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(Citation)

Psychiatry Research, 342:116151

(Issue Date)

2024-12

(Resource Type)

journal article

(Version)

Accepted Manuscript

(Rights)

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(URL)

<https://hdl.handle.net/20.500.14094/0100491643>



Preliminary development of a risk predictor for severe complication in patients with anorexia nervosa

Running title: Development of a risk score for prevention of serious physical complications in patients with anorexia nervosa

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¹ Abbreviations: ALB, albumin; AN, anorexia nervosa; AST, aspartate transaminase; BMI, body mass index; BUN, blood urea nitrogen; Ca, calcium; CRP, C-reactive protein; IMW, internal medicine ward; PW, psychiatric ward

Highlights

- Anorexia nervosa (AN) can be life-threatening due to variable complications
- A quantitative indicator for judgement of early therapeutic intervention through hospitalization of patients with AN is needed.
- BMI, BUN, Ca, ALB, AST, and CRP are components of the risk score created in this study.
- The cut-off of this score is 12 out of 19 points, having area under the ROC curve of 0.824.
- This score helps decide whether early hospitalization is required and whether those patients should be admitted to the medical ward before starting on the psychiatric ward.

Abstract

Anorexia nervosa (AN) is life-threatening because of many physical complications, hence a quantitative indicator for early therapeutic intervention through hospitalization is needed. Here, we compared the demographics of 21 patients with AN who required intensive treatment in the internal medicine ward and those of 61 patients with AN who directly admitted to the psychiatric ward. We developed a risk score for severe physical complications in patients with AN, by using six items with significant differences between two groups; body mass index, blood urea nitrogen, corrected calcium, albumin, aspartate transaminase, and C-reactive protein (area under the curve = 0.824).

Keywords: eating disorder, anorexia nervosa, physical complications, hospitalization, risk score

1 Introduction

Eating disorders, especially anorexia nervosa (AN), can be life-threatening owing to various physical complications. Its mortality rate is reported to be 7–18%, which is the highest mortality rate among psychiatric disorders (Bryant et al., 2022). The low body weight and malnutrition caused by AN can lead to physical complications, such as hypoglycemia, electrolyte abnormalities, liver dysfunction, refeeding syndrome, cardiovascular diseases, severe infections, and sepsis, which can directly lead to death (Hundemer et al., 2022; Yamamoto et al., 2021).

The decision to admit a patient to a hospital is almost based solely on the empirical judgment of doctors and body mass index (BMI). Establishing quantitative evaluation indicators to quickly identify patients who have a poor prognosis and need early therapeutic intervention through hospitalization is necessary to prevent severe physical illnesses of patients with AN (Zipfel et al., 2015). In addition, it is important to decide whether those patients should be admitted to the medical ward before the psychiatric ward, to provide appropriate care. In this study, we aimed to analyze and compare the characteristics of patients with AN who were hospitalized in internal medicine wards and psychiatric wards, to develop a predictive score for severe physical complications requiring intensive internal

treatment.

2 Methods

2.1 Participants

This retrospective study was conducted at Kobe University Hospital. It was approved by the ethics committee of the Kobe University Graduate School of Medicine. We included 82 participants with AN admitted in the psychiatric ward of Kobe University Hospital between April 2016 and December 2023, and with adequate information on vital signs and blood data at admission. We used the data at first admissions within this interval for the present study.

The diagnosis of AN was made by two or more psychiatrists according to the *DSM-5*.

Consent was waived owing to the study's retrospective design. Instead, the participants were given the opportunity of refusal by written release of information in advance, and it was confirmed that there was no request for refusal.

We allocated patients who required intensive treatment for physical complications in the internal medicine ward before admission to a psychiatric ward, because of various physical complications, to the internal medicine ward (IMW) group, and the other patients were allocated to the psychiatric ward (PW) group. Data at the time of admission were used

for analysis. We obtained data for each patient from their medical records. We described sampling details in the **Supplementary Text**.

2.2 Statistical analyses and development of risk scores for complications in patients with AN

Statistical analyses were performed using R version 4.2.1 (The R Foundation, Vienna, Austria). Statistical significance was defined as $P < .05$, using a two-tailed test. We compared the continuous variables of applicable items at admission between the IMW and PW groups using the Mann-Whitney U test. Fisher's exact test was performed for categorical variables. Each item with $P < .05$ was fitted to a logistic regression model, with sex, age, and BMI as independent variables. When we performed the logistic regression analysis, missing values were completed by the multiple assignment method using the R package mice. Sex was determined as a dummy variable (1 for females and 0 for males). To create dummy variables for the continuous variables of items with significant differences between the two groups, the overall median was used as the threshold. The dependent variable was 1 for the IMW group and 0 for the PW group.

To develop a practical risk score with reference to the methods of a previous study

(Elbaz et al., 2008), we assigned weighted points proportional to the odds ratio (OR) values. The integer value obtained by dividing the OR of each item by the OR of the item with the lowest OR and rounding was used as the distribution of points for each item. We then calculated the risk score for each patient using this developed score and examined the predictive accuracy using receiver operating characteristic (ROC) curves to determine the cutoff points.

3 Results

Demographic data and clinical information of 82 patients are presented in **Table S1 and S2**. BMI ($P = .0135$), the blood urea nitrogen (BUN) ($P < .001$), corrected calcium (Ca) ($P = .0277$), albumin (ALB) ($P = .0465$), aspartate transaminase (AST) ($P = .00411$), and CRP levels ($P < .001$) significantly differed between the two groups. The medical history of each patient is presented in **Table S3**. The overall quartiles and medians for these six parameters are presented in **Table S4**.

These six items were evaluated using logistic analyses. We adjusted the values of Ca in four patients and CRP in five patients because of missing data due to unmeasured. Dummy variables were assigned to six items considered in relation to the IMW group: BMI of < 12.1 ,

Ca < 9.1, ALB < 4.4, BUN > 18.3, AST > 31.5, and CRP > 0.01 were assigned with 1 respectively, and otherwise, each was set to 0. We performed logistic analyses to assess the association between the two groups and the parameters (BUN, Ca, ALB, AST, CRP, and BMI) in model 1 to adjust for age and sex as confounding factors, and using age, BMI, and sex as confounding factors in model 2 (**Table 1**). We used BMI from model 1 and the others from model 2. The lowest OR among the six items was that of ALB; therefore, the integer values obtained by dividing the ORs for BMI, BUN, Ca, ALB, AST, and CRP by the OR for ALB and then rounding off were 2, 6, 2, 1, 3, and 5, respectively (**Table 1**). Integer values were used as risk score distributions.

We evaluated the predictive value of the risk score and whether the patients were in the IMW or PW group using ROC curves. At the cutoff of 12 points, the area under the ROC curve (AUC) was 0.824 (**Figure 1**).

4 Discussion

In our study, the increase in BUN, AST, and CRP levels and the decrease in BMI, Ca, and ALB were related to admission to the internal medicine department for treatment of complications. To the best of our knowledge, we preliminary have developed the first

predictive score to determine severe physical complications that require admission to an internal medicine ward.

AST are sensitive indicators of hepatocellular damage. When glycogen from the liver is depleted due to prolonged energy deprivation, autophagy acts on skeletal muscles and hepatocytes through gluconeogenesis to maintain blood glucose, which is indispensable for the maintenance of multiple functions in the organism (Kheloufi et al., 2014). Excess blood urea can cause various serious illnesses, including oxygen deprivation, kidney failure, shock, and gastrointestinal bleeding (Botewad et al., 2023). CRP shows a minor increase in various factors, including abnormal T axis on ECG, osteopenia, depression, and diminished glomerular filtration, leading to poor physical prognosis, not only in infection (Kushner et al., 2006). Hypocalcemia causes such symptoms as abnormal sensory perception of the limbs and spasm of the larynx (Bilezikian, 2020).

Our study has several limitations. It was a retrospective study that relied on historical data from medical records. We need to conduct further prospective studies on patients with AN using our risk scores to validate their accuracy and to be clinically applied. The sample size was too small, and data regarding blood test results were missing. Lack of some data for some patients could affect the accuracy of statistical analysis and results. The risk scores

generated in this study would still be preliminary. Our study was conducted at a single university hospital, and it did not include those who were admitted to a medical ward but did not transfer to a psychiatric ward, which may make it difficult to generalize our conclusions to a wide range of situations. We found it difficult to accurately evaluate the severity of physical complications; therefore, we substituted physical complications requiring treatment in the internal medicine ward to define as severe.

We developed a preliminary risk score scale to predict the development of severe physical complications requiring admission to the internal medicine ward. This may help us prevent patients with AN from developing serious conditions.

Author contributions

Toshiyuki Shirai: Data curation, formal analysis, investigation, visualization, writing of the original draft. Takaki Tanifuji: Data curation, formal analysis, investigation, visualization, writing of the original draft. Ikuo Otsuka: Conceptualization, methodology, data curation, formal analysis, writing – review & editing. Satoshi Okazaki: Data curation, Formal analysis. Tadasu Horai: Data curation, formal analysis. Naruhisa Yamaki: Data curation, formal analysis. Haruka Minami: Data curation, formal analysis. Masao Miyachi: Data curation,

formal analysis. Shohei Okada: Data curation, formal analysis. Akitoyo Hishimoto: Conceptualization, Supervision, Writing – review & editing.

Declaration of competing interest

None.

Data availability statement

The data supporting the findings of this study are available in the Supplementary Materials “Supplementary_PSY-D-23-03784.docx.” The datasets of this study are available from the corresponding author upon reasonable request.

Funding

This work was partially supported by JSPS KAKENHI [grant numbers JP18K15483 and JP21K07520 to Satoshi Okazaki and JP17H04249 and JP21H02852 to Akitoyo Hishimoto].

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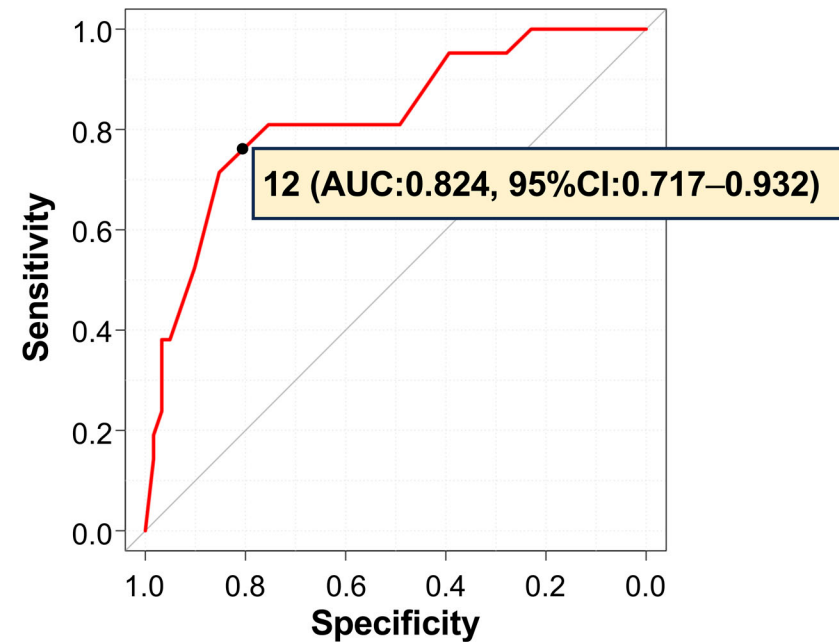
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Figure Legend

Figure 1. ROC curves indicate that the cutoff point for predicting the risk score for physical complications required to admit in the internal medicine ward. The horizontal axis indicates $1 - \text{specificity}$, and the vertical axis indicates sensitivity. A score ≥ 12 points in patients with AN indicates the risk of being admitted to an internal medicine ward because of physical complications. Cutoff: ≥ 12 out of 19 points (area under the curve = 0.824, 95% CI = 0.717–0.932, sensitivity = 0.803, specificity = 0.762).

AN, anorexia nervosa; AUC, area under the curve; ROC, receiver operating characteristic

Reference value	Risk score
BMI<12.1	2
BUN>18.3 (mg/dL)	6
Ca<9.1 (mg/dL)	2
ALB<4.4 (g/dL)	1
AST>31.5 (U/L)	3
CRP>0.01 (mg/dL)	5
Total	19



≥ 12 points

**Patients are likely admitted to
an internal medicine hospital because of physical complications.
(Sensitivity: 0.762/ Specificity: 0.803)**

Table

Table 1. Logistic regression models for prediction score for hospitalized AN in internal medicine to treat physical complications.

	Model 1 ^a		Model 2 ^b		Risk score ^c	Reference value ^d
	OR (95% CI)	P value	OR (95% CI)	P value		
BMI	2.10 (0.71 – 6.50)	.1839			2 (2.10/1.03)	<12.1
BUN	5.94 (1.81 – 24.08)	.00587	5.96 (1.76 – 25.06)	.00723	6 (5.96/1.03)	>18.3 mg/dL
Ca	2.73 (0.93 – 8.41)	.0702	2.26 (0.72 – 7.22)	.1607	2 (2.26/1.03)	<9.1 mg/dL
ALB	1.33 (0.39 – 4.60)	.6451	1.03 (0.27 – 3.79)	.9609	1 (1.03/1.03)	<4.4 g/dL
AST	4.32 (1.40 – 15.51)	.0155	3.18 (0.96 – 12.07)	.0688	3 (3.18/1.03)	>31.5 U/L
CRP	5.42 (1.70 – 19.66)	.00593	5.68 (1.71 – 21.59)	.00648	5 (5.68/1.03)	>0.01 mg/dL

^a Model 1: adjusted for sex and age.

^b Model 2: adjusted for sex, age, and BMI.

^c The integer value was used as the distribution of the risk score for each item, which was obtained by dividing the OR of each item by the lowest OR. Model 1 ORs were used for BMI, and model 2 ORs were used for other variables.

^d The reference values were based on the total median of each item.

There were missing data in CRP (three patients in the IMW group and two patients in the PW groups) and Ca (two patients in the IMW group and two patients in the PW groups).

ALB, albumin; AN, anorexia nervosa; AST, aspartate transaminase; BUN, blood urea nitrogen; BMI, body mass index; Ca, calcium; CRP, C-reactive protein; IMW, internal medicine ward; OR, odds ratio; PW, psychiatric ward.