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

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Abbreviations list:

AN: anorexia nervosa

AN-R: restricting type

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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

1 **ABSTRACT**

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

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

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

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

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

22

23

24 **Keywords:**

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

26

27 **Significant outcomes**

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

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

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

36 - A prolonged hospitalization was a protective factor.

37 **Limitations**

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

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

42

43

44

45 **Introduction**

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

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

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

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

74 **Material and Methods**

75 **Study Design and Aims**

76 We conducted an observational mortality study including a sample of patients with AN admitted to
77 the CNU for severe malnutrition ($BMI < 13 \text{ kg/m}^2$) and/or medical complications related to
78 malnutrition or refeeding.

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

82 **Patients**

83 **Inclusion criteria**

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

89

90

91 **Exclusion criteria**

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

94

95 **Clinical Nutrition Unit treatment program**

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

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

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

111 **Parameters studied**

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

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

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

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

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

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

139 - AN characteristics (restricting type (AN-R), binge-eating/purging type (AN-BP), purging
140 behaviours).

141 - anamnestic data (age at AN onset, AN duration¹, history of hospitalization, minimum BMI since
142 puberty, history of suicide attempt or discharge against medical advice or compulsory admission).

143 -nutritional data (BMI and albumin plasma level at admission, EN prescription, weight gain during
144 hospitalization, BMI at discharge).

145 - history of somatic comorbidities unrelated to AN (cardiovascular, dermatological, digestive,
146 endocrine, genetic, hematological, infectious, immunological, nephrological, neurological,
147 otolaryngological, ophthalmic, pulmonary, rheumatological, urological, solid cancer).

148 - psychiatric comorbidities¹ (personality disorders, obsessive-compulsive disorders, mood and/or
149 anxiety disorders, non-suicidal self-injury disorder, attention-deficit hyperactivity disorder,
150 kleptomania).

151 - addictions (alcohol, substance use, tobacco).

152 - referral, reason for hospitalization, requirement for compulsory admission, requirement for MICU
153 transfer, length of stay, discharge against medical advice from the unit, hospital facility receiving the
154 patient after discharge from the CNU.

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

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

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

162 - metabolic conditions such as hypokalemia, hypophosphatemia, hypoglycemia, dysnatremia, acute
163 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.

- 164 - hematological conditions such as neutropenia (neutrophil count < 2000/mm³), frank neutropenia
165 (neutrophil count < 1000/ mm³), lymphopenia (lymphocyte count < 1500/mm³), frank
166 lymphopenia (lymphocyte count < 1000/ mm³), anemia (hemoglobin (hb) level < 13 g/dl for male
167 and < 12 g/dl for female), frank anemia (hb ≤ 9g/dl), thrombocytopenia (platelet level < 150
168 000/mm³), frank thrombocytopenia (platelet level < 80 000/mm³).
- 169 - hypertransaminasemia defined by AST (aspartate transaminase) > 31 IU/L and/or ALT (alanine
170 transaminase) > 65 IU/L, related to malnutrition or refeeding. Mild hypertransaminasemia (< 10 X
171 normal) and marked hypertransaminasemia (≥ 10 X normal) and were specified.
- 172 - cardiac complications such as cardiac rhythm disorders (bradycardia < 40/min, tachycardia,
173 cardiac repolarization abnormalities), cardiac failure (acute pulmonary edema and/or left
174 ventricular ejection fraction (LVEF) ≤ 50%), elevated troponin without myocardial infarction,
175 pericardial effusion.
- 176 - digestive conditions such as gastroesophageal reflux and / or esophagitis, constipation, biological
177 pancreatitis (lipase > 3N).
- 178 - neurological conditions such as axial hypotonia, lower limb hypoesthesia, cerebellar syndrome,
179 central pontine myelinolysis.
- 180 - bladder-sphincter dysfunctions (urinary incontinence, urinary retention) and
181 - infectious complications.

182 Chronic complications of AN highlighted during the hospitalization such as low bone mineral density
183 (LBMD) were also recorded. Osteoporosis was defined by a T score < -2.5 on DEXA scan.
184 During the hospitalization, patient runaway and suicide attempts were recorded.

185 **Procedures and ethical approval**

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

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

194 **Statistical analysis**

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

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

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

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

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

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

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

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

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

224 **Results**

225 **Patient characteristics**

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

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

236 Length of stay was 35 (\pm 30.2) days. BMI at admission was 12.7 (\pm 2.2) kg/m². BMI at discharge was
237 14.2 (\pm 1.9) kg/m². During hospitalization, 314 (82%) patients received EN and the average weight
238 gain was 3.8 \pm 4 kg (0.777 kg per week). At the time of discharge from the CNU, 135 (35.2%)
239 patients were still on EN. The patients' nutritional parameters are presented in Table 1.

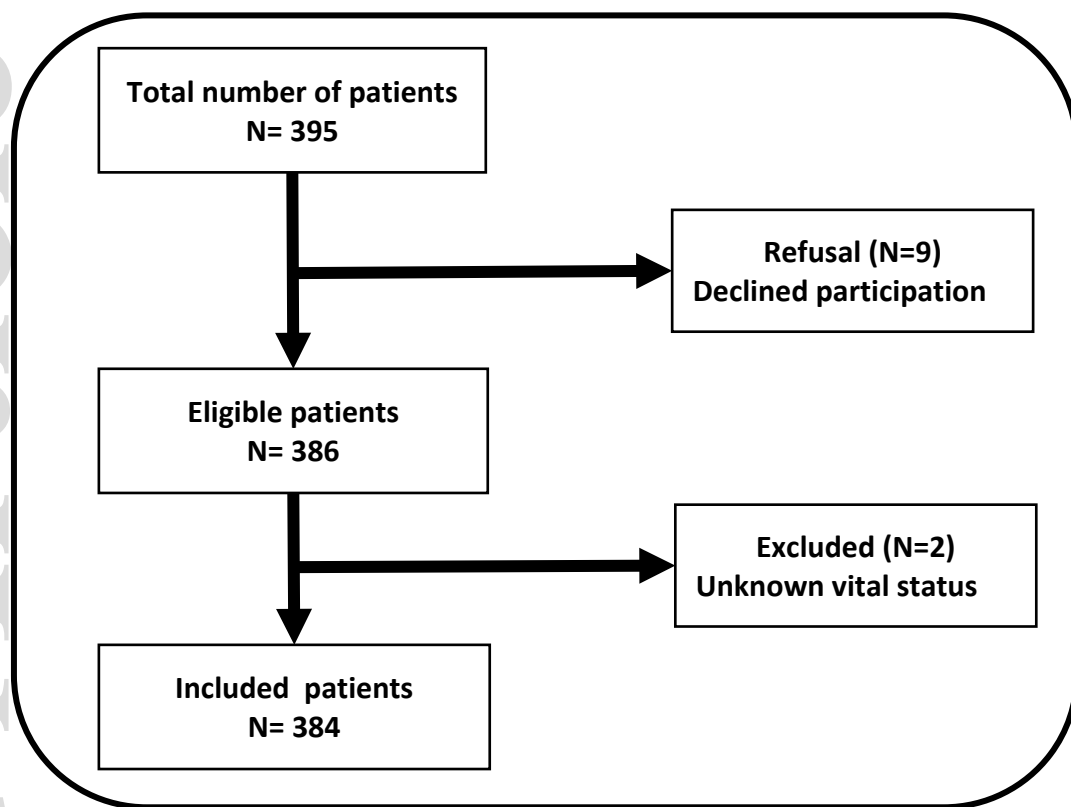


Figure 1: Flow chart of the study.

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241

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

Patient Characteristics	Mean \pm SD or N (Percentage)
Female /Male	363 (94.5 %) / 21(5.5 %)
Age at admission (years)	29.3 (\pm 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 \geq 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 \geq 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 (\pm 7.6)
Duration of AN at first admission for ED (years)	6.1 (\pm 8.2)
Duration of AN at admission in the unit (years)	9.8 (\pm 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 (\pm 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/m ²)	12.7 (± 2.2)
BMI at discharge (kg/m ²)	14.2 (± 1.9)

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

246

247 **Follow up period**

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

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

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

255

256 **Standardized mortality ratio and patient survival probability**

257 Total SMR was 15.9 [CI 95 % (11.6-21.4)]: total observed deaths was 44, total expected deaths was
 258 2.76, total person year 2204, p <0.001. SMR for female was 15.7 [CI 95% (11.4-20.9)]: number of
 259 observed deaths was 42, number of expected death was 2.68, total person year 2060.3, p <0.001. SMR
 260 for male was 22.4 [CI 95% (3.7-69.1)]: number of observed deaths was 2, number of expected death
 261 was 0.09, total person year 143.4, p <0.001.

262 SMR for AN restricting type was 15.1 [CI 95% (9.3–22.9)]: number of observed deaths was 19,
 263 number of expected death was 1.26, total person year 1071.2, p <0.001. SMR for AN binge-
 264 eating/purging type was 16.1 [CI 95% (10.3-23.9): number of observed deaths was 22, number of
 265 expected death was 1.36, total person year 1055.6, p <0.001.

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

268 increased for patients whose first admission to the CNU took place while they were between 25 and
269 35 years old. For the oldest patients (> 50 years old), SMR was the lowest.

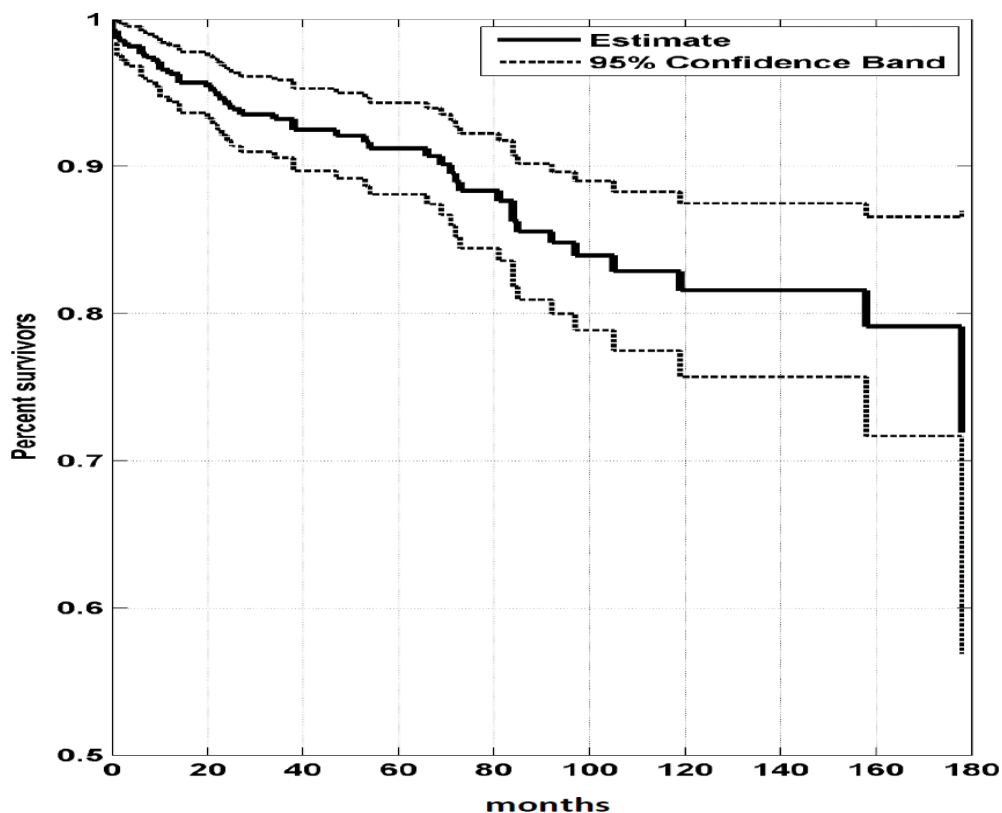
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277 **TABLE 2.** SMR according to age at first admission to the clinical nutrition unit

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

278
279
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281

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



282
 283 **Figure 2.** Kaplan-Meier survival curve.

284
 285 **Predictive factors of mortality**

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

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

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

292
 293 **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

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

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

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

297 ³: Cardiac rhythm disorders (bradycardia < 40/min, tachycardia, cardiac repolarization abnormalities),

298 cardiac failure (acute pulmonary edema and/or left ventricular ejection fraction ≤ 50%), elevated

299 troponin without myocardial infarction pericardial effusion.

300 ⁴: Referred to patients who were discharged against medical advice before their hospitalization in the

301 CNU and/or at the time of their hospitalization in the CNU.

302

303 **Causes of death**

304 Six patients (13.6% of deaths) died of unnatural causes (5 suicides and 1 motor vehicle accident) and
305 24 patients (54.5% of deaths) died of natural causes. For 21 patients (47.7%), AN was recorded as one
306 of the causes of death. For 7 patients (15.9%), cachexia was recorded as one of the causes of death.
307 Causes of death were not defined for 14 patients (32% of deaths) on their death certificates. On
308 average, 3 different causes of death were recorded on the death certificate for each patient.
309 Primary cause of patient death (defined according to the methodology described in paragraph 2.4) is
310 presented in Supplemental Figure 1.

311

312 **Discussion**

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

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

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

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

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

340 These lower SMRs in studies analyzing the mortality of patients with AN after hospitalization in
341 psychiatric department may be explained by the fact that patients with AN hospitalized in these
342 studies tend to be less severely malnourished and less clinically compromised than patients with AN
343 hospitalized in our unit. Thus, mean BMI on admission was higher in these studies compared to our
344 cohort: 14.5 kg/m² in the study published by Huas *et al.* (14), between 10.5 and 17.5 kg/m² in the
345 study published by Rosling *et al.* (19), 13.9 kg/m² for the deceased group in the study published by
346 Fichter *et al.* (14). And a lower BMI has been associated with a higher mortality in the literature (8,
347 19, 25, 28).

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

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

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

366 The rare mortality studies carried out on AN patient cohorts hospitalized on medical units had lower
367 mortality rates than in our study. We found three recent studies. In a series of 206 patients with AN,
368 with a mean BMI of 14.5 kg/m², CMR was 1.8 %, 8 years after hospitalization in an endocrinology
369 department (23). In another series of 484 patients with AN, with a mean age of 22.8 years and a mean
370 BMI of 12.8 kg/m², CMR was 1.2 %, 13 years after hospitalization in a CNU (18). In these last 2
371 studies, the methodology followed biased the results: the national death registers were not used to
372 obtain the patients vital status. Instead, patients were contacted by phone and the number of patients
373 lost to follow up was high: 28% and 10% respectively. Therefore, actual mortality rates may have
374 been underestimated in these studies. Moreover, SMR which is the determining factor in comparing
375 mortality between different cohorts was not calculated. *Amemiya et al.* in 2012 found a CMR of 6%
376 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
377 13.4 kg/m², 6.3 years after admission in an internal medicine unit: all patients were female and the
378 total number of patients was limited (16).

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

385 Among the causes of death, suicide appeared in the literature as one of the main causes of death (41)
386 (5) (19). In our study, the proportion of suicide seemed to be lower. However, the description of the
387 causes of death retained a share of imprecision with 32% of deaths from unknown or undefined
388 causes. As suicide is probably under-declared, the rate could be higher.

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

391 detail. As for somatic comorbidities unrelated to AN, only a past medical history of hematological
392 pathology was associated with a higher risk of mortality. We found predictors of mortality related to
393 somatic complications (linked to AN) that had not been identified in the literature: dysnatremia and
394 cardiac complications increased the risk of death by a factor of three whereas infectious complications
395 and frank anemia doubled the risk of death. Anemia has been reported, not as a specific predictor of
396 mortality but as a predictor of poor outcome (i.e. including mortality and chronicity of the disorder)
397 (25).

398 We found predictors of mortality previously identified in the literature: a history of suicide attempt
399 (7,42), premature discharge (14) and MICU transfer (43). An older age at presentation, which can be
400 connected to a chronic illness and a longer duration of illness, has also been identified as a predictor
401 of mortality in the literature (5,7,8). Helwitt et al. showed that although AN is predominant in
402 adolescent or early adulthood, the majority of deaths occurred among older patients (44). Mortality
403 risk increased in older populations. The SMR observed in a cohort of 195 adolescents, with a mean
404 age of 17 years, 9 years after hospitalization in a tertiary psychiatric center in Paris was lower (SMR
405 of 6) (43) than in adults (SMR of 10.6) (7).

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

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

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

425 The strengths of our study include: the large sample size, the homogeneous sample in terms of
426 severity of malnutrition, the presence of male patients (many studies include only female patients).
427 The very low rate of patients lost to follow up (vital status was not ascertained for only 2 patients or
428 0.5%) and the rigor and quality of the methodology used (vital status determined by the national death
429 register and the quality of the statistical model) characterize this study.

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

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

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

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446 JCM is the Co-Director of the CNU, designed the study, analyzed the patients' data and contributed to
447 writing the manuscript. MAB performed the statistical analyzes and analyzed the data. NG helped
448 design the study, analyzed the data, and she contributed to writing the manuscript. MH is the Co-

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