RESEARCH

General psychopathological symptoms in children, adolescents, and young adults with anorexia nervosa—a naturalistic study on follow-up and treatment

Jacopo Pruccoli[1,2] · Francesca Chiavarino[1,2] · Camilla Nanni[2] · Antonia Parmeggiani[1,2]

Abstract

Recent research has assessed the role of general psychopathological symptoms in the natural history of mental health conditions, including anorexia nervosa (AN) in adults and obesity in children. Nevertheless, literature assessing general psychopathological symptoms in young patients with AN and their potential prognostic role in long-term outcomes is lacking. Observational, naturalistic study, involving young patients hospitalized for AN. General psychopathological symptoms were assessed by administering Symptom Check List-90-R (SCL-90-R) at admission (T0) and discharge (T1). AN-specific psychopathology was assessed with Eating Disorders Inventory-3 Eating Disorder Risk (EDRC) and Body Uneasiness Test Global Severity Index (BUT-GSI). Potential T0-T1 modifications of general psychopathological symptoms and their possible associations with baseline psychopathological, weight, and psychopharmacological variables were assessed with a generalized linear model (GLM), corrected for baseline SCL-90-R scores. Then, possible associations between T0 general psychopathological symptoms and the risk of re-hospitalization at 1 year were assessed with the Kaplan–Meier method and Cox regression. This study enrolled 133 patients (mean age 16.9 ± 2.9 years, F = 91.8%). A significant T0-T1 reduction ($p < 0.001$) in almost all the general psychopathological symptoms (except paranoia) emerged. The GLM revealed that higher EDI-3 EDRC scores were associated with higher T1 SCL-90-R scores in multiple domains. Cox regressions revealed a predictive role of SCL-90-R interpersonal sensitivity ($B = 0.113$, hazard ratio = 1.119, $p = 0.023$) on the risk of re-hospitalization at 1 year.

Conclusion: General psychopathological symptoms in young patients with AN may be influenced by hospital treatment interventions and have a potential prognostic role on post-discharge outcomes. Further longitudinal studies are required.

What is Known:
- *General psychopathological symptoms represent a relevant feature that clinicians should consider in the diagnosis, treatment, and prognosis of multiple psychiatric conditions. Co-occurring psychiatric comorbities, moreover, have been documented to impact individuals diagnosed with Anorexia Nervosa (AN) in the developmental age. Despite this evidence, the literature lacks studies assessing the occurrence and impact of general psychopathological symptoms in young patients with AN.*

What is New:
- *The clinical picture of children, adolescents, and young adults with AN mays be impacted by multiple general psychopathological symptoms, including Somatization, Obsession-compulsion, Interpersonal sensitivity, Depression, Anxiety, Hostility, Phobia, Paranoia, and Psychoticism, which may improve with a multidisciplinary hospital intervention. The occurrence of these symptoms, particularly "interpersonal sensitivity", may negatively impact the prognosis of the affected patients.*

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✉ Antonia Parmeggiani
  Antonia.parmeggiani@unibo.it

Extended author information available on the last page of the article

Abbreviations

ADR	Adverse drug reactions
APC	Affective problems
AN	Anorexia nervosa
AAP	Atypical antipsychotics

BED	Binge eating disorder
ANBP	Binge-purging AN
BD	Body dissatisfaction
BMI	Body mass index
BUT-GSI	Body Uneasiness Test Global Severity Index
B	Bulimia
BN	Bulimia nervosa
DT	Drive for thinness
EDRC	Eating disorder risk
EDI-3	Eating Disorders Inventory-3
EDRC	Eating Disorders Inventory-3 Eating Disorder Risk
EKG	Electrocardiograms
FED	Feeding and eating disorders
DSM-5	Fifth edition of the Diagnostic and Statistical Manual of Mental Disorders
GLM	Generalized linear model
GPMC	Global psychological maladjustment
GSI	Global Severity Index
IC	Ineffectiveness
IPC	Interpersonal problems
IPS	Interpersonal sensitivity
NGT	Nasogastric tube feeding
NSSI	Non-suicidal self-injury
OC	Overcontrol
ANR	Restrictive AN
SSRI	Selective serotonin reuptake inhibitors
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
SCL-90-R	Symptom Check List-90-R
UFED	Unspecified feeding or eating disorders

Introduction

Feeding and eating disorders (FED) represent a group of psychiatric illnesses characterized by a persistent disturbance of eating or eating-related behavior, which results in the altered consumption or absorption of food and significantly impairs physical health or psychosocial functioning [1].

Several studies have shown that eating disorders are often associated with psychiatric comorbidities [2, 3]. The fact that comorbid psychiatric disorders and suicidal ideation are frequent in patients with FED and have a great impact on long-term outcomes is well demonstrated in the literature [4, 5]. However, psychiatric comorbidities have mostly been examined only in adult samples [4]. Moreover, evidence exists of the relationship between specific and general psychopathology in FED.

An increasing number of studies are assessing the clinical role and the predictive value of general psychopathological symptoms for the natural history and treatment of

different mental health conditions [6–8]. Previous studies have described the prevalence and clinical impact of general psychopathological symptoms in subjects with euthymic bipolar disorder [6] and problematic smartphone use [8].

The assessment of general psychopathological symptoms in subjects with FED represents a specific topic in the scientific literature, which has gained greater attention most recently. Monteleone et al. characterize general psychopathological symptoms in subjects with mixed diagnoses of FED, to assess the effect of the COVID-19 pandemic in an Italian sample (mean age 29.19 ± 12.05 years) [7]. In another sample of adults with mixed diagnoses of FED, general psychopathological symptoms have shown direct correlations with overweight and obesity, but not in subjects with AN [9].

Anorexia nervosa (AN) is a severe psychiatric disorder, classified in the chapter "Feeding and Eating Disorders" of the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [1]. The three crucial features of AN are a persistent energy intake restriction, leading to a body weight below the minimally normal level, intense fear of weight gain or persistent behavior that interferes with it, and a disturbance in self-perceived weight or shape [1]. AN is particularly common among adolescent females; its peak incidence is between 15 and 19 years [2]: in a recent systematic review, the weighted means of lifetime prevalence for AN were 1.4% (0.1–3.6%) for women and 0.2% (0–0.3%) for men [10]. Furthermore, anorexia nervosa often takes a chronic and disabling course and is characterized by substantial morbidity and the highest mortality of all mental disorders: its standardized mortality rate is approximately 6 and about one-fifth of those who die commit suicide [11]. Beyond completed suicides, non-suicidal self-injury (NSSI) has been reported to have a high prevalence among individuals with AN [12]. Individuals with AN and NSSI may show elevated rates of episodes of binging and purging, internalizing and externalizing psychopathology, and lower intelligence quotient [13, 14]. Specific personality traits, moreover, have been documented in individuals with FED and comorbid NSSI, such as harm avoidance and self-transcendence [15].

As regards children and adolescents, a recent study has assessed the relationship between general psychopathology and clinical outcomes in children with overweight/obesity [11]. General psychopathology has been investigated in adult subjects with AN to assess potential correlations with psychosocial [16] and cultural factors [17]. Despite the relevant role of general psychopathological symptoms in the natural history and management of FED, the literature describing general psychopathological symptoms in children and adolescents with AN and their potential prognostic role in long-term outcomes is considerably scarce.

The present study aims to investigate general psychopathological symptoms and their prognostic role in re-hospitalization after hospital treatment in a sample of children and adolescents with AN.

Methods

Study design and participants

The present paper describes an observational, retrospective, naturalistic study. The study took place in the context of a wider observational study assessing the use of psychopharmacological interventions in the treatment of FED in children, adolescents, and young adults, including both treated and untreated subjects, which was conducted in a third-level Italian reference center and was approved by the local ethical committee (code NPI-DAPSIFA2020). During the planning and conduction of this study, the authors observed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) [18]. The evidence here reported focuses on the included hospitalized children and adolescents with AN, who underwent a standardized protocol of assessments during the treatment and represent a clinical group for whom targeted literature evidence for general psychopathological symptoms is almost absent. The study received no sponsorship or funding from any company.

The study was conducted in April 2022, by retrospectively and consecutively enrolling all the patients assessed at the study center between 01/01/2016 and 31/12/2020, and with at least one hospitalization for FED; all subjects with potentially complete follow-up documentation were included. In the reference center, the day-hospital service represents a third-level treatment, including intensive psychological, nutritional, and medical support. Patients admitted to day-hospital treatment are required to attend the hospital 5 days per week and receive daily assistance from dedicated nurses and physicians. Assisted meals are provided daily, and the patients are separated from their families during their stay in the hospital. All the subjects included in this study underwent the same multidisciplinary program, delivered by the same clinical team, in the same hospital, and following the same international clinical guidelines [19]. Intensive day-hospital interventions have been equated to inpatient interventions previously in European clinical studies involving individuals with FED [20]. Thus, admittance to day-hospital or inpatient treatment regimes was considered "hospitalization" for the present study.

The data of all the eligible patients were collected and organized. For this study, inclusion criteria were (a) a diagnosis of AN, according to the DSM-5 criteria; (b) acquisition of informed consent; and (c) a complete standardized assessment of general psychopathological symptoms with the Symptom Check List-90-R (SCL-90-R) [21, 22]. The exclusion criterion was (1) insufficient clinical documentation. The selection of the sample was performed including all the consecutive, eligible patients during the selected period, to provide an unbiased and naturalistic observation. Given the naturalistic character of the study, no missing data has been replaced.

Assessment methods

This study had two main objectives. The primary aim was to document the general psychopathological symptomatology of a sample of children and adolescents with AN and its potential modifications with a multidisciplinary hospital treatment for eating disorders (ED) in the developmental age, for individuals receiving and not receiving psychopharmacological interventions. All the included patients received an assessment for ED at hospital admittance, covering psychopathological, biochemical, and nutritional parameters. The following variables were considered: demographics (age and declared gender), clinical (AN subtype, comorbidities, duration of untreated illness, and hospitalization), as well as anthropometric variables (BMI at hospital admission, T0, and hospital discharge, T1). Child and adolescent neuropsychiatrists and clinical psychologists—all of them trained and specializing in the field of FED in developmental age—performed the diagnostic process according to DSM-5 diagnostic criteria [1]. This process was supported by the systematic administration of the following tests, all validated for the assessment of children and adolescents with ED in the Italian language:

1. The Symptom Check List-90-R (SCL-90-R) [21, 22] is a self-report questionnaire assessing the severity of 90 psychiatric symptoms during the last week. A 5-point Likert scale is used to rate the severity of each symptom, with a range from 0 (not at all) to 4 (extremely). The referring items are organized to calculate subscales. These include somatization, obsession-compulsion, interpersonal sensitivity, depression, anxiety, hostility, phobia, paranoia, and psychoticism. A Global Severity Index (GSI), calculated from a mean of all 90 items, represents the best single indicator of the current psychiatric disturbance. The SCL-90-R has a reported good internal consistency (alpha values for the subscales range from 0.70 to 0.96) [21, 22]. This test, moreover, has an adequate 1-week test–retest reliability, with correlation coefficients concerning the subscales which range from 0.80 to 0.90 [21].

2. The Eating Disorders Inventory-3 (EDI-3), a self-assessment questionnaire routinely used in the diagnosis of ED symptoms, expressed in the form of six composite

scores: eating disorder risk (EDRC), ineffectiveness (IC), interpersonal problems (IPC), affective problems (APC), overcontrol (OC), global psychological maladjustment (GPMC) [23]. These scores are the combination of 12 subscales; ED-specific subscales are drive for thinness (DT), bulimia (B), and body dissatisfaction (BD) [18]. The EDI-3 has reliability coefficients that range from 0.83 to 0.90. The composite scales present test–retest reliability coefficients ranging between 0.84 and 0.87. The Italian version of EDI-3 presents a reportedly very good test–retest reliability, good discriminating validity, and cross-informant agreement [24]. For this study, to minimize multiple comparison-related risks of biases, only the EDRC score composite was maintained.

3. The Body Uneasiness Test-A (BUT) is a self-report questionnaire for the screening and the clinical assessment of abnormal body image attitudes and eating disorders. The test consists of 34 items, which account for a total score and disease-specific subscales, namely Global Severity Index (GSI), weight phobia, body image concerns, avoidance, compulsive self-monitoring, detachment, and estrangement feelings towards one's own body (depersonalization) [25]. The BUT-A has reported good psychometric properties, with a satisfactory internal consistency (Cronbach's alpha: WP = 0.84; BIC = 0.90; A = 0.79; CSM = 0.82; and D = 0.85), and significant test–retest correlation coefficients (0.90) [26]. For this study, to minimize multiple comparison-related risks of biases, only the GSI score was maintained.

All these tests were administered in the same setting, both at hospital admission (T0) and hospital discharge (T1).

The clinical assessment of the included patients was completed considering further variables related to the administered hospital intervention. Psychopharmacological treatment variables were collected by thoroughly assessing clinical documentation and included the dates and duration of any single treatment, initial and maximum dosages, any reasons for treatment interruption, and possible emerging adverse drug reactions (ADR) for both atypical antipsychotics (AAP) and selective serotonin reuptake inhibitors (SSRI). During hospitalization, patients were subjected to repeated standard laboratory exams (including blood counts, electrolytes, transaminases, lipid profile, and coagulation) and repeated electrocardiograms (EKG). Nutritional interventions were collected and coded as well, including the use of nasogastric tube feeding (NGT). Only data relevant to the detection of comorbid psychopathological symptoms were reported and analyzed in this paper. All the subjects received a multidisciplinary psychotherapeutic treatment for AN, including individual and group psychotherapeutic interventions for both the patients and their parents.

The second objective of this study was to investigate the potential predictive role of general psychopathological symptomatology at admission in the risk of re-hospitalization after 1 year of discharge. To do so, the clinical documentation of all patients was assessed to detect any re-hospitalization due to an ED or psychiatric symptoms in the 365 days following discharge from the inpatient/day hospital treatment setting of the study center.

Statistical analysis

Descriptive analyses were conducted for the whole sample. The significance level was set at 0.05 and all tests were two-tailed. The normality of data distribution and the homogeneity of variance was assessed with Shapiro–Wilk's and Levene's tests. The modification of psychopathological measures (SCL-90-R scores) between T0 and T1 was studied with paired-sample T-tests for the whole group (Wilcoxon signed rank when needed). Bonferroni correction was applied for multiple comparisons.

A generalized linear model was conducted to assess potential psychopathological, weight, and psychopharmacological factors associated with the modification of T0-T1 SCL-90-R scores. Generalized linear models (GLMs, for Tweedie distribution) were carried out, with SCL-90-R at T1 (discharge) scores as a dependent variable. These analyses were screened using treatment with AAP (yes/no), treatment with SSRI (yes/no), admission BMI, admission EDI-3 EDRC, and admission BUT-GSI as independent variables, one at a time in the univariate model. Potential multiple significant associations were included in a multivariate generalized linear model. All the analyses were corrected considering potential confounders in the respective baseline (T0) SCL-90-R scores.

Finally, potential associations between SCL-90-R scores at admission and the risk of re-hospitalization after 1 year of discharge were calculated with the Kaplan–Meier method. The Cox regression analysis model was used to estimate the hazard ratio and 95% confidence interval for the different SCL-90-R subscales at admission. The sample size was determined based on the number of subjects enrolled within the study period. All the statistical analyses were performed using SPSS, version 26 for Windows.

Results

Selection of the sample

A total of 390 children and adolescents with FED, who accessed our center during the considered period, were identified and included in the study. This group comprised 340

children and adolescents with FED (mean age 15.9 years, F = 350, 92.6%), who accessed the center during the considered period and with a record of hospitalization. Among them, 298 met the inclusion criteria. However, 135 patients were subsequently removed from this sample after applying exclusion criteria. A total of 163 subjects with FED, including 133 subjects with AN, met the selected criteria and were retained for the final analyses.

Sample characteristics

One-hundred sixty-four patients with FED were assessed, with a mean age of 17.2 ($\pm$2.9) years. The diagnoses of FED included AN (n = 133, 81.6%), BN (n = 17, 10.4%), binge eating disorder (BED) (n = 9, 5.5%), and unspecified feeding or eating disorders (UFED) (n = 4, 2.5%). AN subtypes were restrictive AN (ANR) (n = 113), binge-purging AN (ANBP) (n = 16), and atypical AN (n = 4). Table 1 reports the main clinical variables of the sample. The following results focus on subjects diagnosed with AN. The mean age of the included patients with AN was 16.9 ($\pm$2.9), ranging from 9.4 to 27.5 years (median: 16.5 years, interquartile range: 3.1 years). The clinical symptoms reported by the patients with AN at their first admission were caloric restriction (n = 133, 100%), physical hyperactivity (n = 70, 52.7%), binging/purging (n = 35, 26.3%), NSSI (n = 21, 15.8%), and suicidality (n = 10, 7.5%). It should be noted that, despite 35 patients experiencing episodes of binging/purging, only 16 of them presented a clinical picture requiring a diagnosis of ANBP.

Outcome measures

The main results obtained at different SCL-90-R subscales at admission and discharge are reported in Table 2. In all the single subscales, a statistically significant reduction between admission and discharge was documented; the scale for paranoia showed a statistically significant difference (p = 0.005), but this value was slightly out of the chosen significance cut-off after applying Bonferroni correction (p = 0.05/10 = 0.005). The comparisons of general psychopathological symptoms between patients with and without NSSI are reported in Table 3. No difference between these two groups was found.

Table 1 Demographic and clinical characteristics of the whole sample and the patients with AN

Variables	FED (all diagnoses) (n = 163)	AN (n = 133)
Demographics		
Age (years)	17.2 ($\pm$3.0)	16.9 ($\pm$2.9)
Genre	F = 152 (93.3%) M = 11 (6.7%)	F = 122 (91.8%) M = 11 (8.3%)
Clinical variables		
Duration of untreated illness (months)	21.1 ($\pm$20.8)	19.1 ($\pm$19.5)
Admission BMI	16.7 ($\pm$4.0)	15.4 ($\pm$2.6)
Discharge BMI	18.0 ($\pm$3.6)	16.9 ($\pm$2.6)
Diagnosis	AN = 133 (81.6%) BN = 17 (10.4%) BED = 9 (5.5%) UFED = 4 (2.5%)	ANR = 106 (85.0%) ANBP = 16 (12.0%) ANA = 2 (3.0%)
Comorbidity	OCD = 10 (6.1%) MDD = 9 (5.5%) Anxiety disorders = 6 (3.7%)	OCD = 10 (7.5%) MDD = 8 (6.0%) Anxiety disorders = 4 (3.0%)
Length of hospitalization	140.9 ($\pm$94.4)	135.2 ($\pm$93.6)
Admission EDI-3 EDRC	67.5 ($\pm$24.1)	65.1 ($\pm$24.3)
Admission BUT GSI	2.8 ($\pm$1.2)	2.6 ($\pm$1.2)
Treatment variables		
SSRI	142 (87.1%)	110 (82.7%)
AAP	105 (64.4%)	96 (72.2%)
NGT	35 (21.5%)	35 (26.3%)

AAP atypical antipsychotics, *AN* anorexia nervosa, *ANBP* anorexia nervosa binge-purging subtype, *ANR* anorexia nervosa restrictive subtype, *BED* binge eating disorder, *BMI* body mass index, *BUT GSI* Body Uneasiness Test Global Severity Index, *EDI-3 EDRC* Eating Disorders Inventory-3 Eating Disorder Risk Composite, *MDD* major depressive disorder, *NGT* nasogastric tube feeding, *OCD* obsessive–compulsive disorder, *SSRI* selective serotonin reuptake inhibitors, *UFED* unspecified feeding or eating disorders

Table 2 Admission and discharge SCL-90-R subscales for the patients with AN

Subscales	Admission	Discharge	Wilcoxon	p value
GSI	59.3 (±12.8)	52.9 (±14.7)	4238.000	<0.001
Somatization	55.8 (±12.9)	50.4 (±12.5)	3962.000	<0.001
Obsession compulsion	58.8 (±13.1)	54.2 (±14.9)	3459.500	<0.001
Interpersonal sensitivity	58.5 (±12.4)	54.3 (±13.9)	3421.000	<0.001
Depression	61.9 (±13.1)	54.4 (±14.7)	4194.500	<0.001
Anxiety	59.8 (±12.4)	54.4 (±13.4)	3951.500	<0.001
Hostility	51.1 (±10.2)	47.9 (±10.3)	3508.500	<0.001
Phobia	58.0 (±11.9)	54.4 (±12.9)	3041.000	<0.001
Paranoia	53.4 (±11.1)	50.7 (±12.2)	2801.500	0.005
Psychoticism	58.0 (±11.3)	52.9 (±12.2)	3512.000	<0.001

Bonferroni corrected significance level for multiple comparisons adjusted for a number of $10 = 0.05/10 = 0.005$

GSI Global Severity Index, *SCL-90* Symptom Checklist-90-R

The generalized linear model for discharge SCL-90-R subscales is reported in Table 4. The generalized linear model, corrected for baseline (T0) SCL-90-R scores, showed statistically significant associations between baseline EDI-3 EDRC scores and discharge (T1) SCL-90-R scores. Namely, subjects with higher EDI-3 EDRC baseline scores presented, at discharge, higher GSI ($B = 0.003$, $p = 0.007$), interpersonal problems ($B = 0.003$, $p = 0.001$), depression ($B = 0.003$, $p = 0.007$), anxiety ($B = 0.003$, $p = 0.006$), phobia ($B = 0.002$, $p = 0.015$), paranoia ($B = 0.003$, $p = 0.007$), and psychoticism ($B = 0.003$, $p = 0.005$). Baseline BMI, baseline BUT GSI, the use of AAP, and the use of SSRI were not associated with

Table 3 Comparisons of single SCL-90-R subscales between AN patients with and without NSSI

Subscales	No. evidence of NSSI	NSSI	p value
GSI	58.9 (±12.9)	61.4 (±12.6)	0.413
Somatization	55.9 (±12.6)	55.6 (±13.7)	0.916
Obsession compulsion	58.3 (±13.0)	61.0 (±13.5)	0.381
Interpersonal sensitivity	58.0 (±12.6)	61.0 (±11.7)	0.312
Depression	61.7 (±13.1)	62.5 (±13.7)	0.812
Anxiety	59.7 (±12.4)	60.3 (±12.3)	0.841
Hostility	50.7 (±10.2)	53.0 (±10.4)	0.353
Phobia	57.3 (±11.8)	61.4 (±11.9)	0.145
Paranoia	52.9 (±10.9)	56.3 (±11.9)	0.206
Psychoticism	57.8 (±11.1)	58.8 (±12.3)	0.731

AN anorexia nervosa, *GSI* Global Severity Index, *NSSI* non-suicidal self-injury, *SCL-90* Symptom Checklist-90-R

Table 4 Generalized linear model assessing associations between the SCL-90-R subscales at discharge and specific anthropometric, psychopathological, and treatment variables. All the analyses are corrected considering as potential confounders the respective baseline (T0) SCL-90-R scores

Dependent variables	GSI	Somatization	Obsession compulsion	Interpers. sensitivity	Depression	Anxiety	Hostility	Phobia	Paranoia	Psychoticism
BMI	B=0.006 p=0.509	B=0.012 p=0.145	B=0.003 p=0.741	B=0.002 p=0.836	B=0.007 p=0.462	B=0.004 p=0.685	B=0.013 p=0.096	B=0.004 p=0.654	B=−0.002 p=0.786	B=0.026 p=0.276
EDI-3 EDRC	**B=0.003** **p=0.007**	B=0.002 p=0.115	B=0.002 p=0.060	**B=0.003** **p=0.001**	**B=0.003** **p=0.007**	**B=0.003** **p=0.006**	**B=0.002** **p=0.015**	B=0.002 p=0.130	**B=0.003** **p=0.007**	**B=0.003** **p=0.005**
BUT GSI	B=−0.009 p=0.768	B=0.018 p=0.419	B=−0.027 p=0.370	B=0.016 p=0.582	B=0.007 p=0.821	B=0.033 p=0.166	B=0.020 p=0.235	B=0.006 p=0.776	B=−0.001 p=0954	B=0.002 p=0.830
AAP	B=−0.027 p=0.603	B=−0.036 p=0.465	B=0.037 p=0.480	B=0.014 p=0.789	B=−0.058 p=0.281	B=0.036 p=0.483	B=−0.007 p=0.879	B=0.028 p=0.573	B=0.016 p=0.759	B=0.039 p=0.431
SSRI	B=0.006 p=0.926	B=0.006 p=0.916	B=0.040 p=0.534	B=0.005 p=0.941	B=−0.021 p=0.745	B=0.014 p=0.825	B=0.038 p=0.506	B=0.011 p=0.855	B=0.047 p=0.450	B=0.074 p=0.239

Statistically significant correlations are marked in bold and underlined

AAP atypical antipsychotics, *BUT GSI* Body Uneasiness Test Global Severity Index, *EDI-3 EDRC* Eating Disorders Inventory-3 Eating Disorder Risk Composite, *GSI* Global Severity Index, *SCL-90* Symptom Checklist-90-R, *SSRI* selective serotonin reuptake inhibitors

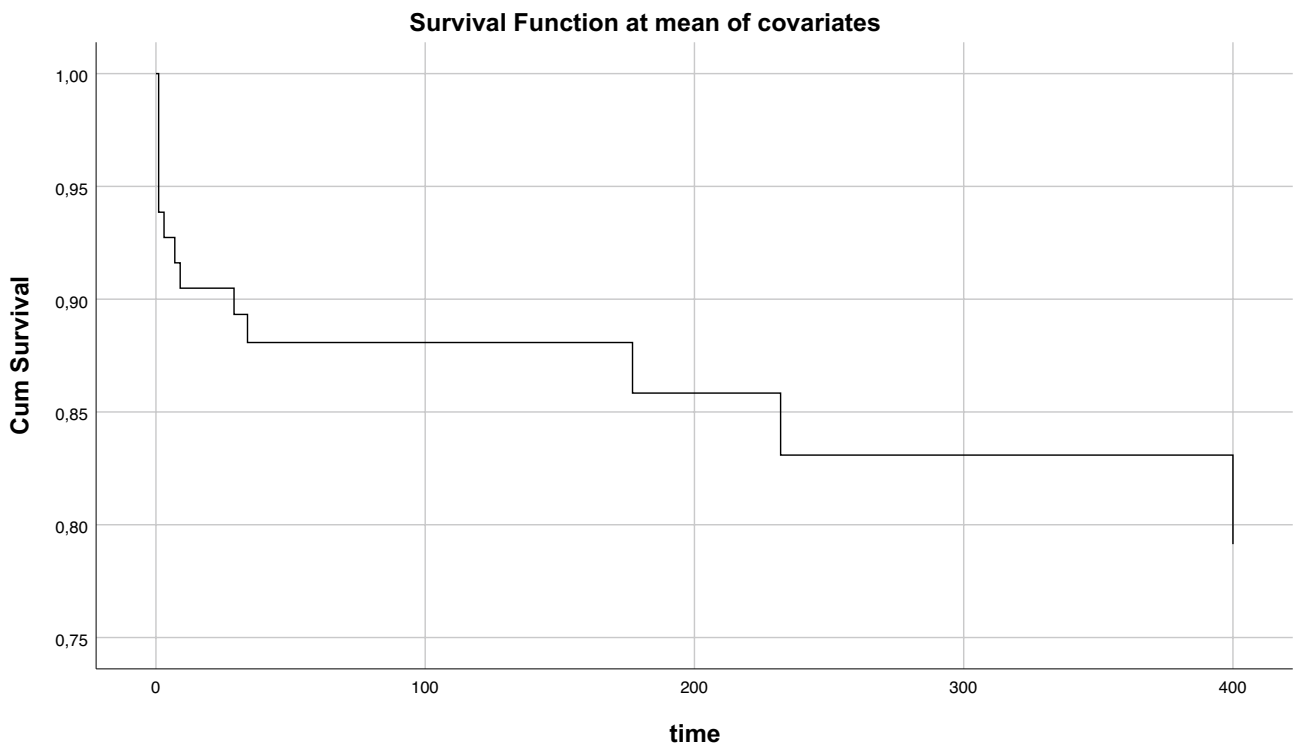## Survival Function at mean of covariates

Fig. 1 Kaplan–Meier curve, assessing the survival function (freedom from re-hospitalization at 1 year after discharge) at mean of covariates (SCL-90-R subscales) for the patients with AN. Abbreviations: SCL-90, Symptom Checklist-90-R

SCL-90-R discharge scores. Since only EDI-3 EDRC scores were associated with SCL-90-R scores, no multivariate generalized linear model analysis was necessary.

Analysis of survival function at 1-year follow-up

The survival function at the mean of covariates is reported in Fig. 1 and Table 5. The mean survival time from re-hospitalization was 334.8 (95% CI, 304.5–365.0) days. The

cumulative survival from re-hospitalization at 12 months was 77.5% (95% CI, 66.5–88.5). The Cox proportional hazard model revealed that a higher risk of re-hospitalization was significantly predicted by SCL-90-R interpersonal sensitivity scores at admission ($B = 0.113$, hazard ratio = 1.119, $p = 0.023$). No predictive value for other SCL-90-R subscales was documented in the Cox proportional hazard model.

Overall, 18 patients underwent re-hospitalization in the considered period. At the moment of hospital readmission,

Table 5 Cox regression analysis, assessing potential associations between SCL-90-R scores at admission and the risk of re-hospitalization after 1 year of discharge, for the patients with AN

	B	SE	Wald	df	*p* value	Exp(*B*)	Lower CI for Exp(*B*)	Upper CI for Exp(*B*)
Covariates								
GSI	−0.156	0.089	3.054	1	0.081	0.856	0.718	1.019
Somatization	−0.004	0.034	0.016	1	0.900	0.996	0.932	1.064
Obsession compulsion	0.001	0.036	0.001	1	0.977	1.001	0.934	1.073
Interpersonal sensitivity	0.113	0.050	5.161	1	**<u>0.023</u>**	1.119	1.016	1.234
Depression	0.021	0.048	0.186	1	0.667	1.021	0.929	1.122
Anxiety	0.025	0.040	0.398	1	0.528	1.026	0.948	1.109
Hostility	0.020	0.033	0.357	1	0.550	1.020	0.956	1.088
Phobia	−0.004	0.030	0.015	1	0.903	0.996	0.939	1.057
Paranoia	0.022	0.041	0.278	1	0.598	1.022	0.943	1.108
Psychoticism	0.004	0.037	0.014	1	0.906	1.004	0.934	1.080

Statistically significant correlations are marked in bold and underlined

GSI Global Severity Index, *SCL-90* Symptom Checklist-90-R

the clinical symptoms identified in the patients included caloric restriction ($n = 18$, 100%), physical hyperactivity ($n = 5$, 27.8%), binging/purging ($n = 5$, 27.8%), and NSSI ($n = 2$, 11.1%). No patients reported suicidality at read-mission. None of the included patients was hospitalized, during the considered period, in a dedicated psychiatric ward. One patient was admitted to a therapeutic residence. Among those who were re-hospitalized, however, psychiatric comorbidities impacted the clinical picture and influenced the decision to a second hospitalization; this happened in two (1.5%) patients with OCD and two (1.5%) patients with major depressive disorder.

Discussion

This study evaluates general psychopathological symptoms in a sample of children and adolescents with AN in a third-level center for FED. It represents the first research to investigate general psychopathological symptoms in this population and to assess its potential predictive role for the risk of re-hospitalization at a long-term follow-up.

For the assessment of psychological distress, Symptom Checklist 90-R was used. This is a self-report questionnaire widely used in clinical research and practice, which investigates 9 different symptom clusters [27]. Several studies have shown that FED occur often together with psychiatric comorbidities and can arise both before and during acute illness or in the long-term follow-up. These studies have typically been carried out on adult samples, while few articles have investigated psychiatric comorbidities in developmental age. The data obtained from the analysis of samples of adult patients show that the most frequent psychiatric comorbidities are depression, anxiety disorders, and substance use disorders [2, 4, 28]. Solmi et al. analyzed the main psychopathological symptoms in patients with AN, comparing the differences between the group with ANR and the group with ANBP. In their study, they highlighted that depression, anxiety, interpersonal sensitivity, and ineffectiveness were the nodes with the highest centrality in the network of symptoms in patients with AN [29].

In our study, we compared the scores obtained at different SCL-90-R subscales at admission and discharge in a sample of 133 adolescent patients with AN. The analysis of the SCL-90-R subscales at admission highlighted psychopathological symptoms in multiple domains. In all the single subscales, a statistically significant reduction between admission and discharge was documented. In particular, our sample showed an average GSI score at the admission of 59.3 ($\pm$ 12.8), which corresponds to a level of general discomfort of moderate to high intensity. For all the psychopathological scales assessed here, except for paranoia, the administered multidisciplinary hospital intervention resulted in a significant admission-discharge reduction. By comparing their study of general and eating disorder-specific psychopathology in patients with acute AN with healthy control women, Schneider et al documented a reduction in psychopathology in long-term weight-recovered patients [30]. These data suggest (a) the link between the reduction of psychopathological symptoms after partial weight recovery; (b) the complex treatment interventions for AN may target general psychopathology, as well as weight and FED-specific psychopathological variables. Further research should aim to disentangle and identify the specific treatment interventions that could directly address general psychopathology in subjects with AN.

Further analyses in this study investigated potential predictors for the reduction of general psychopathological symptoms. Admission BMI, drug therapies, and eating disorder psychopathology (assessed through EDI-3 and BUT questionnaires) were screened in this phase. Interestingly, baseline BMI was not associated with SCL-90-R discharge scores. By analyzing other possible outcome measures, such as baseline BUT GSI, the use of AAP, and the use of SSRI, we also did not find a correlation with SCL-90-R discharge scores in these variables. We found, nonetheless, statistically significant associations between baseline EDI-3 EDRC scores and discharge SCL-90-R scores. In particular, we highlighted that in our sample the severity of ED psychopathology is a negative predictor of response to treatment. Indeed, the more severe the ED symptoms are, the lower the improvement in SCL-90-R scores is at discharge. Interestingly, Latner et al investigated the association of general psychopathology with objective and subjective bulimic episodes. The authors found that their regression model accounted for 39% of the variance in general psychopathology, as expressed by the Depression Anxiety Stress Scale (DASS). The frequency of objective bulimic episodes and self-induced vomiting was independently associated with general psychopathology [31]. The comprehensive evidence resulting from these data points to the need for specific studies systematically targeting the potential effect of ED psychopathology in influencing general psychopathology in subjects with AN and other FED.

The last section of our work assessed if SCL-90-R domains could be a negative predictor of re-hospitalization after 1 year from hospital discharge. In our sample, a statistically significant correlation was found only in the interpersonal sensitivity domain, which is associated with a greater risk of re-hospitalization. Interpersonal sensitivity (IPS) has been described as an unwarranted and excessive awareness and responsiveness to the feelings and actions of others [32]. Hamann et al. assessed the predictive capacity of IPS and related constructs in the development of bulimic symptomatology both cross-sectionally and longitudinally [33]. The authors found that

IPS (particularly fragile inner self) may represent a suitable candidate in the dual pathway model of bulimic symptomatology [33]. More recently, Kolar et al studied interpersonal, affective, and compulsive features of driven exercise in AN using multilevel structural equation modeling. The authors reported that patients with more affect-regulatory difficulties or stronger IPS tended to engage more significantly in driven exercise. Moreover, the effect of IPS on driven exercise across time was amplified by high levels of trait compulsivity [34]. Despite no difference reported between patients with and without NSSI concerning IPS or other SCL-90-R domains documented in our sample, a role for IPS has been associated, in non-AN samples, with suicidality and NSSI in previous studies. In a large community-based study in Canada, IPS has been found to mediate cutaneous body image dissatisfaction and suicidal ideation [35]. Rejection sensitivity, similarly, was documented to influence NSSI in a sample of Chinese secondary school students, through the mediation of depressive symptoms [36]. These results suggest that IPS should represent a future topic for research and clinicians, to identify potential targets for multidisciplinary interventions in subjects with FED.

Our study has some limitations. We analyzed a sample of 133 adolescent patients with AN hospitalized in our third-level center for FED. The retrospective nature may have influenced the data collection. Moreover, the assessment provided by the SCL-90-R test detects only a series of specific domains of general psychopathological symptoms. The presence of healthy controls and a more complete assessment could have provided a chance for unbiased comparisons and further insights into different psychopathological dimensions. This study also has several strengths. It is the first study on general psychopathology and AN to consider a long-term follow-up and to systematically assess general psychopathological symptoms in a sample of children and adolescents with AN. The use of standardized measures permitted a clear evaluation of general psychopathological symptoms, in a manner potentially reproducible in different samples and settings.

In conclusion, the data here presented provide preliminary evidence on the presence of general psychopathological symptoms in a sample of children and adolescents with AN. Although general psychopathological symptoms improved after a multidisciplinary treatment intervention, higher levels of ED-specific psychopathology were associated with lower admission-discharge improvements, and higher levels of general psychopathological symptom "interpersonal sensitivity" were associated with a poorer prognosis at 1-year follow-up. Further longitudinal and controlled studies should investigate and verify these results.

Declarations

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Authors and Affiliations

Jacopo Pruccoli[1,2] · Francesca Chiavarino[1,2] · Camilla Nanni[2] · Antonia Parmeggiani[1,2]

1　IRCCS Istituto delle Scienze Neurologiche di Bologna, UOC Neuropsichiatria dell'Età Pediatrica, Centro Regionale per i Disturbi della Nutrizione e dell'Alimentazione in età evolutiva, Bologna, Italy

2　Dipartimento di Scienze Mediche e Chirurgiche (DIMEC), Università di Bologna, Via Massarenti 9, Bologna 40138, Italy