total questionnaire has good reliability (the intraclass correlation coefficient (ICC) was 0.870 [95% CI: 0.734-0.937]) and construct validity proved by the moderate to strong correlations [0.39-0.62] between the QoLACC and the EORTC item 29 and item 30, the QoLACC financial section and the COST (0.47), and the QoLACC spiritual section and the JSWBS (0.60). We defined and validated the Italian questionnaire aiming to explore ACC patients' quality of life, to help the Health Care Professionals to manage and support these patients.

Keywords adrenocortical carcinoma, quality of life, PROMs, content validity, psychometric validation

Significance

Adrenocortical carcinoma (ACC) is a rare malignancy associated with significant symptom burden and treatment-related toxicity, yet tools specifically designed to evaluate its multidimensional impact on patients' quality of life remain limited. We developed and psychometrically validated the QoLACC, a new Italian patient-reported outcome measure specifically designed for ACC patients. Unlike existing instruments, QoLACC captures not only physical symptoms and treatment-related toxicity but also psychosocial, financial, and spiritual dimensions of patient experience. The questionnaire demonstrated excellent content validity, good reliability, and construct validity in ACC patients. This tool may help clinicians better identify unmet needs and guide supportive care strategies, ultimately improving the comprehensive management of patients with endocrine malignancies such as ACC.

Introduction

Adrenocortical carcinoma (ACC) is a rare tumor, with an incidence of 0.7-2/1 000 000 people per year. Mitotane is the only adrenolytic drug currently approved by the FDA with specific cytotoxic activity on adrenal cortex cells. Surgical resection is the standard practice for resectable ACC, which may be followed by a minimum of two years of adjuvant therapy with Mitotane.

Received: April 29, 2025. **Revised:** March 9, 2026. **Accepted:** March 11, 2026

Polychemotherapy with Mitotane is typically the primary treatment for unresectable/metastatic tumors.[1-3] Both Mitotane and chemotherapy are associated with high toxicity.[4-6]

Specifically regarding Mitotane, even when its plasma concentration is maintained within the therapeutic range (14-20 mg/L), numerous toxic effects may be observed, likely due to interpatient variability in the activity of hepatic CYP enzymes metabolizing the drug.[7] Mitotane potential related toxic effects include gastrointestinal, endocrine, and neuropsychiatric manifestations. Gastrointestinal effects may include anorexia, diarrhea, nausea, and vomiting; endocrine effects may include hypogonadism, gynecomastia, erectile dysfunction, adrenal insufficiency, and hypothyroidism; neuropsychiatric signs and symptoms may include ataxia, tremors, memory loss, polyneuropathy, dysarthria, dizziness, confusion, sleepiness and depression.[7,8] Other treatments such as surgery, radiotherapy, target therapy and immunotherapy also have many potential side-effects in ACC patients.[9-14]

ACC itself causes a variety of clinical manifestations, which include cancer-related symptoms like weight loss, pain, and fatigue, and specific symptoms of hormonal hypersecretion like Cushing syndrome, virilization, abdominal swelling, and early satiety.[1,15]

Literature indicates that in addition to physical symptoms and toxicity, cancer patients present other reasons that impact their QoL such as loneliness, financial, existential and spiritual distress.

Social isolation and/or loneliness affect cancer patients' quality of life and may lead to feeling excluded from their social network. Moreover, studies have shown that loneliness worsens cancer outcomes both in terms of overall mortality and by weakening the immune system, and it is associated with the onset of depression, fatigue, pain, and insomnia.[16-18]

In addition, the financial burden of cancer patients and their families may be negatively impacted by their medical condition, which can increase anxiety and depression and decrease their chances of survival.[19-21]

Lastly, patients with chronic disease need assessment and support for their spiritual/existential needs, which can reduce symptoms such as anxiety and depression[22,23] and improve hope[24] and quality of life.[23,25-27]

Literature data show that the impact of the disease and its treatments on patients' daily lives is multidimensional and variable depending on the primary tumor, treatment-related toxicity, and patients' personal experiences. Therefore, it is necessary to develop a specific questionnaire to avoid underestimating the total suffering of ACC's patients' cancer and/or treatment- related.

Two questionnaires are available and validated in Italian language to assess the cancer patient's quality of life: EORTC QLQ-C30 and AddiQoL for symptoms.[28-30] However, if we want to examine the patient's suffering and unmet needs in detail, these questionnaires are not sufficient.

In 2022 a questionnaire for ACC patients was published,[31] designed to be used alongside the EORTC QLQ-C30. Questions about financial toxicity and spiritual pain are not part of this questionnaire. Hence, there is a need to develop a specific Patient-Reported Outcome Measure (PROM) to assess the quality of life of ACC patients, and to validate its content and psychometric properties in Italian.

This study is designed to validate a new PROM called QoLACC in patients with ACC, which was created by integrating EORTC QLQ-C30[28,30] and AddiQoL,[29] and adding new items.

Materials and methods

The study was conducted from October 2024 to January 2025 at the Oncology Unit of Brescia's ASST, all patients signed an informed consent. Protocol has been approved by the local Committee for Ethics (approval number N6361). This study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Study population

Consecutive ACC patients who were being visited for active adjuvant/palliative treatment or follow-up after discontinuation of adjuvant therapy were invited to take part in the study.

Inclusion criteria were the followings: age ≥18 years; histological diagnosis of ACC; current mitotane treatment or previous mitotane therapy; adequate knowledge of the Italian language to understand the questionnaires; life expectancy >6 months; Karnofsky Performance Status >60; health conditions that enabled autonomy in filling out questionnaires, providing personal information to medical staff, and signing informed consent; absence of cognitive impairments that could interfere with comprehension. Treatment with antipsychotic, antidepressant, or anxiolytic medications for < 3 months were exclusion criteria.

Measures and procedures

The study was designed as a prospective monocentric observational study and consisted in 2 phases.

Phase 1, CONTENT SELECTION AND VALIDATION:

For the content validation phase, ACC patients were asked to grade the comprehensibility and difficulty of QoLACC's items, previously selected both by integrating items from the EORTC QLQ-C30,[28] AddiQoL,[29] and the ACC-QOL (Dutch questionnaire)[31] and by adding specific items, defined by us, not included in these questionnaires.

At the same time a group of physicians, faculty of the Oncology Unit, were asked to grade comprehensibility, difficulty and content validity (relevance) of each item.

Phase 2, PSYCHOMETRIC VALIDATION:

For the psychometric validation phase, at the time of enrollment (T0) patients completed the QoLACC questionnaire during a scheduled visit along with five other international questionnaires validated in Italian: COmprehensive Score for financial Toxicity (COST);[32-34] Three-Item UCLA Loneliness Scale (3-ULS);[35] Jarel Spiritual Well-Being Scale (JSWBS);[36,37] EORTC QLQ-C30[28] (only questions not included in QoLACC); AddiQoL[29] (only questions not included in QoLACC).

After 20-30 days (T1), patients were asked to complete only the QoLACC questionnaire again to assess test-retest reliability and construct validity.

Before filling out the questionnaires, the researchers explained the aims and procedures of the study to the patients. After obtaining informed consent, participants were asked to complete a socio-demographic data form, which included initials, gender, nationality, age, education level, marital status, housing situation, caregiver autonomy, occupation, geographic origin, travel or transfers for treatment, financial support, and religious beliefs. Physicians then completed the clinical data section, which included the date of first cancer diagnosis, disease stage, recent oncological treatments (last two months), Karnofsky performance status, non-oncological comorbidities, and current medical therapy. During patient participation, at least one physician was available to clarify to patients that they were not expected to answer the questions but to evaluate their comprehensibility and difficulty, and to address any questions the patients might have. The questionnaires were anonymous.

Going into detail, the following questionnaires were filled at T0 and took ∼20 minutes to complete by the patients.

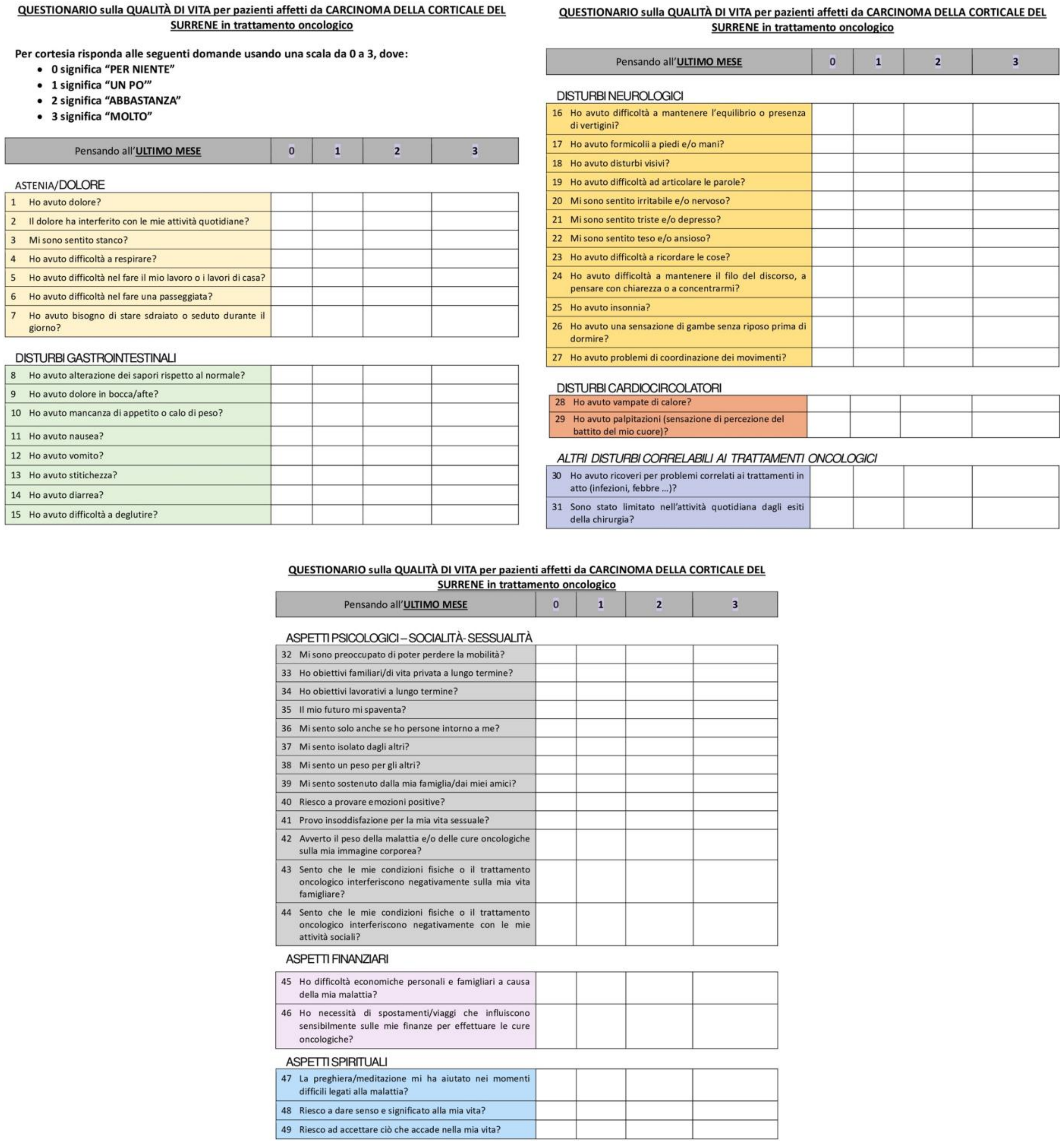
1. QoLACC—reported in Figure 1 (translation in English is available as Figure S1) a 49-item questionnaire divided into eight sections: fatigue/pain; gastrointestinal symptoms; neuropsychiatric symptoms (labeled neurological symptoms for less negative patient impact); cardiovascular symptoms; other symptoms related to oncological treatments; psychological, social, and sexual aspects; financial aspects; spiritual aspects. The questionnaire was developed through the integration of items from the EORTC QLQ-C30[28] and the AddiQoL[29] questionnaires. Additional items were included based on specific symptoms and concerns of ACC patients, and four items were derived from Steenaard et al.'s tool.[31] Patients rated each item on a Likert type 4-point scale based on the intensity of symptoms experienced in the last month, where: 0 = "Not at all"; 1 = "A little"; 2 = "Moderately"; 3 = "A lot". The scores for the different subscales were computed by adding the scores of the individual items included in each subscale. Similarly, the total score was obtained by adding together the scores of all items in the questionnaire. The following modifications were made to enhance the relevance of the questionnaire for ACC patients:
    - (a) Gastrointestinal symptoms: we added item 8 on taste alterations, item 9 on oral ulcers and pain, item 15 on difficulty swallowing, and on item 10 weight loss was also included, differently from the existing QLQ-C30 item that only mentioned loss of appetite.
    - (b) Neurological symptoms: we added item 16 on dizziness, item 17 on tingling, item 18 on visual disturbances, item 19 on dysarthria and item 26 on restless legs. We also derived item 27 on movement coordination problems from Steenaard et al.[31]
    - (c) Cardiovascular symptoms: we added item 28 on flushing, and we derived item 29 on palpitations from Steenaard et al.[31]
    - (d) Other symptoms related to oncological treatments: we added this section that includes item 30 on the impact of treatments on hospitalization and item 31, derived from Steenaard et al.,[31] about the impact of surgical outcomes.
    - (e) Psychological, social, and sexual aspects: we added this section that has items about long-term family/social and work goals (items 33 and 34), feelings of loneliness and isolation (items 36 and 37), feeling like a burden and family support (items 38 and 39), being able to experience positive emotions (item 40), concerns about loss of mobility (item 32), derived from Steenaard et al.,[31] and concerns about future prospects (item 35), body image (item 42) and the impact of disease/treatment on family life and social activities (items 43 and 44). There is also an item (41) on sexual satisfaction (included in AddiQoL but absent in QLQ-C30).
    - (f) Financial aspects: we included this section of two items (45 and 46) to assess financial burden, an area missing from AddiQoL and Steenaard et al.'s[31] tool.
    - (g) Spiritual aspects: we added this section of three items (47-49) to explore spiritual well-being, which is not covered by QLQ-C30, AddiQoL, or Steenaard et al's tool.[31]
2. COST: an 11-item questionnaire measuring financial toxicity related to illness. It is part of the Functional Assessment of Chronic Illness Therapy (FACIT) system.[32,33] The Italian version[34] includes a 5-point Likert scale ranging from 0 ("not at all") to 4 ("very much"), with higher scores indicating lower financial toxicity.
3. 3-ULS: a brief scale measuring social isolation and loneliness,[35] derived from the revised UCLA Loneliness Scale.[38] Each item is rated on a 3-point scale (1 = "hardly ever", 2 = "sometimes", 3 = "often"). Higher scores indicate greater loneliness.
4. JSWBS: a scale measuring spiritual well-being, adapted to Italian culture. It consists of 16 items rated on a 5-point Likert scale (1 = "strongly disagree" to 5 = "strongly agree"), divided into three factors: Faith and Belief, Meaning in Life, and Quality of Relationships.[37]
5. EORTC QLQ-C30: a widely used tool to assess quality of life in cancer patients, incorporating multiple functional and symptom scales, and one global health scale.[28,39] Only the items not already covered by QoLACC (Items 1, 5, 29, and 30) were administered in this study.
6. AddiQoL: a 30-item disease-specific questionnaire for patients with Addison's disease,[29] used here because ACC patients often experience adrenal insufficiency due to surgery or mitotane treatment. Only selected items[1,8,9,11,15,17,19-22,24-30] not covered by QoLACC were administered.

At T1, after 20-30 days, patients completed only the QoLACC, which took less than 8 minutes (5-8 minutes). T1 responses could be submitted during a follow-up visit or sent via email from home.

Analysis strategy

All analyses were conducted on SPSS (version 28.0). Descriptive statistics, such as frequencies, percentages, mean ± standard deviation (SD) were used to describe the sample's characteristics.

For content validity, the relevance, comprehensibility and difficulty scores were recoded into "present/absent" and the indices of comprehensibility (CI), difficulty (DI) and content validity (CVI) were calculated dividing the number of respondents who believed the item was "present" by the total number of respondents. Item indices <0.78 were considered inadequate and require further analysis, values between 0.80 and 0.89 were considered acceptable and over 0.90 excellent. Global indices of



QUESTIONARIO sulla QUALITÀ DI VITA per pazienti affetti da CARCINOMA DELLA CORTICALE DEL SURRENE in trattamento oncologico

Per cortesia risponda alle seguenti domande usando una scala da 0 a 3, dove:

- **0 significa "PER NIENTE"**
- **1 significa "UN PO'"**
- **2 significa "ABBASTANZA"**
- **3 significa "MOLTO"**

Pensando all'**ULTIMO MESE**	0	1	2	3
ASTENIA/DOLORE				
1 Ho avuto dolore?				
2 Il dolore ha interferito con le mie attività quotidiane?				
3 Mi sono sentito stanco?				
4 Ho avuto difficoltà a respirare?				
5 Ho avuto difficoltà nel fare il mio lavoro o i lavori di casa?				
6 Ho avuto difficoltà nel fare una passeggiata?				
7 Ho avuto bisogno di stare sdraiato o seduto durante il giorno?				
DISTURBI GASTROINTESTINALI				
8 Ho avuto alterazione dei sapori rispetto al normale?				
9 Ho avuto dolore in bocca/afte?				
10 Ho avuto mancanza di appetito o calo di peso?				
11 Ho avuto nausea?				
12 Ho avuto vomito?				
13 Ho avuto stitichezza?				
14 Ho avuto diarrea?				
15 Ho avuto difficoltà a deglutire?				

QUESTIONARIO sulla QUALITÀ DI VITA per pazienti affetti da CARCINOMA DELLA CORTICALE DEL SURRENE in trattamento oncologico

Pensando all'**ULTIMO MESE**	0	1	2	3
DISTURBI NEUROLOGICI				
16 Ho avuto difficoltà a mantenere l'equilibrio o presenza di vertigini?				
17 Ho avuto formicolii a piedi e/o mani?				
18 Ho avuto disturbi visivi?				
19 Ho avuto difficoltà ad articolare le parole?				
20 Mi sono sentito irritabile e/o nervoso?				
21 Mi sono sentito triste e/o depresso?				
22 Mi sono sentito teso e/o ansioso?				
23 Ho avuto difficoltà a ricordare le cose?				
24 Ho avuto difficoltà a mantenere il filo del discorso, a pensare con chiarezza o a concentrarmi?				
25 Ho avuto insonnia?				
26 Ho avuto una sensazione di gambe senza riposo prima di dormire?				
27 Ho avuto problemi di coordinazione dei movimenti?				
DISTURBI CARDIOCIRCOLATORI				
28 Ho avuto vampate di calore?				
29 Ho avuto palpitazioni (sensazione di percezione del battito del mio cuore)?				
ALTRI DISTURBI CORRELABILI AI TRATTAMENTI ONCOLOGICI				
30 Ho avuto ricoveri per problemi correlati ai trattamenti in atto (infezioni, febbre ...)?				
31 Sono stato limitato nell'attività quotidiana dagli esiti della chirurgia?				

QUESTIONARIO sulla QUALITÀ DI VITA per pazienti affetti da CARCINOMA DELLA CORTICALE DEL SURRENE in trattamento oncologico

Pensando all'**ULTIMO MESE**	0	1	2	3
ASPETTI PSICOLOGICI – SOCIALITÀ- SESSUALITÀ				
32 Mi sono preoccupato di poter perdere la mobilità?				
33 Ho obiettivi familiari/di vita privata a lungo termine?				
34 Ho obiettivi lavorativi a lungo termine?				
35 Il mio futuro mi spaventa?				
36 Mi sento solo anche se ho persone intorno a me?				
37 Mi sento isolato dagli altri?				
38 Mi sento un peso per gli altri?				
39 Mi sento sostenuto dalla mia famiglia/dai miei amici?				
40 Riesco a provare emozioni positive?				
41 Provo insoddisfazione per la mia vita sessuale?				
42 Avverto il peso della malattia e/o delle cure oncologiche sulla mia immagine corporea?				
43 Sento che le mie condizioni fisiche o il trattamento oncologico interferiscono negativamente sulla mia vita famigliare?				
44 Sento che le mie condizioni fisiche o il trattamento oncologico interferiscono negativamente con le mie attività sociali?				
ASPETTI FINANZIARI				
45 Ho difficoltà economiche personali e famigliari a causa della mia malattia?				
46 Ho necessità di spostamenti/viaggi che influiscono sensibilmente sulle mie finanze per effettuare le cure oncologiche?				
ASPETTI SPIRITUALI				
47 La preghiera/meditazione mi ha aiutato nei momenti difficili legati alla malattia?				
48 Riesco a dare senso e significato alla mia vita?				
49 Riesco ad accettare ciò che accade nella mia vita?				

Figure 1 ACC patients quality of life questionnaire (Italian version).

comprehensibility, difficulty, and relevance were obtained computing the mean of the item CIs, DIs, and CVIs.

The management of missing data was considered during the preliminary analysis. However, no missing values were detected, as the questionnaire was designed to require mandatory responses for all items. This design choice, together with the relatively small sample size, ensured complete data collection. Therefore, no missing data exclusion techniques were required.

The psychometric evaluation included item analysis, reliability assessment, and validity testing. Item analysis was performed by calculating descriptive statistics for each item, including range, mean, and SD. Reliability was assessed using the intraclass correlation coefficient (ICC). According to ICC values, test–retest reliability was interpreted as poor (<0.50), moderate (0.50-0.75), good (>0.75-0.90), or excellent (>0.90). Finally, construct validity was examined by calculating Pearson's

Table 1 Patients' characteristics.

Patients' characteristics	*N* (%)
Age	
31-50 years	10 (27)
51-60 years	13 (35)
61-70 years	11 (30)
Median age [range]	
≥71 years	3 (8)
Sex	
F	24 (65)
M	13 (35)
Nationality	
Italian	37 (100)
Educational level	
Secondary school	7 (19)
High school	21 (57)
University	9 (24)
Marital status	
Single	2 (5)
Married	30 (81)
Divorced	3 (8)
Widowed	2 (5)
Housing situation	
Alone	1 (3)
With relative(s)	34 (92)
Missing	2 (5)
Caregiver autonomy	
Yes	35 (95)
No	1 (3)
Missing	1 (3)
Occupation	
Self-employed	4 (11)
Employee	18 (49)
Retired	9 (24)
Other	6 (16)
Geographic origin	
Northern Italy	22 (60)
Central Italy	7 (19)
Southern Italy	8 (22)
Travel for treatment	
Yes	31 (84)
No	5 (13)
Missing	1 (3)
Transfer for treatment	
Yes	10 (27)
No	26 (70)
Missing	1 (3)
Financial support	
Family	9 (24)
Disability benefits	9 (24)
Other	19 (51)
Religious belief	
Practicing believer	19 (51)
Non-practicing believer	16 (43)
Non-believer	2 (5)

Table 2 Tumor stage and treatments.

ACC stage and treatments	*N* (%)
Disease stage	
Adjuvant treatment	13 (35)
Metastatic treatment	24 (65)
Recent oncological treatments	
Mitotane alone	26 (70)
Mitotane + chemotherapy	4 (11)
Mitotane + chemotherapy + immunotherapy	5 (13)
Mitotane + immunotherapy	1 (3)
Mitotane + radiotherapy	1 (3)
Karnofsky performance status	
60	1 (3)
80	2 (5)
90	7 (19)
100	26 (71)
Missing	1 (3)

correlation coefficients between the QoLACC and the other variables measured in the study. Correlation coefficients of 0.10, 0.30, and 0.50 or higher were interpreted as indicating weak, moderate, and strong associations, respectively.[40]

Results

Study population

For content validation, QoLACC was administered to 15 consecutive patients (67% women), median age 56 years (range 37-71 years), all of them had been treated or were in treatment with mitotane.

The 15 clinicians enrolled (73% women) were part of the Oncology Unit of the Spedali Civili in Brescia, 53% had <5 years' experience as faculty, 33% between 5 and 10 years, and 13% had more than 10 years as oncologist. Their median age was 29 years (range 25-68).

For psychometric validation, 37 consecutive patients were recruited for T0 (out of 38 patients contacted, only one refused to participate in the study due to excessive fatigue). The patients (65% women) had a median age of 56 years (range 32-81), and their socio-demographic and clinical features are shown in Table 1 and Table 2 respectively. At T1, 33 out of the 37 enrolled patients filled out the QoLACC questionnaire (4 patients were unable to complete it due to logistic problems).

Content validity

The content validity indices for the physician group were excellent across all items (0.93-1.00). The difficulty indices ranged from acceptable to excellent (0.80-1.00), with the exception of items 26 and 49 in the physician group, which showed inadequate values (0.67 and 0.73, respectively). However, these items demonstrated adequate indices in both the patient group and the combined ("all") group, supporting their inclusion in the final version of the questionnaire. Regarding the global scale indices, the questionnaire demonstrated excellent values for the CVI (0.98; 0.97-0.98) and DI (0.94-0.96) (Table 3).

Item analysis

Descriptive analyses for individual items showed good discriminative capability, as for 45 out of 49 items all response options from 0 to 3 were selected. Furthermore, there was good response variability, as for 43 out of 49 items the SD was around 1.

Reliability analysis

The ICC for the total questionnaire showed good test–retest reliability (0.870 [95% CI: 0.734-0.937]). The ICCs for the gastrointestinal symptoms, cardiovascular symptoms, financial aspects, and spiritual aspects sections also showed good reliability (gastrointestinal: 0.862 [95% CI: 0.721-0.932]; cardiovascular: 0.801 [95% CI: 0.592-0.903]; financial: 0.800 [95% CI: 0.595-0.901]; spiritual: 0.845 [95% CI: 0.685-0.923]). The fatigue/pain and psychological, social, and sexual aspects sections showed moderate reliability (fatigue/pain: 0.620 [95% CI: 0.230-0.812]; psychological, social, and sexual aspects: 0.713 [95% CI: 0.419-0.858]), while the neurological symptoms section showed excellent reliability (ICC = 0.911 [95% CI: 0.819-0.956]).

Validity analysis

The questionnaire's construct validity was also provided. In fact, Pearson's coefficients calculated by correlating items 29 and 30 of the EORTC QLQ-C30 both with the total questionnaire and with the individual sections closely related to quality of life (fatigue/pain, gastrointestinal symptoms, neurological symptoms, cardiovascular symptoms, psychological, social, and sexual aspects) demonstrated moderate or strong correlations [0.390-0.623], which reached statistical significance. An exception is represented by 4 coefficients, specifically those correlating the neurological symptoms and psychological, social, and sexual aspects sections with item 29 of the EORTC, and those correlating the cardio section with items 29 and 30 of the EORTC: these, in fact, showed weak correlations [0.199-0.251], which however were not statistically significant. The correlation between the financial section of QoLACC and the COST was moderate (r0.472), while a strong correlation was found between the spiritual section of QoLACC and the JSWBS (0.602); both correlations were statistically significant.

Discussion

The aim of this study was the development and psychometric validation of a new PROM called QoLACC for measuring QoL in patients with ACC, obtained by integrating the items included in the EORTC QLQ-C30,[28] AddiQoL[29] with the addition of aspects regarding the spiritual needs, presence of financial burden and/or social isolation.

Table 3 Relevance (content validity, CVI), comprehensibility (CI), and difficulty (DI) indices of the QoLACC questionnaire's items.

	Physicians (*N* = 15)			Patients (*N* = 15)		All (*N* = 30)	
ITEM	CVI	CI	DI	CI	DI	CI	DI
1	.93	1.00	1.00	1.00	1.00	1.00	1.00
2	.93	1.00	1.00	1.00	.93	1.00	.97
3	1.00	1.00	1.00	1.00	1.00	1.00	1.00
4	.93	1.00	1.00	1.00	1.00	1.00	1.00
5	1.00	1.00	1.00	1.00	1.00	1.00	1.00
6	1.00	1.00	.93	1.00	1.00	1.00	.97
7	1.00	1.00	1.00	1.00	1.00	1.00	1.00
8	.93	1.00	1.00	1.00	.93	1.00	.97
9	.93	1.00	1.00	1.00	1.00	1.00	1.00
10	1.00	1.00	1.00	1.00	1.00	1.00	1.00
11	1.00	1.00	1.00	1.00	1.00	1.00	1.00
12	1.00	1.00	1.00	1.00	1.00	1.00	1.00
13	.93	1.00	1.00	1.00	1.00	1.00	1.00
14	1.00	1.00	1.00	1.00	1.00	1.00	1.00
15	.93	1.00	1.00	1.00	.93	1.00	.97
16	1.00	1.00	1.00	1.00	1.00	1.00	1.00
17	.93	1.00	1.00	1.00	1.00	1.00	1.00
18	1.00	1.00	1.00	1.00	.93	1.00	.97
19	1.00	.93	.93	1.00	1.00	.97	.97
20	1.00	1.00	1.00	1.00	.93	1.00	.97
21	1.00	1.00	1.00	1.00	.93	1.00	.97
22	1.00	1.00	1.00	1.00	.93	1.00	.97
23	1.00	1.00	1.00	1.00	1.00	1.00	1.00
24	1.00	1.00	1.00	1.00	.93	1.00	.97
25	1.00	1.00	1.00	1.00	1.00	1.00	1.00
26	.93	.80	.67	1.00	.93	.90	.80
27	1.00	.87	.93	1.00	1.00	.93	.97
28	1.00	1.00	1.00	1.00	1.00	1.00	1.00
29	1.00	1.00	1.00	1.00	1.00	1.00	1.00
30	1.00	1.00	.93	1.00	.93	1.00	.93
31	1.00	1.00	1.00	1.00	.93	1.00	.97
32	1.00	.87	.80	1.00	.93	.93	.87
33	1.00	.93	.93	.87	.80	.90	.87
34	1.00	.93	.87	.93	.80	.93	.83
35	.93	.93	.80	1.00	1.00	.97	.90
36	1.00	1.00	.87	1.00	1.00	1.00	.93
37	1.00	.87	.80	1.00	1.00	.93	.90
38	1.00	1.00	.87	1.00	1.00	1.00	.93
39	1.00	1.00	.93	1.00	1.00	1.00	.97
40	1.00	.93	.87	1.00	1.00	.97	.93
41	1.00	1.00	1.00	1.00	1.00	1.00	1.00
42	1.00	.87	.87	.80	.87	.83	.87
43	1.00	.93	.80	1.00	1.00	.97	.90
44	1.00	.87	.80	.93	.93	.90	.87
45	.93	1.00	1.00	.93	.93	.97	.97
46	1.00	.93	.93	.93	.93	.93	.93
47	.93	1.00	1.00	.93	.87	.97	.93
48	.93	.87	.80	.93	.93	.90	.87
49	1.00	.87	.73	1.00	1.00	.93	.87
Scale Indices	.98	.97	.94	.98	.96	.98	.95

For ACC standard treatments are limited: surgery and mitotane for early stage, chemotherapy (EDP-M regimen) for metastatic setting, while target therapy and immune therapy can be considered for specific case in clinical trial.[1,3,41] Each of these therapeutic approaches correlate with well-known potential toxicities, such as hospitalization for surgical complications, infections, gastrointestinal, haematological, psychological issues.[4-7,9,11,13-15]

The cost of necessary drugs and treatments is covered by the Italian National Health System. It's worth noting, however, that patients come from all over Italy to ASST Spedali Civili Oncology Unit, which is a referral center for ACC. The patient's clinical condition may necessitate a lengthy trip to the hospital for hospitalization, therapies, or medical examinations, especially if remote examinations are not feasible. Patients and their families are responsible for paying for travel and accommodations themselves, and these expenses, which may occur monthly and last for several days, (eg, for chemotherapy treatment requiring hospitalization), can significantly affect finances.

In order to better understand the QOL impact of peculiar aspects of ACC, in 2022, the ACC-QOL questionnaire was proposed along with the EORTC QLQ-C30, consisting of 26 questions and including three scales (mitotane side-effects, hypercortisolism/hydrocortisone effects and emotional effects) and three single items (physical limitations due to surgery, virilization, need for peer support).[31]

The potential toxicity of ACC treatments and the specific symptoms that ACC patients may experience due to the tumor characteristics necessitate the creation of a specific PROM for them,[15] that could also gauge potential financial difficulties, loneliness/social isolation, and spiritual needs, in addition to specific clinical aspects. Therefore, QoLACC was developed. It is the first Italian tool designed specifically to assess the quality of life of ACC patients, which include gastrointestinal, neurological, cardiovascular symptoms, and other symptoms related to oncological treatments, in addition to psychological, social, sexual, financial and spiritual aspects. The objective is to thoroughly evaluate the primary negative consequences of the disease and/or the oncological treatments. Unlike the ACC-QOL—which was constructed to complement the EORTC QLQ-C30—the QoLACC was intentionally developed as a stand-alone, wide-spectrum instrument capturing all symptom clusters relevant to ACC, including those outside the EORTC item bank.

The questionnaire's contents were validated based on the analysis indicating that the comprehensibility, difficulty, and relevance of the items ranged from acceptable to excellent for all items, except for the difficulty of items 26 and 49, but only for the physicians' group. These items deal with the sensation of restless legs (item 26) and the ability to accept the circumstances in one's life (item 49). The reason why physicians thought these two items were difficult globally could be that they underestimated patients' intuition in answering questions about restless leg syndrome. Furthermore, they may have considered question 49 as being emotionally challenging for patients. However, the difficulty of these questions was found to be adequate in the patients' group and the "whole" group, leading to their inclusion in the final questionnaire.

The psychometric properties of the questionnaire were also tested. Item analysis revealed both a good discriminative capability of the questions and good response variability. As shown by the ICCs, reliability was globally good, with moderate to excellent indices for the total score and individual sections. Construct validity of the questionnaire was demonstrated, with moderate to strong correlations with other QoL indicators (items 29 and 30 of the EORTC QLQ-C30), a moderate correlation with the COST, an indicator of financial toxicity, and a strong correlation with the JSWBS, an indicator of spiritual well-being.

Ultimately, the statistical analyses conducted led to the validation of the QoLACC questionnaire. Although the study sample may appear limited for this type of analysis it was composed of 15 patients and 15 physicians for content validation, 37 patients for psychometric validation at T0 and 33 patients at T1 it can be considered adequate given the rarity of ACC, a tumor that only has a few referral centers in Italy and in Europe.

Due to the rarity of this tumor a multicentric study could be useful to confirm our results involving other referral Italian center for ACC. In future research, with a larger and more representative sample, we plan to perform confirmatory factor analyses (CFA) to test the dimensionality of the instrument. Alternatively, preliminary exploratory approaches (eg, PCA) may be used in an exploratory and purely descriptive manner, with appropriate caution.

The questionnaire was accepted by the patients who were able to complete it out anonymously in about 5-8 minutes, complaining no issues.

Conclusions

This study provides the first Italian PROM to globally assess the quality of life for ACC patients. This is a new tool able to investigate in a comprehensive manner the cancer/treatment-related symptoms besides spiritual/financial/psycho-social aspects. Considering the rarity and complexity of the ACC, this questionnaire could assist clinicians in gaining a more thorough understanding of the patient's potential total suffering.

Acknowledgments

The authors would like to thank all clinicians and patients involved in psychometric validation of QoLACC.

Authors' contributions

Marta Laganà (Conceptualization, Data curation, Formal analysis, Supervision, Validation [equal]), Deborah Cosentini (Formal analysis, Investigation, Supervision [equal]), Nichole Farina (Conceptualization, Data curation, Formal analysis, Investigation, Writing—original draft [equal]), Francesca Consoli (Investigation, Methodology, Supervision, Writing—review & editing [equal]), Carlotta Tagliaferro (Formal analysis, Methodology [equal]), Francesca Chiesi (Methodology, Resources, Supervision, Validation [equal]), Benedetta Trevisan (Writing—original draft [equal]), Valentina Cremaschi (Formal analysis, Methodology, Writing—original draft [equal]), Davide Lorenzo Bettini (Conceptualization, Formal analysis, Validation, Visualization, Writing—original draft [equal]), Alfredo Berruti (Formal analysis, Writing—review & editing [equal]), and Carla Ida Ripamonti

(Conceptualization, Methodology, Writing—review & editing [equal])

Supplementary material

Supplementary material is available at *European Journal of Endocrinology* online.

Conflict of interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

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