Five-year mortality of severely malnourished patients with chronic anorexia nervosa admitted to a medical unit

Marie Guinhut, Nathalie Godart, Mohamed-amine Benadjaoud, Jean-claude Melchior, Mouna Hanachi

DR MARIE GUINHUT (Orcid ID : 0000-0002-4502-8416)

Article type : Original Article

Five-year mortality of severely malnourished patients with chronic anorexia nervosa admitted to a medical unit

Marie Guinhut (1), Nathalie Godart (2) (3), Mohamed-Amine Benadjaoud (4), Jean-Claude Melchior* (5) (6), Mouna Hanachi* (5) (6) (7)

(1) Paris-Descartes University, Paris, France

(2) Fondation Santé des Etudiants de France, Paris, France

(3) CESP, INSERM, UMR 1018, Paris-Saclay University, Paris, France

(4) Institut de Radioprotection et de Sûreté Nucléaire, Fontenay-Aux-Roses, France (MAB)

(5) Clinical Nutrition Unit, Paul Brousse Hospital, Villejuif, France, APHP

(6) Paris-Saclay University, France

(7) UMR Micalis Institut, INRA, Jouy-En-Josas, France

* Jean-Claude Melchior and Mouna Hanachi are equally last author of this publication

Corresponding Author: Marie GUINHUT

Mailing address: Service de nutrition Clinique, Hôpital Paul Brousse**,** 12 Avenue Paul Vaillant Couturier, 94800 - Villejuif, France

Phone Number: 0033 684091405

Email Address: marieguinhut@live.fr

Abbreviations list:

AN: anorexia nervosa

AN-R: restricting type

AN-BP**:** binge-eating/purging type

ALT: alanine transaminase

AST: aspartate transaminase

BMD: bone mineral density

BMI: body mass index

CBC: complete blood count

CMR: crude mortality rate

CNU: clinical nutrition unit

DEXA: Dual-energy x-ray absorptiometry

ED: eating disorder

EN: enteral nutrition

LVEF: left ventricular ejection fraction

MICU: medical intensive care unit

PH: proportional hazards

SMR: standardized mortality ratio

ABSTRACT

Objective: Anorexia nervosa (AN) is associated with one of the highest mortality rates of any psychiatric disorder but limited mortality data were reported for those with extremely severe malnutrition. This study aimed to estimate Standardized Mortality Ratio (SMR), investigate predictive factors of mortality and causes of death among a sample of patients with AN admitted to a specialized clinical-nutrition-unit (CNU) because of extremely severe malnutrition.

Methods: Between 11/27/1997 and 01/15/ 2014, vital status was determined for 384 patients admitted for AN at the first time in the CNU. Sociodemographic, anamnestic and clinical data were collected. We calculated the SMR. Univariate and multivariate Cox regression analysis were performed to identify mortality predictors.

Results: Crude mortality rate was 11.5%. (44 deaths) and SMR 15.9 [CI 95% (11.6-21.4)], 5.2 years post in-patient treatment.

Mortality predictors at the time of hospitalization were: older age, occurrence of a in-hospital suicide attempt, transfer to medical intensive care unit and the following somatic complications: frank anemia, dysnatremia, infectious and cardiac complications. Other predictors of mortality were: past or present history of discharge against medical advice, hematological comorbidities (not related to AN). A longer inpatient length of stay was a protective factor.

Conclusion: Very severely malnourished patients with AN hospitalized in a medical unit because of extremely severe somatic issues have a medium-term mortality rate higher than the general population and even higher than patients in tertiary specialised ED units. This study highlights predictive factors of mortality that will help clinicians in recognizing and managing patients at risk of death.

Keywords:

Anorexia nervosa, inpatient, malnutrition, mortality, risk factors.

Significant outcomes

- Crude mortality rate was 11.5%, in a large cohort of patients with AN, five years on average after a first hospitalization in a clinical nutrition unit, for extremely severe undernutrition and / or somatic

complications. Mortality risk was 15 times higher (SMR = 15.9) than in the general French population.

-Predictive factors of mortality at the time of hospitalization were: older age, occurrence of a in-hospital suicide attempt, transfer to MICU, frank anemia, dysnatremia, infectious and cardiac complications. Other predictors of mortality were: past or present history of discharge against medical advice, hematological comorbidities (not related to AN).

- A prolonged hospitalization was a protective factor.

Limitations

- The study included a selection of severely malnourished patients with AN with predominant somatic severity criteria, so the results cannot be extrapolated to all patients with AN treated.

-There were a high proportion of missing data concerning the causes of death indicated on death certificates (32%).

Introduction

Anorexia nervosa (AN) is a psychiatric disorder defined by the following DSM 5 criteria: a restriction of energy intake relative to requirements leading to a significantly low body weight, a fear of gaining weight or becoming fat, or persistent behaviour that interferes with weight gain and a disturbance in the way in which one's body weight or shape is experienced (1). This eating disorder (ED) causes malnutrition and requires both somatic and psychiatric care (2–4). Hospital admission is necessary in case of severe malnutrition and/or medical complications (2–4). When BMI is below 13 kg/m², an initial and cautious refeeding treatment should be provided in a medical unit, to stabilize the patient's medical condition before his transfer to a psychiatric ward (2–4). Indeed, morbidity and mortality in AN are high (5). Patients with AN present one of the highest mortality rate among all psychiatric disorders (6). In a meta-analysis, Arcelus mentioned a Standardized Mortality Ratio (SMR) of 5.86

(5) in AN. However, mortality is even higher in tertiary care centers that treat the most severe forms of the disorder: SMR at 10.6 among adult inpatients in tertiary ED center (7). Mortality rates in AN adults after an inpatient treatment have been largely studied (7–33). However, the results vary widely depending on the characteristics of the cohort studied (size, outpatient or inpatient, medical or psychiatric department, severity of malnutrition, duration of ED, duration of follow up), and on the methodology used. Most AN mortality studies have been carried out in AN inpatient populations hospitalized in psychiatric departments. Limited mortality data have been reported from adult patients hospitalized in somatic (medical) units due to the severity of their malnutrition (16,18,23,31,33).

Since 1997, our team has developed and operated a clinical nutrition unit (CNU) specialized in the management of extremely severe undernutrition and its somatic complications in adult patients with AN. Intensive medical care is provided to stabilize the patients prior to their being transferred to a tertiary ED Programs in a psychiatric unit. This CNU is considered a national nutritional reference center specialized in medical care for extremely severely malnourished patients with ED in France.

This study aims to contribute to the existing mortality literature data by investigating mortality rate (Crude and Standardized Mortality Ratio), predictive factors of mortality and causes of death among a specific sample of extremely malnourished patients with AN. These patients were admitted to a somatic unit (a Clinical Nutrition Unit) and not a psychiatric unit, because of the severity of the malnutrition.

Material and Methods

Study Design and Aims

We conducted an observational mortality study including a sample of patients with AN admitted to the CNU for severe malnutrition (BMI < 13 kg/m²) and/or medical complications related to malnutrition or refeeding.

The primary objective was to specify the crude mortality rate (CMR) and the SMR in the patient cohort. Secondary objectives were to determine predictive factors of mortality and causes of death in the cohort.

Patients

Inclusion criteria

We considered all patients hospitalized for the first time in the CNU between November 27th, 1997 and January 15th, 2014, because of extremely severe malnutrition and/or medical complications related to malnutrition or refeeding, aged 15 years or older, diagnosed with AN according to the DSM IV criteria. The complete patient selection was provided by the hospital's department of statistics and medical information.

Exclusion criteria

We excluded from the study any patients who did not allow the use of their data for the study and any patients whose vital status was unknown.

Clinical Nutrition Unit treatment program

A multidisciplinary team including physicians specialized in the management of extremely severe malnutrition (clinical nutritionists), psychiatrists specialized in the care of ED, a clinical psychologist, a dietician, a physiotherapist, nurses and nursing assistants, provides patient care. In severely malnourished patients, refeeding treatment is performed according to the recommendations of the French National Authority for Health (2) in accordance with international guidelines (3,4,34).

All patients received an initial intravenous supplementation with vitamins, phosphorus and trace elements. In any patients with a BMI below 13 kg/m², enteral nutrition (EN) via a nasogastric feeding tube was started during the first 48 hours of admission. Oral nutrition was initiated slowly according to the weight evolution under EN.

When a patient left the zone of critical danger, and his/her clinical condition was stable, he/she could be discharged. Discharge criteria were: the absence of metabolic and hemodynamic complications, the absence of somatic complications that would require inpatient treatment or monitoring, a minimum BMI. The refeeding process should achieve a minimum BMI of 13 kg/m². From then on, usually patients were transferred to an ED psychiatric unit to continue the refeeding process and initiate ED specialized therapies.

Parameters studied

Patient vital status (living or deceased) was provided by the French National death register (CESP = *Centre de Recherche en Epidémiologie et Santé des Populations* – INSERM) which reports the deaths of any person resident in France whether born in France or abroad. Patient identification was based on name, surname, date and place of birth. The moment of inclusion in the study (which represents the beginning of follow-up) was defined by the first admission to the unit during that period. The endpoint of the mortality status research was the 25th of April 2014 (date of death data collection).

Causes of patient death were given by CépiDc (*Centre d'épidémiologie sur les causes médicales de Décès*), the French epidemiological centre charged with registering data on cause of death (which is based on the cause identified on an individual's death certificate).

For each patient, the files could contain up to 6 different causes of death. To determine the primary cause of death, we used the methodology proposed by Huas et al (7) referring to the Papadopoulos classification (20). Hence, the rules to determine the primary cause of death were:

- select suicide when suicide was mentioned at least once in the causes of death, whatever their position.
- select cardiac arrest whatever its position except if suicide or accident were mentioned.
- if neither of the above causes were cited, select the cause you consider as the most likely direct cause of death.
- then classify the cause of death according Papadopoulos' classification, as follows:
- natural (infection, cancer, endocrine, hematopoietic, mental including psychoactive substance use and AN, nervous system, cardiovascular, respiratory, gastrointestinal, urogenital, dermatological, autoimmune, other).
- unnatural (suicide, homicide, traffic accident, other).
- undefined.
- unknown, if there is no information in the death file.

For each patient, we performed a chart review and we recorded:

- demographic data (age at index admission, sex).
- social data (qualification level, professional status, marital status, having at least one child).

- AN characteristics (restricting type (AN-R), binge-eating/purging type (AN-BP), purging behaviours).
- anamnesic data (age at AN onset, AN duration[1], history of hospitalization, minimum BMI since puberty, history of suicide attempt or discharge against medical advice or compulsory admission).
-nutritional data (BMI and albumin plasma level at admission, EN prescription, weight gain during hospitalization, BMI at discharge).
- history of somatic comorbidities unrelated to AN (cardiovascular, dermatological, digestive, endocrine, genetic, hematological, infectious, immunological, nephrological, neurological, otolaryngological, ophthalmic, pulmonary, rheumatological, urological, solid cancer).
- psychiatric comorbidities[1] (personality disorders, obsessive-compulsive disorders, mood and/or anxiety disorders, non-suicidal self-injury disorder, attention-deficit hyperactivity disorder, kleptomania).
- addictions (alcohol, substance use, tobacco).
- referral, reason for hospitalization, requirement for compulsory admission, requirement for MICU transfer, length of stay, discharge against medical advice from the unit, hospital facility receiving the patient after discharge from the CNU.

Laboratory test results were followed during hospitalization including CBC, platelets count, electrolytes, urea, creatinine, phosphorus, albumin, glycemia and liver enzymes.

A DEXA scan (Dual-energy x-ray absorptiometry) was performed to assess bone mineral density (BMD) of all patients who did not have any BMD evaluation during the 2 years prior to admission as recommended (2). All clinical events occurring during the hospital stay and documented in physicians notes or nursing assessments were noted.

We reported any acute medical complications that occurred during the hospital stay including:

- metabolic conditions such as hypokalemia, hypophosphatemia, hypoglycemia, dysnatremia, acute kidney failure (creatinine clearance < 60 ml/min).

[1] The data "AN duration" was collected from medical records. It was based on declarative data given by the patient at the time of hospitalization in the CNU. Psychiatric comorbidities and diagnoses were collected from medical records. At the time of hospitalization in the CNU, they were based on information from previous psychiatric records and assessment of psychiatrists working in the CNU.

- hematological conditions such as neutropenia (neutrophil count < 2000/mm³), frank neutropenia (neutrophil count < 1000/ mm³), lymphopenia (lymphocyte count < 1500/mm³), frank lymphopenia (lymphocyte count < 1000/ mm³), anemia (hemoglobin (hb) level < 13 g/dl for male and < 12 g/dl for female), frank anemia (hb ≤ 9g/dl), thrombocytopenia (platelet level < 150 000/mm³), frank thrombocytopenia (platelet level < 80 000/mm³).
- hypertransaminasemia defined by AST (aspartate transaminase) > 31 IU/L and/or ALT (alanine transaminase) > 65 IU/L, related to malnutrition or refeeding. Mild hypertransaminasemia (< 10 X normal) and marked hypertransaminasemia (≥ 10 X normal) and were specified.
- cardiac complications such as cardiac rhythm disorders (bradycardia < 40/min, tachycardia, cardiac repolarization abnormalities), cardiac failure (acute pulmonary edema and/or left ventricular ejection fraction (LVEF) ≤ 50%), elevated troponin without myocardial infarction, pericardial effusion.
- digestive conditions such as gastroesophageal reflux and / or esophagitis, constipation, biological pancreatitis (lipase > 3N).
- neurological conditions such as axial hypotonia, lower limb hypoesthesia, cerebellar syndrome, central pontine myelinolysis.
- bladder-sphincter dysfunctions (urinary incontinence, urinary retention) and
- infectious complications.

Chronic complications of AN highlighted during the hospitalization such as low bone mineral density (LBMD) were also recorded. Osteoporosis was defined by a T score < -2.5 on DEXA scan.

During the hospitalization, patient runaway and suicide attempts were recorded.

Procedures and ethical approval

This study was conducted in accordance with the relevant French guidelines and regulations. The protocol of our mortality study was approved by the French data protection authority (CNIL, *Commission Nationale de l'Informatique et des Libertés*) and by two independent review boards (CCTIRS, *Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé* and CPP*, Comité de Protection des Personnes*). A notification was sent to all patients selected for the study. Patient non-opposition was a prerequisite for the use of their data. The

data collected and used were anonymized. The study was conducted with full regard to confidentiality and protection of the individual patients' data privacy.

Statistical analysis

All the analyses were performed with R statistical software. Data were expressed as frequencies and percentages for nominal variables, and as means ± standard deviations (SDs) for continuous variables, to describe the sample.

CMR was calculated according to the following formula: number of deaths observed x 100/ total number of patients in the cohort with vital status defined.

SMR was calculated according to the following formula: total number of observed deaths/ total number of expected deaths during the study period. The expected number of deaths was obtained by applying age, gender and specific mortality for the general French population for each year of the study period, information obtained from the National Institute of statistics and Economics Studies (INSEE, *Institut National de la Statistique et des Etudes Economiques)* for the corresponding cumulative person-year in the study cohort.

SMR was initially calculated separately for female and male patients and by period of follow-up in year. SMR confidence interval was calculated using the maximum likelihood method on a Poisson regression model. All the SMR calculations were done using the "popEpi" R package.

With regards to the survival analysis, Kaplan-Meier curve was generated using the Survival R Package.

In order to identify the mostly impacting covariates on the time-to-death, a univariate and multivariate Cox proportional hazard regression were conducted. The proportional hazards (PH) assumption was checked using statistical tests based on the scaled Schoenfeld residuals through the function cox.zph in the survival package of the R Software.

Univariate Cox logistic regression analyses were initially performed. Variables included in univariate analysis corresponded to patient data listed in paragraph 2.4. These variables were either factors reported to be significantly linked to death in the literature or previously unreported factors believed to be linked to death (to test a new clinical hypothesis).

Multivariate Cox logistic regressions analysis was based on variable selection process using the AIC criterion (Akaike information Criterion (35)) which penalizes the deviance of the model with the

number of the model predictors. This ensures to obtain of a parsimonious model; the robustness of the final model was investigated using a bootstrap resampling procedure (36). A *P*-value < 0.05 was considered statistically significant.

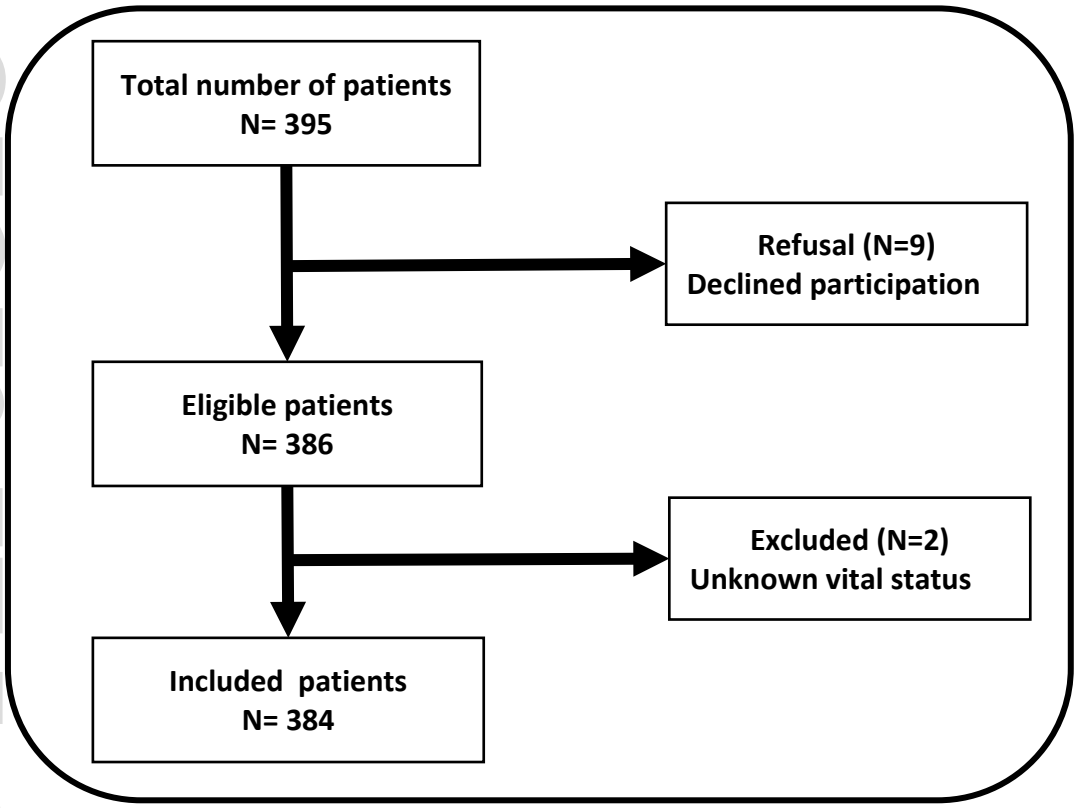
Results

Patient characteristics

A total of 384 patients were included (refer to Figure 1): 363 (94.5%) were female and 21 (5.5%) were male. More than half of them (58%) were referred by another inpatient unit. Mean age at admission was 29.4 (± 11.5) years old and 46.6% of patients had AN-R subtype while 48.2% had AN-BP subtype. Duration of AN at admission was 9.8 (± 9.3) years**.** Before this first admission in the CNU, 301 (78.4%) patients had been admitted previously for AN. Patients' socio-demographic characteristics and AN characteristics are presented in Table 1.

Eighty-eight (22.7%) patients had somatic comorbidities and 185 (48.2%) had psychiatric comorbidities. During their hospitalization in the CNU, 25% of patients were transferred to the medical intensive care unit (MICU). Reasons for these MICU transfers are presented in Supplemental Table 1.

Length of stay was 35 (± 30.2) days. BMI at admission was 12.7 (± 2.2) kg/m². BMI at discharge was 14.2 (± 1.9) kg/m². During hospitalization, 314 (82%) patients received EN and the average weight gain was 3.8 ± 4 kg (0.777 kg per week). At the time of discharge from the CNU, 135 (35.2%) patients were still on EN. The patients' nutritional parameters are presented in Table 1.



240

241 **Figure 1**: Flow chart of the study.

242 **TABLE 1.** Patient characteristics (N=384).

Patient Characteristics	Mean ± SD or N (Percentage)
Female /Male	363 (94.5 %) / 21(5.5 %)
Age at admission (years)	29.3 (± 11.5)
Marital status:	
Couple or married	82 (21.4 %)
Divorced or separated	28 (7.3 %)
Single	269 (70.1 %)
Widowed	5 (1.3 %)
Having at least one child	56 (14.6 %)
Qualification level ≥ 4 years of higher education	97 (25.3 %)

Student status	123 (32 %)
Professional activity:	
Part-time work	7 (1.8 %)
Full time work/job	63 (16.4 %)
Interruption of professional activity ≥ 6 months	123 (32 %)
Recent interruption of professional activity < 6 months	60 (15.6 %)
Admitted for:	
Severe under-nutrition	293 (76.3 %)
Somatic complications	54 (14.1 %)
Nutritional evaluation	19 (4.9 %)
Weaning of purging behaviours	18 (4.7 %)
AN subtype:	
AN restricting type	179 (46.6 %)
AN binge-eating/purging type	185 (48.2 %)
Atypical anorexia nervosa	20 (5.2 %)
Age at AN onset (years)	19 (± 7.6)
Duration of AN at first admission for ED (years)	6.1 (± 8.2)
Duration of AN at admission in the unit (years)	9.8 (± 9.3)
History of hospitalization for AN in other hospitals before index admission	301 (78.4 %)
Number of hospitalizations for AN (before index admission)	2.9 (± 3.4)
Patients' regular behavior:	
Self induced vomiting	162 (42.2 %)
Laxative misuse	80 (20.8 %)
Potomania[1]	53 (13.8 %)
Diuretic use	15 (3.9 %)

Nutritional parameters:	
Albumin level at admission (g/l)[2]	35.7 (± 6.8)
BMI at admission (kg/m²)	12.7 (± 2.2)
BMI at discharge (kg/m²)	14.2 (± 1.9)

AN: anorexia nervosa. BMI: body mass index.[1]: Potomania is a permanent and urgent internal need to drink water apart from a feeling of thirst resulting in the consumption of more than 4 liters of water per day. [2]: normal plasma albumin range is [34-50] g/l.

Follow up period

All patients were followed from the date of their first admission to the CNU until April 25th 2014, which corresponded to an average duration of follow up of 5.2 (± 4.1) years, range [0.003-15.5].

Crude mortality rate, time to death and patients' age at death

Between November 27th 1997 and April 25th 2014, 44 deaths (2 males and 42 females) were reported. Five deaths occurred during the hospital stay in the CNU. The CMR was 11.5 % (44 x 100/384). In the deceased patient subgroup, median time to death was 2 years, range [0.003-14.8], post admission to the CNU. Mean age at death was 41.3 (±15.3) years.

Standardized mortality ratio and patient survival probability

Total SMR was 15.9 [CI 95 % (11.6-21.4)]: total observed deaths was 44, total expected deaths was 2.76, total person year 2204, p <0.001. SMR for female was 15.7 [CI 95% (11.4-20.9)]): number of observed deaths was 42, number of expected death was 2.68, total person year 2060.3, p <0.001. SMR for male was 22.4 [CI 95% (3.7-69.1)]: number of observed deaths was 2, number of expected death was 0.09, total person year 143.4, p <0.001.

SMR for AN restricting type was 15.1 [CI 95% (9.3–22.9)]: number of observed deaths was 19, number of expected death was 1.26, total person year 1071.2, p <0.001. SMR for AN binge-eating/purging type was16.1 [CI 95% (10.3-23.9): number of observed deaths was 22, number of expected death was 1.36, total person year 1055.6, p <0.001.

The influence of age at admission to the CNU on SMR is summarized in Table 2. For the youngest patients (15-24 years old), SMR corresponded to the total SMR of the cohort. SMR was maximally

increased for patients whose first admission to the CNU took place while they were between 25 and 35 years old. For the oldest patients (> 50 years old), SMR was the lowest.

TABLE 2. SMR according to age at first admission to the clinical nutrition unit

Patient age at index admission (in years)	Number of deaths observed	Number of deaths expected	Total person-years	SMR	CI 95%	P value
15-19	3	0.19	421.1	15.5	[3.8-40.1]	<0,0001
20-24	6	0.39	681.6	15.4	[6.1-31.2]	<0,0001
25-29	6	0.26	360.9	23.3	[9.3-47.2]	<0,0001
30-34	6	0.23	240.6	26.0	[10.3-52.7]	<0,0001
35-39	6	0.32	199.5	18.8	[7.5-38.0]	<0,0001
40-49	9	0.57	194.2	15.7	[7.6-28.4]	<0,0001
50 and more	8	0.80	105.7	9.9	[4.6-18.6]	<0,0001

Patient survival probability over time is presented graphically by the Kaplan Meier curve in Figure 2.

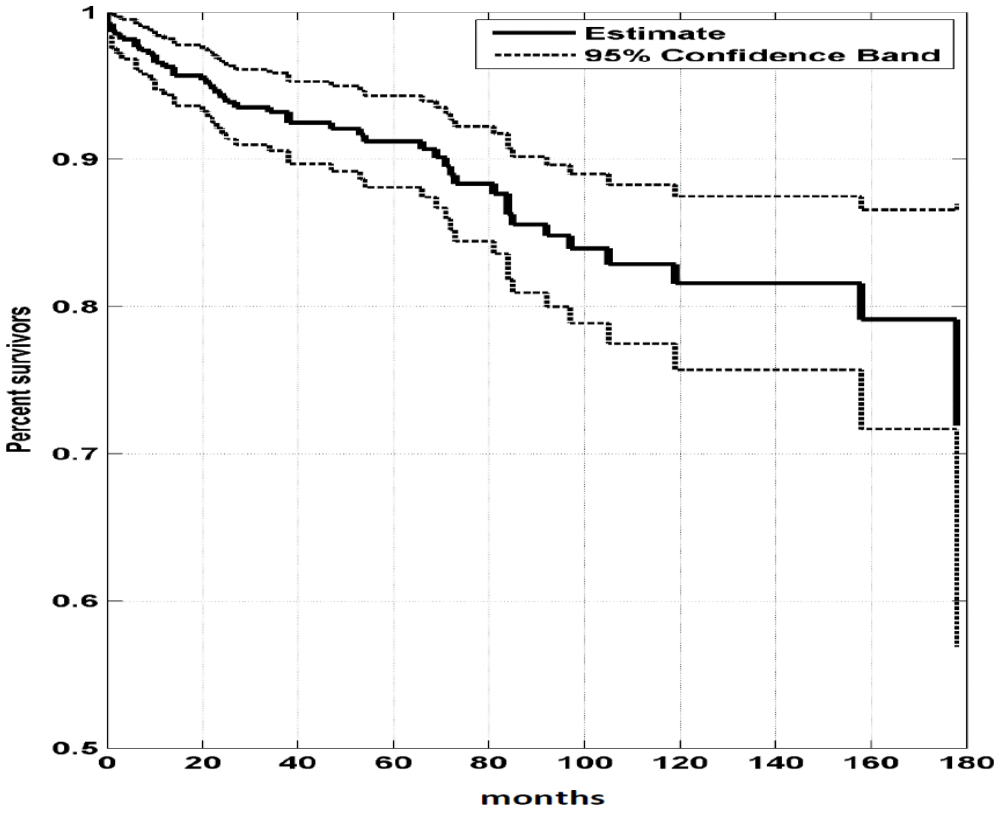


Figure 2. Kaplan-Meier survival curve.

Predictive factors of mortality

The Schoenfeld Residuals Test was not statistically significant (p-value = 0.2248 for the global PH test) and therefore, the proportional hazards was assumed in cox regression.

Results of univariate cox regression analyses presenting variables selected to be included in the multivariate cox regression model are presented in Supplemental Table 2. A total of 45 variables were included in the multivariate Cox regression analysis.

Multivariate Cox regression analysis highlighted predictive factors of mortality presented in Table 3.

TABLE 3. Predictive factors of mortality

Predictive factors of mortality	Hazard Ratio [CI 95%]	P value

Suicide attempt (during index admission)[1]	34.25 [11.04- 106.24]	<0.00001
History of hematological comorbidity (unrelated to AN)[2]	5.77 [1.05-31.78]	0.043
Cardiac complications (during index admission)[3]	3.29 [1.27-8.55]	0.014
Dysnatremia (during index admission)	2.96 [1.45- 6.05]	0.003
Transfer to MICU (during index admission)	2.88 [1.38-6.01]	0.005
Past or present history of discharge against medical advice[4]	2.78 [1.25-6.19]	0.012
Frank anemia (Hb ≤ 9 g/dl) (during index admission)	2.43 [1.16-5.10]	0.018
Infectious complications (during index admission)	2.12 [1.01-4.44]	0.046
Patient age at admission	1.07 [1.04-1.11]	<0.00001
Length of stay	0.98 [0.97-1.00]	0.049

MICU: medical intensive care unit, Hb: hemoglobin plasma level.

[1]: Referred to patients who attempted suicide during their hospital stay in the CNU, inside the hospital

[2]: Past medical history of Hodgkin's disease or MALT lymphoma or myelodysplastic syndrome.

[3]: Cardiac rhythm disorders (bradycardia < 40/min, tachycardia, cardiac repolarization abnormalities), cardiac failure (acute pulmonary edema and/or left ventricular ejection fraction ≤ 50%), elevated troponin without myocardial infarction pericardial effusion.

[4]: Referred to patients who were discharged against medical advice before their hospitalization in the CNU and/or at the time of their hospitalization in the CNU.

Causes of death

Six patients (13.6% of deaths) died of unnatural causes (5 suicides and 1 motor vehicle accident) and 24 patients (54.5% of deaths) died of natural causes. For 21 patients (47.7%), AN was recorded as one of the causes of death. For 7 patients (15.9%), cachexia was recorded as one of the causes of death. Causes of death were not defined for 14 patients (32% of deaths) on their death certificates. On average, 3 different causes of death were recorded on the death certificate for each patient.

Primary cause of patient death (defined according to the methodology described in paragraph 2.4) is presented in Supplemental Figure 1.

Discussion

The aim of the study was to determine the medium-term mortality, risk factors and causes of death in a large cohort of patients with AN hospitalized for extremely severe undernutrition and / or somatic complications in a CNU recognized as a tertiary reference center. Crude mortality rate was 11.5%. SMR was 15.9. The identified predictive factors of mortality 5.2 years after a first hospitalization in the CNU were an older age, the occurrence of a in-hospital suicide attempt, a transfer to MICU and the following somatic complications: frank anemia, dysnatremia, infectious and cardiac complications. Other predictors of mortality were: a past or present history of discharge against medical advice, hematological comorbidities (not related to AN). On the contrary, a prolonged hospitalization was a protective factor since the length of stay had a hazard ratio < 1 in multivariate Cox regression analysis (refer to Table 3). Somatic causes (43% of causes) and suicides (11.4% of causes) were the leading causes of death. Somatic causes included: cardiogenic shock (13.6%), infections (11.4%), digestive complications (6.8%), cancer (6.8%), hypoglycemic coma (4.5%).

This study has the particularity of highlighting somatic predictive factors of mortality that had not previously been demonstrated in the literature: dysnatremia, cardiac and infectious complications, frank anemia.

The mortality rate was higher than reported in other series of AN adult inpatients, published in the literature, particularly after hospitalization in specialized ED tertiary centers. In 2011, Huas *et al* highlighted a SMR of 10.6, 10 years after hospitalization in a tertiary psychiatric department specialized in ED, in a cohort of 601 adult patients with AN (7). Rosling *et al* reported a SMR of 11.7 in a cohort of 157 adult patients with AN, 14 years after hospitalization in a tertiary care center for ED

(19). In these last 2 studies, patient populations were similar in terms of disease severity and SMRs were comparable.

Fichter *et al* in 2016 (14) and Papadopoulos *et al* in 2009 (20) showed an even lower SMR. In the cohort of 1639 adult patients with AN published by Fichter *et al* in 2016, SMR was 5.35, 7 years after admission in an ED unit (14). In the study that analyzed mortality of 6009 patients, 13.4 years after hospitalization with a main or secondary diagnosis of AN, based on data from Swedish national death registers, published by Papadopoulos *et al* in 2009, SMR was 6.2 (20)**.**

These lower SMRs in studies analyzing the mortality of patients with AN after hospitalization in psychiatric department may be explained by the fact that patients with AN hospitalized in these studies tend to be less severely malnourished and less clinically compromised than patients with AN hospitalized in our unit. Thus, mean BMI on admission was higher in these studies compared to our cohort: 14.5 kg/m^2 in the study published by Huas et al. (14), between 10.5 and 17.5 kg/m^2 in the study published by Rosling et al. (19), 13.9 kg/m^2 for the deceased group in the study published by Fichter et al. (14). And a lower BMI has been associated with a higher mortality in the literature (8, 19, 25, 28).

The higher SMR found in our cohort could also be explained by a particular profile of patients more chronically ill, with an older age and a longer duration of ED, compared to the literature data: mean age at admission was 26.4, 26.8, 25 and 19.4 years old, respectively in the study by Huas et al. (7), Rosling et al. (19), Fichter et al. (14), Papadopoulos et al. (20). Mean duration of AN was respectively in these last studies 8.4 (7), 7 (19), 7.1 years (14). And a longer duration of ED has been associated with a higher mortality in the literature (7, 38). The chronicity of the disease is accompanied by strongly negative effect on the social life of patients; 32% of them were on medical leave for over six months at the time of hospitalization. To our knowledge there is no literature data on medical leave prevalence in patients with AN. However literature data show that patients with EDs have poor quality of life and impairment increases with illness severity (37,38) **.**

The higher mortality in the AN patient cohort admitted to medical units in comparison to patients admitted to psychiatry was demonstrated by Emborg *et a*l in a study published in 1999 (39). In this last study, mortality of 2763 patients with AN, 10 years after hospitalization was analyzed using data from national death registers in Denmark. Mortality of patients hospitalized in psychiatry was lower

(SMR of 2.7**)** than that of patients hospitalized in medicine (SMR of 9.8). Mortality was even higher in our sample which recruited patients on criteria of somatic severity (cachexia and/or somatic complications). To our knowledge, our unit is the only one in France or in Europe that hospitalizes patients with these severe somatic profiles.

The rare mortality studies carried out on AN patient cohorts hospitalized on medical units had lower mortality rates than in our study. We found three recent studies**.** In a series of 206 patients with AN, with a mean BMI of 14.5 kg/m², CMR was 1.8 %, 8 years after hospitalization in an endocrinology department (23). In another series of 484 patients with AN, with a mean age of 22.8 years and a mean BMI of 12.8 kg/m², CMR was 1.2 %, 13 years after hospitalization in a CNU (18). In these last 2 studies, the methodology followed biased the results: the national death registers were not used to obtain the patients vital status. Instead, patients were contacted by phone and the number of patients lost to follow up was high: 28% and 10% respectively. Therefore, actual mortality rates may have been underestimated in these studies. Moreover, SMR which is the determining factor in comparing mortality between different cohorts was not calculated. *Amemiya et al.* in 2012 found a CMR of 6% and a SMR of 2, in a cohort of 67 patients with AN with a mean age of 22.3 years and a mean BMI of 13.4 kg/m², 6.3 years after admission in an internal medicine unit: all patients were female and the total number of patients was limited (16).

The analysis of SMRs according to patient age at first admission to the CNU revealed a maximum excess mortality for patients who were admitted between 25 and 34 years old. This result is similar with a lag of 5 years with the analysis published by Moller-Madsen et al. (29): maximum excess mortality for patients with first psychiatric admission between 20 and 29 years old. The trend for oldest patients to have the lowest excess mortality was also found by Moller-Madsen et al. (29) and Patton et al.(40).

Among the causes of death, suicide appeared in the literature as one of the main causes of death (41) (5) (19). In our study, the proportion of suicide seemed to be lower. However, the description of the causes of death retained a share of imprecision with 32% of deaths from unknown or undefined causes. As suicide is probably under-declared, the rate could be higher.

Several mortality studies in AN have shown that having somatic comorbidities (whether or not they are linked to AN) could increase mortality (8,17,19,20). Our study identified these comorbidities in

detail. As for somatic comorbidities unrelated to AN, only a past medical history of hematological pathology was associated with a higher risk of mortality. We found predictors of mortality related to somatic complications (linked to AN) that had not been identified in the literature: dysnatremia and cardiac complications increased the risk of death by a factor of three whereas infectious complications and frank anemia doubled the risk of death. Anemia has been reported, not as a specific predictor of mortality but as a predictor of poor outcome (i.e. including mortality and chronicity of the disorder) (25).

We found predictors of mortality previously identified in the literature**:** a history of suicide attempt (7,42), premature discharge (14) and MICU transfer (43). An older age at presentation, which can be connected to a chronic illness and a longer duration of illness, has also been identified as a predictor of mortality in the literature (5,7,8). Helwitt et al. showed that although AN is predominant in adolescent or early adulthood, the majority of deaths occurred among older patients (44). Mortality risk increased in older populations. The SMR observed in a cohort of 195 adolescents, with a mean age of 17 years, 9 years after hospitalization in a tertiary psychiatric center in Paris was lower (SMR of 6) (43) than in adults (SMR of 10.6) (7).

Some predictors of mortality identified in the literature were not found in our study. Examples include a lower BMI (8,19,25,28) and a longer duration of illness (7,42). A lower BMI did not appear possibly due to the fact that the majority of patients in our cohort had an extremely low BMI. A longer duration of illness was significantly associated with death in univariate analysis but could not be included in multivariate analysis because of missing data and imprecise data regarding the duration of the patients' AN previous admission to the unit. Psychiatric comorbidities (10,12,20,42) also did not appear in our predictors, nor did alcohol use disorder (10,12,30,41,42,45). An explanation could be an underestimation of psychiatric comorbidities in our cohort of patients hospitalized in medicine rather than in psychiatry. However, even if alcohol use disorder was not found as a risk factor of mortality, it appeared as the cause of death in 4 of 44 cases, (one death from acute alcoholic hepatitis, one death from infected ascites on ethyl cirrhosis, one death from digestive hemorrhage on ethyl cirrhosis and one death from ethyl coma).

In light of the results obtained in our study, different interventions to prevent death in patients with AN could be evaluated. First, when a patient is admitted for specialized treatment, it seems important

not to interrupt the hospitalization prematurely. The medical team should work to help the patient complete the care program and achieve the treatment objectives. After the patient's discharge, a specialized treatment should be continued. Then, if other prospective studies confirm the predictive factors of mortality identified in our study, it would be judicious to identify patients with risk factors for death and to intensify monitoring, management and multidisciplinary care of these patients.

The strengths of our study include: the large sample size, the homogeneous sample in terms of severity of malnutrition, the presence of male patients (many studies include only female patients). The very low rate of patients lost to follow up (vital status was not ascertained for only 2 patients or 0.5%) and the rigor and quality of the methodology used (vital status determined by the national death register and the quality of the statistical model) characterize this study.

There are some limitations to our study. First, this observational study is monocentric because the unit is a referral national center. Second, there are a high proportion of missing data concerning the causes of death indicated on death certificates (32%). However, this finding, which is mentioned in other studies (46) is a worldwide problem which is not specific to France or any given country.

In conclusion, mortality of patients with AN, 5.2 years after admission to a tertiary CNU for extremely severe malnutrition, was very high. By identifying the predictors of a reduced life expectancy, the goal of this study is to allow early recognition and management of the most vulnerable patients.

Intensive, close and prolonged multidisciplinary follow-up appears essential, in particular for patients with identified risk factor of mortality. It would be interesting to determine, in this cohort, the 10-year mortality and potential variability in the predictors of mortality.

Acknowledgements

The authors would like to thank Dr. Jacques Ropers for his advice in statistical methodology and Catherine Tellaa for her help in bibliographic research.

The authors' contributions were as the following: MG helped design the study, collected the data, managed the administrative procedures, analyzed the patients' data and wrote the initial manuscript. JCM is the Co-Director of the CNU, designed the study, analyzed the patients' data and contributed to writing the manuscript. MAB performed the statistical analyzes and analyzed the data. NG helped design the study, analyzed the data, and she contributed to writing the manuscript. MH is the Co-

Director of the CNU, helped design the study, analyzed the data and contributed to writing the manuscript. All authors read and approved the final manuscript. The authors report no conflict of interest.

References

1. American Psychiatric Association (APA). Diagnostic and Statistical Manual of Mental Disorders (DSM-5). Washington, DC: American Psychiatric Association; 2013.

2. Haute Autorité de Santé. Clinical practice guidelines: anorexia nervosa: management. [Internet]. 2010. Disponible sur: https://www.has-sante.fr/upload/docs/application/pdf/2013-05/anorexia_nervosa_guidelines_2013-05-15_16-34-42_589.pdf

3. National Institute for Health and Care Excellence. eating-disorders-recognition-and-treatment-pdf-1837582159813.pdf [Internet]. 2017 [cité 8 avr 2020]. Disponible sur: https://www.nice.org.uk/guidance/ng69/resources/eating-disorders-recognition-and-treatment-pdf-1837582159813

4. Yager J, Devlin MJ, Halmi KA, et al. Practice guideline for the treatment of patients with eating disorders. [Internet]. 3rd ed. Washington, DC: APA; 2012. Disponible sur: psychiatryonline.org/pb/assets/ raw/sitewide/practice_guidelines/guidelines/eatingdisorders-watch.pdf.

5. Arcelus J, Mitchell AJ, Wales J, Nielsen S. Mortality rates in patients with anorexia nervosa and other eating disorders. A meta-analysis of 36 studies. Arch Gen Psychiatry. juill 2011;68(7):724‑31.

6. Chesney E, Goodwin GM, Fazel S. Risks of all-cause and suicide mortality in mental disorders: a meta-review. World Psychiatry Off J World Psychiatr Assoc WPA. juin 2014;13(2):153‑60.

7. Huas C, Caille A, Godart N, Foulon C, Pham-Scottez A, Divac S, et al. Factors predictive of ten-year mortality in severe anorexia nervosa patients. Acta Psychiatr Scand. janv 2011;123(1):62‑70.

8. Edakubo S, Fushimi K. Mortality and risk assessment for anorexia nervosa in acute-care hospitals: a nationwide administrative database analysis. BMC Psychiatry. 13 janv 2020;20(1):19.

9. Quadflieg N, Strobel C, Naab S, Voderholzer U, Fichter MM. Mortality in males treated for an eating disorder-A large prospective study. Int J Eat Disord. 2019;52(12):1365‐9.

10. Kask J, Ramklint M, Kolia N, Panagiotakos D, Ekbom A, Ekselius L, et al. Anorexia nervosa in males: excess mortality and psychiatric co-morbidity in 609 Swedish in-patients. Psychol Med. juin 2017;47(8):1489‐99.

11. Fichter MM, Quadflieg N, Crosby RD, Koch S. Long-term outcome of anorexia nervosa: Results from a large clinical longitudinal study. Int J Eat Disord. 2017;50(9):1018‐30.

12. Kask J, Ekselius L, Brandt L, Kollia N, Ekbom A, Papadopoulos FC. Mortality in Women With Anorexia Nervosa: The Role of Comorbid Psychiatric Disorders. Psychosom Med. 2016;78(8):910‐9.

13. Errichiello L, Iodice D, Bruzzese D, Gherghi M, Senatore I. Prognostic factors and outcome in anorexia nervosa: a follow-up study. Eat Weight Disord EWD. mars 2016;21(1):73‐82.

14. Fichter MM, Quadflieg N. Mortality in eating disorders - results of a large prospective clinical longitudinal study. Int J Eat Disord. avr 2016;49(4):391‐401.

15. Ward A, Ramsay R, Russell G, Treasure J. Follow-up mortality study of compulsorily treated patients with anorexia nervosa. Int J Eat Disord. nov 2015;48(7):860‐5.

16. Amemiya N, Takii M, Hata T, Morita C, Takakura S, Oshikiri K, et al. The outcome of Japanese anorexia nervosa patients treated with an inpatient therapy in an internal medicine unit. Eat Weight Disord EWD. mars 2012;17(1):e1-8.

17. Erdur L, Kallenbach-Dermutz B, Lehmann V, Zimmermann-Viehoff F, Köpp W, Weber C, et al. Somatic comorbidity in anorexia nervosa: First results of a 21-year follow-up study on female inpatients. Biopsychosoc Med. 2 févr 2012;6(1):4.

18. Rigaud D, Pennacchio H, Bizeul C, Reveillard V, Vergès B. Outcome in AN adult patients: a 13-year follow-up in 484 patients. Diabetes Metab. sept 2011;37(4):305‑11.

19. Rosling AM, Sparén P, Norring C, von Knorring A-L. Mortality of eating disorders: a follow-up study of treatment in a specialist unit 1974-2000. Int J Eat Disord. mai 2011;44(4):304‑10.

20. Papadopoulos FC, Ekbom A, Brandt L, Ekselius L. Excess mortality, causes of death and prognostic factors in anorexia nervosa. Br J Psychiatry J Ment Sci. janv 2009;194(1):10‑7.

21. Fichter MM, Quadflieg N, Hedlund S. Twelve-year course and outcome predictors of anorexia nervosa. Int J Eat Disord. mars 2006;39(2):87‑100.

22. Fichter MM, Quadflieg N. Six-year course and outcome of anorexia nervosa. Int J Eat Disord. déc 1999;26(4):359‑85.

23. Viricel J, Bossu C, Galusca B, Kadem M, Germain N, Nicolau A, et al. [Retrospective study of anorexia nervosa: reduced mortality and stable recovery rates]. Presse Medicale Paris Fr 1983. 19 nov 2005;34(20 Pt 1):1505‑10.

24. Nielsen S, Emborg C, Mølbak A-G. Mortality in concurrent type 1 diabetes and anorexia nervosa. Diabetes Care. févr 2002;25(2):309‑12.

25. Löwe B, Zipfel S, Buchholz C, Dupont Y, Reas DL, Herzog W. Long-term outcome of anorexia nervosa in a prospective 21-year follow-up study. Psychol Med. juill 2001;31(5):881‑90.

26. Tanaka H, Kiriike N, Nagata T, Riku K. Outcome of severe anorexia nervosa patients receiving inpatient treatment in Japan: an 8-year follow-up study. Psychiatry Clin Neurosci. août 2001;55(4):389‑96.

27. Ramsay R, Ward A, Treasure J, Russell GF. Compulsory treatment in anorexia nervosa. Short-term benefits and long-term mortality. Br J Psychiatry J Ment Sci. août 1999;175:147‑53.

28. Herzog W, Deter HC, Fiehn W, Petzold E. Medical findings and predictors of long-term physical outcome in anorexia nervosa: a prospective, 12-year follow-up study. Psychol Med. mars 1997;27(2):269‑79.

29. Møller-Madsen S, Nystrup J, Nielsen S. Mortality in anorexia nervosa in Denmark during the period 1970-1987. Acta Psychiatr Scand. déc 1996;94(6):454‑9.

30. Eckert ED, Halmi KA, Marchi P, Grove W, Crosby R. Ten-year follow-up of anorexia nervosa: clinical course and outcome. Psychol Med. janv 1995;25(1):143‑56.

31. Ratnasuriya RH, Eisler I, Szmukler GI, Russell GF. Anorexia nervosa: outcome and prognostic factors after 20 years. Br J Psychiatry J Ment Sci. avr 1991;158:495‑502.

32. Theander S. Outcome and prognosis in anorexia nervosa and bulimia: some results of previous investigations, compared with those of a Swedish long-term study. J Psychiatr Res. 1985;19(2‑3):493‑508.

33. Morgan HG, Russell GF. Value of family background and clinical features as predictors of long-term outcome in anorexia nervosa: four-year follow-up study of 41 patients. Psychol Med. nov 1975;5(4):355‑71.

34. Robinson P, Rhys Jones W. MARSIPAN: management of really sick patients with anorexia nervosa. BJPsych Adv. janv 2018;24(1):20‑32.

35. Hirotugu Akaike. Information theory and an extension of the maximum likelihood principle. In: Second International Symposium on Information Theory; 1973. p. 267‑81.

36. Efron Bradley, R.J. Tibshirani. An introduction to the Bootstrap. In New York, Chapman and Hall/CRC.; 1994. p. 436.

37. DeJong H, Oldershaw A, Sternheim L, Samarawickrema N, Kenyon MD, Broadbent H, et al. Quality of life in anorexia nervosa, bulimia nervosa and eating disorder not-otherwise-specified. J Eat Disord. 2013;1:43.

38. Winkler LA-D, Christiansen E, Lichtenstein MB, Hansen NB, Bilenberg N, Støving RK. Quality of life in eating disorders: a meta-analysis. Psychiatry Res. 30 sept 2014;219(1):1‑9.

39. Emborg C. Mortality and causes of death in eating disorders in Denmark 1970-1993: a case register study. Int J Eat Disord. avr 1999;25(3):243‑51.

40. Patton G.C. Mortality in eating disorders. Psychological Medicine. 1988;18:947‑51.

41. Herzog DB, Greenwood DN, Dorer DJ, Flores AT, Ekeblad ER, Richards A, et al. Mortality in eating disorders: a descriptive study. Int J Eat Disord. juill 2000;28(1):20‑6.

42. Keel PK, Dorer DJ, Eddy KT, Franko D, Charatan DL, Herzog DB. Predictors of mortality in eating disorders. Arch Gen Psychiatry. févr 2003;60(2):179‑83.

43. Stheneur C, Ali A, Tric L, Curt F, Hubert T, Godart N. Impact of somatic severity on long-term mortality in anorexia nervosa. Eat Weight Disord EWD. juin 2017;22(2):285‑9.

44. Hewitt PL, Coren S, Steel GD. Death from anorexia nervosa: age span and sex differences. Aging Ment Health. févr 2001;5(1):41‑6.

45. Suzuki K, Takeda A, Yoshino A. Mortality 6 years after inpatient treatment of female Japanese patients with eating disorders associated with alcoholism. Psychiatry Clin Neurosci. juin 2011;65(4):326‑32.

46. Muir A, Palmer RL. An audit of a British sample of death certificates in which anorexia nervosa is listed as a cause of death. Int J Eat Disord. nov 2004;36(3):356‑60.