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Development and internal validation of a multivariable model for the prediction of the probability of 1-year readmission to the emergency department for acute alcohol intoxication

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Abstract
To develop and internally validate a multivariable logistic regression model (LRM) for the prediction of the probability of 1-year readmission to the emergency department (ED) in patients with acute alcohol intoxication (AAI). We developed and internally validated the LRM on a previously analyzed retrospective cohort of 3304 patients with AAI admitted to the ED of the Sant'Orsola-Malpighi Hospital (Bologna, Italy). The benchmark LRM employed readmission to the same ED for AAI within 1 year as the binary outcome, age as a continuous predictor, and sex, alcohol use disorder, substance use disorder, at least one previous admission for trauma, mental or behavioral disease, and homelessness as the binary predictors. Optimism correction was performed using the bootstrap on 1000 samples without replacement. The benchmark LRM was gradually simplified to get the most parsimonious LRM with similar optimism-corrected overall fit, discrimination and calibration. The 1-year readmission rate was 15.7% (95% CI 14.4–16.9%). A reduced LRM based on sex, age, at least one previous admission for trauma, mental or behavioral disease, and homelessness, performed nearly as well as the benchmark LRM. The reduced LRM had the following optimism-corrected metrics: scaled Brier score 17.0%, C-statistic 0.799 (95% CI 0.778 to 0.821), calibration in the large 0.000 (95% CI − 0.099 to 0.099), calibration slope 0.985 (95% CI 0.893 to 1.088), and an acceptably accurate calibration plot. An LRM based on sex, age, at least one previous admission for trauma, mental or behavioral disease, and homelessness can be used to estimate the probability of 1-year readmission to ED for AAI. To begin proving its clinical utility, this LRM should be validated in external cohorts.

Keywords Acute alcohol intoxication · Alcohol use disorder · Emergency department · Hospital readmission

Francesco Palmese and Maria Elena Bonavita share the first authorship.

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Introduction

Acute alcohol intoxication (AAI) is a frequent cause of admission to the emergency department (ED) [1, 2]. AAI usually does not lead to serious complications, but it might signal an underlying alcohol use disorder (AUD), which is a major cause of short-term and long-term mortality [3]. AUD is characterized by a lack of control over alcohol consumption, a compulsion to consume alcohol, a negative emotional state when abstaining from alcohol, and a persistent recurrence pattern [3].

The notion that the ED could serve as a hub for the identification of patients with alcohol-related disorders to direct them to specific alcohol treatment centers is widely supported [1, 3]. In fact, patients with AUD could be identified using questionnaires such as the 10-item alcohol use disorder identification test (AUDIT) or its condensed version, the 3-item AUDIT-C. However, these tools are underutilized in the ED due to time pressure and other factors [1, 3, 4].

Many studies have therefore been conducted with the aim of identifying readily available predictors of hospital readmission for AAI. However, these studies usually lasted for 30 days, and few studies have evaluated potential predictors of the probability of 1-year readmission [4, 5]. In a previous study [4], we developed a scoring system to figure out how likely it was that a patient with AAI would be readmitted to the ED within 1 year. The proportion of patients readmitted within 1 year for AAI was 16.3%, and we found that psychiatric disease, at least one previous admission for trauma, homelessness, and alcohol abuse were predictors of readmission at multivariable analysis. The absence of a formal prediction equation in the previous study was principally due to the low total number of events (92/563), which would have reduced the precision of the algorithm [6].

The present study aimed therefore to develop and internally validate a multivariable prediction model for estimating the probability of 1-year readmission to the ED for AAI.

Subjects and methods

The reporting of the present study is performed according to the TRIPOD guidelines [7]. The TRIPOD checklist is enclosed as Appendix 1.

Source of data

The development and internal validation of the multivariable model for the prediction of the probability of 1-year readmission to the ED was performed using an already available retrospective cohort of AAI patients who accessed the ED of the Sant'Orsola-Malpighi Hospital from January 1, 2005, to December 31, 2017 [2].

The study was approved by the Ethical Committee of the Emilia-Romagna Region (CE-AVEC, number of approval 302/2020/Oss/AOUBo). Written informed consent was waived in view of the retrospective nature of the study [2].

Participants

Patients with AAI who were admitted to the ED of the Sant'Orsola-Malpighi Hospital between January 1, 2005, and December 31, 2017, were eligible for the present study [2].

AAI was defined as at least one of the following diagnoses: (1) alcohol abuse; (2) alcohol dependence; (3) alcohol toxicity; (4) accidental alcohol poisoning; (5) intentional alcohol poisoning; (6) alcohol poisoning (general); (7) alcohol intoxication, as measured by the blood alcohol level. Based on the study period, these diagnoses were made using the International Classification of Disease (ICD) codes version 9 or 10.

The only criterion for exclusion was age < 18 years [2].

Outcome

The binary outcome was readmission to the ED of the Sant'Orsola-Malpighi Hospital for AAI within 365 days from the first admission (0 = no; 1 = yes). AAI was defined as explained in "Participants".

Predictors

Using the data made available by the study database [2] and the findings from our previous study [4], we compiled the following list of potential predictors before performing any modeling: (1) age of the patient at baseline admission (continuous, years); (2) male sex (binary, 0 = no; 1 = yes); (3) alcohol use disorder (AUD; binary, 0 = no; 1 = yes); (4) substance use disorder (SUD; binary, 0 = no; 1 = yes); (5) at least one previous admission for trauma (binary, 0 = no; 1 = yes); 6) mental or behavioral disorder (binary, 0 = no; 1 = yes); (7) homelessness (binary, 0 = no; 1 = yes).

The age of the patient was determined by subtracting the date of admission to the ED from the patient's birthdate, which was found either through the electronic registry of the ED or by asking the patients directly after they had recovered from AAI. Because we expected that the logit of age would not be linear, the functional form of age was pre-specified as having two terms that would be later defined using multivariable fractional polynomials (MFP) with bootstrap evaluation of stability [8–10]. Sex was defined as biological

sex. Based on the study period, the ED electronic registry provided a previous diagnosis of AUD and SUD based on ICD-9 or ICD-10 codes. Additionally, the ED electronic registry was used to evaluate the presence of at least one previous admission for trauma and to obtain a previous diagnosis of a mental or behavioral disorder.

Sample size

This is a retrospective cohort study performed on an available dataset of 3304 patients with AAI [2]. Before performing any modeling, we selected a list of potential predictors (see "Predictors"), determined their functional form (see "Predictors"), and calculated the 1-year readmission rate (15.7%; 518/3304). We used the number of predictors (9 because age was prespecified as being coded by 2 predictors; see "Predictors") and the 1-year readmission rate to evaluate the minimum sample size needed to minimize overfitting and allow a precise estimation of model parameters [6, 11, 12]. In detail, we calculated that 2451 subjects were needed to detect a Cox-Snell R^2 of 0.1078, corresponding to a C-statistic of 0.70, which we deemed as the minimal acceptable optimism-corrected discrimination while ensuring: (1) a shrinkage of predictor effects < 5%; (2) a difference of 5% in the model apparent and adjusted Nagelkerke R^2 and; (3) an estimation within 5% of the average outcome risk in the population [6, 11, 12]. The available sample size of 3304 subjects was thus more than enough to develop a model with the desired discrimination and calibration features.

Missing data

There were no missing data.

Statistical analysis

Most continuous variables were not Gaussian-distributed, and all are reported as median (50th percentile) and interquartile interval (25th and 75th percentiles). Discrete variables are reported as the number and percentage of subjects with the characteristic of interest.

We started modeling by defining a benchmark multivariable logistic regression model (LRM) using 1-year readmission for AAI as the binary outcome, age as a continuous predictor, and sex, AUD, SUD, at least one previous admission for trauma, mental or behavioral disease, and homelessness as binary predictors (see "Predictors"). The hypothesis that AUD and possibly SUD were likely predictors of the probability of 1-year readmission prompted us to compare the calibration and discrimination of the benchmark model with those of simpler prespecified models not including AUD or SUD among predictors. The underlying model development strategy is detailed in Table 2. To this aim, the benchmark LRM was gradually simplified to get the most parsimonious LRM with a similar fit, discrimination, and calibration.

Overall fit was evaluated using the scaled Brier score, i.e., the Brier score scaled by its maximum score ($Brier_{max}$) according to the equation (1 − Brier score)/$Brier_{max}$, with a higher score representing greater accuracy [13].

Discrimination, i.e., the ability to separate subjects with disease from those without disease, was evaluated using Harrell's C-statistic which, for the case of logistic regression, equals the area under receiver-operating characteristic curve [7].

Calibration, i.e., the agreement between observed and predicted risk, was assessed by evaluating: (1) "mean calibration" or "calibration-in-the-large", by comparing the observed event rate with the average predicted risk; (2) "weak calibration", by performing a logistic analysis testing whether the calibration slope is 1; and, (3) "moderate calibration", by using a "calibration plot" to test whether the predicted risks correspond to the observed event rates. Such a graph plots the predicted (expected) outcome probabilities (x-axis) against the observed outcome frequencies (y-axis). As suggested by the TRIPOD guidelines, we performed the calibration using tenths of the predicted risk and superimposed a line obtained by locally weighted scatterplot smoothing. A well-calibrated model shows predictions lying or around the 45-degree line of the calibration plot [7].

All models were internally validated by calculating the scaled Brier score, C-statistic, calibration in the large, calibration slope, and drawing a calibration plot with 95% confidence interval on 1000 bootstrap samples without replacement [7, 12, 14, 15].

The linearity of the logit of age in all models was evaluated using MFP with bootstrap evaluation of stability [9, 10]. Collinearity among predictors was assessed by evaluating the condition matrix [16] and by using Spearman's rho [17]. Unlike our previous study [4], we did not use a previous episode of AAI as a predictor in the present study because it was expected to be collinear with AUD.

Statistical analysis was performed using Stata 18.0 (Stata Corporation, College Station, TX, US) using the *mfpboot* [9], *bsvalidation* [18] and *pmsampsize* [19] user-written commands.

Table 1 Baseline distribution of potential predictors of the probability of 1-year readmission for acute alcohol intoxication

	$N = 3304$
Male sex	2195 (66.4%)
Age (years)	30 (22; 43)
Homeless	262 (7.9%)
Alcohol use disorder	357 (10.8%)
Substance use disorder	175 (5.3%)
At least one previous admission for trauma	425 (12.9%)
Mental or behavioral disease	477 (14.4%)

Continuous variables are reported as median (50th percentile) and interquartile interval (IQI, 25th and 75th percentiles). Discrete variables are reported as the number and proportion of subjects with the characteristic of interest

Results

Distribution of potential predictors

The baseline distribution of the potential predictors of the probability of 1-year readmission for AAI is shown in Table 1.

Readmission for AAI at 1 year

The readmission rate at 1 year was 15.7% (95% CI 14.4% to 16.9%, 518/3304).

The readmission rate increased with increasing decade of age up to the 4th decade to decrease thereafter (6%, 95% CI 5–7% for age ≤ 2nd decade; 23%, 95% CI 20–26% for age < 3rd decade; 35%, 95% CI 31–39% for age < 4th decade; 27%, 95% CI 21–32% for age < 5th decade; 15%, 95% CI 10–21% for age ≥ 6th decade; 13%, 95% CI 6–19% for age ≥ 70 years) and was higher in men (17.9%, 95% CI 16.3–19.5%) than in women (11.4%, 95% CI 9.5–13.2%).

The readmission rate was also higher in homeless (54.6%, 95% CI 48.6–60.6%) patients than in those with a fixed residence (12.3%, 95% CI 11.2–13.5%), in patients with (44.4%, 95% CI 39.3–49.6%) than in those without AUD (12.2%, 95% CI 11.0–13.4%), in patients with (36.0%, 95% CI 28.9–43.1%) than in those without SUD (14.5%, 95% CI 13.3–15.8%), in patients with (32.0%, 95% CI 27.6–36.4%) than in those without (13.3%, 95% CI 12.0–14.5%) one previous admission for trauma, and in patients with (32.2%, 95% CI 28.0–36.4%) than in those without (12.9%, 95% CI 11.6–14.1%) mental or behavioral disease.

Determination of the functional form of age

As readily detected by using a locally weighted scatterplot smoother, the logit of age was not linear for all models [8]. To determine the functional form of age, for which we had prespecified two terms (see "Predictors"), we used MFP with bootstrap evaluation of stability [9, 10]. To this aim, every model reported in Table 2 was run on 1000 bootstrap samples without replacement. Age was selected in all models with an $FP_{(1,1)}$ functional form [17].

Development and internal validation of the multivariable model

Table 3 presents the internally validated LRMs and their metrics of overall fit, calibration, and discrimination. Internal validation, i.e., correction for optimism, was performed on 1000 bootstrap samples without replacement (see "Statistical analysis").

Figure 1 depicts the corresponding calibration plots.

The performance of all models greatly exceeded our expectations (see "Sample size"). The benchmark model M1 and the reduced model M2, which excluded SUD from the predictors, were virtually identical as detected by discrimination, calibration, and model fit statistics. Interestingly, removing AUD from model M2 to get model M3, which is

Table 2 Multivariable modeling strategy for the prediction of the probability of 1-year readmission for acute alcohol intoxication

	M1	M2	M3	M4	M5	M6
Male sex (binary)	✓	✓	✓	✓	✓	✓
Age (continuous)	✓	✓	✓	✓	✓	✓
Alcohol use disorder (binary)	✓	✓	–	–	–	–
Substance use disorder (binary)	✓	–	–	–	–	–
At least one previous admission for trauma (binary)	✓	✓	✓	–	–	–
Mental or behavioral disease (binary)	✓	✓	✓	✓	–	–
Homeless (binary)	✓	✓	✓	✓	✓	–

M1 is the prespecified benchmark model. M4 to M6 are prespecified simplified models aimed at evaluating the hypothesis that the unavailability of SUD and AUD status can be circumvented by knowledge of other readily available predictors

✓ Predictor included in the model, – predictor not included in the model

Table 3 Comparison of multivariable models for the prediction of the probability of 1-year readmission for acute alcohol intoxication

	M1	M2	M3	M4	M5	M6
Male sex	0.25* [0.01 to 0.49]	0.25* [0.01 to 0.49]	0.27* [0.04 to 0.51]	0.30* [0.07 to 0.54]	0.15 [− 0.08 to 0.38]	0.31** [0.08 to 0.53]
Age (years)	0.92*** [0.72 to 1.11]	0.94*** [0.74 to 1.13]	0.94*** [0.75 to 1.14]	0.96*** [0.77 to 1.16]	1.02*** [0.83 to 1.21]	1.15*** [0.96 to 1.34]
Age (years)*ln[age(years)]	− 0.19*** [− 0.23 to − 0.15]	− 0.19*** [− 0.24 to − 0.15]	− 0.19*** [− 0.24 to − 0.15]	− 0.20*** [− 0.24 to − 0.16]	− 0.21*** [− 0.25 to − 0.17]	− 0.24*** [− 0.28 to − 0.20]
Alcohol use disorder	0.90*** [0.62 to 1.18]	0.95*** [0.67 to 1.22]	–	–	–	–
Substance use disorder	0.46* [0.09 to 0.84]	–	–	–	–	–
≥ 1 access for trauma	0.49*** [0.23 to 0.76]	0.50*** [0.24 to 0.77]	0.58*** [0.33 to 0.84]	–	–	0.78*** [0.54 to 1.03]
Mental or behavioral disorder	0.62*** [0.36 to 0.88]	0.67*** [0.41 to 0.92]	0.86*** [0.62 to 1.11]	0.96*** [0.72 to 1.21]	–	–
Homeless	1.55*** [1.26 to 1.84]	1.57*** [1.28 to 1.85]	1.66*** [1.38 to 1.94]	1.69*** [1.41 to 1.97]	1.63*** [1.35 to 1.90]	–
Intercept	− 10.54*** [− 10.65 to − 10.44]	− 10.66*** [− 10.76 to − 10.55]	− 10.85*** [− 10.95 to − 10.74]	− 10.99*** [− 11.09 to − 10.88]	− 11.30*** [− 11.41 to − 11.20]	− 12.38*** [− 12.48 to − 12.28]
Brier-scaled (%)	18.4	18.5	17.0	16.7	14.8	10.7
C-statistic	0.813 [0.794 to 0.835]	0.811 [0.792 to 0.832]	0.799 [0.778 to 0.821]	0.793 [0.773 to 0.815]	0.775 [0.754 to 0.797]	0.753 [0.731 to 0.775]
E:O ratio	0.999 [0.936 to 1.064]	0.999 [0.936 to 1.064]	0.999 [0.936 to 1.070]	0.999 [0.930 to 1.070]	0.999 [0.930 to 1.070]	1.000 [0.930 to 1.064]
CITL	0.000 [− 0.102 to 0.100]	0.000 [− 0.100 to 0.100]	0.000 [− 0.099 to 0.099]	0.000 [− 0.100 to 0.099]	0.000 [− 0.098 to 0.097]	− 0.001 [− 0.088 to 0.094]
Calibration slope	0.979 [0.894 to 1.077]	0.982 [0.896 to 1.081]	0.985 [0.893 to 1.088]	0.988 [0.892 to 1.093]	0.988 [0.890 to 1.106]	0.988 [0.873 to 1.125]

The values are logistic regression coefficients (from male sex to intercept) or performance metrics (from Brier-scaled to calibration slope) with a 95% confidence interval in brackets. The values were adjusted for optimism by bootstrapping 1000 samples without replacement. An overview of the underlying modeling strategies can be found in Table 2

ln natural logarithm, *E:O ratio* expected vs. observed ratio, *CITL* calibration in the large

*p < 0.05, **p < 0.01, ***p < 0.001

based on more easily available predictors, made the prediction only slightly worse, with a scaled Brier score changing from 18.5 to 17%. For models M4 to M6, which were devised with the aim of evaluating the separate contribution of the more readily available predictors, the loss of performance versus model M2 was more evident, with a scaled Brier score changing from 18.5 to 16.7% and 14.8% respectively [4]. Lastly, the probability of 1-year readmission was not accurately predicted by age and sex alone (Model M6, scaled Brier score 10.7%).

Discussion

The aim of the present study was to develop and internally validate a multivariable model for the prediction of the probability of 1-year readmission to ED for AAI.

The prespecified benchmark model (Model M1 of Table 3), which included sex, age, AUD, SUD, at least one previous admission for trauma, mental or behavioral disease, and homelessness, demonstrated both good discrimination and calibration according to current standards [7]. It is useful to remember that calibration is central for a diagnostic model to be properly employed in clinical practice and that it plays a more important role than discrimination [7].

Importantly, a simplified model excluding AUD and SUD from the predictors (Model M3 of Table 3), performed only slightly worse and is certainly acceptable for practical usage. Model M3, which we developed based on the results of a previous study performed on a much lower number of events and patients [4], is the one that we suggest to externally validate for clinical application. The corresponding equation is reported in Appendix 2 with a worked-out example.

This study has several limitations. A limitation is that this study was performed at a single ED and evaluated the probability of 1-year readmission for AAI at the same ED. We had in fact not the possibility of checking whether other admissions for AAI were performed at EDs other than ours. More importantly, we wanted to be sure that AAI was operationally

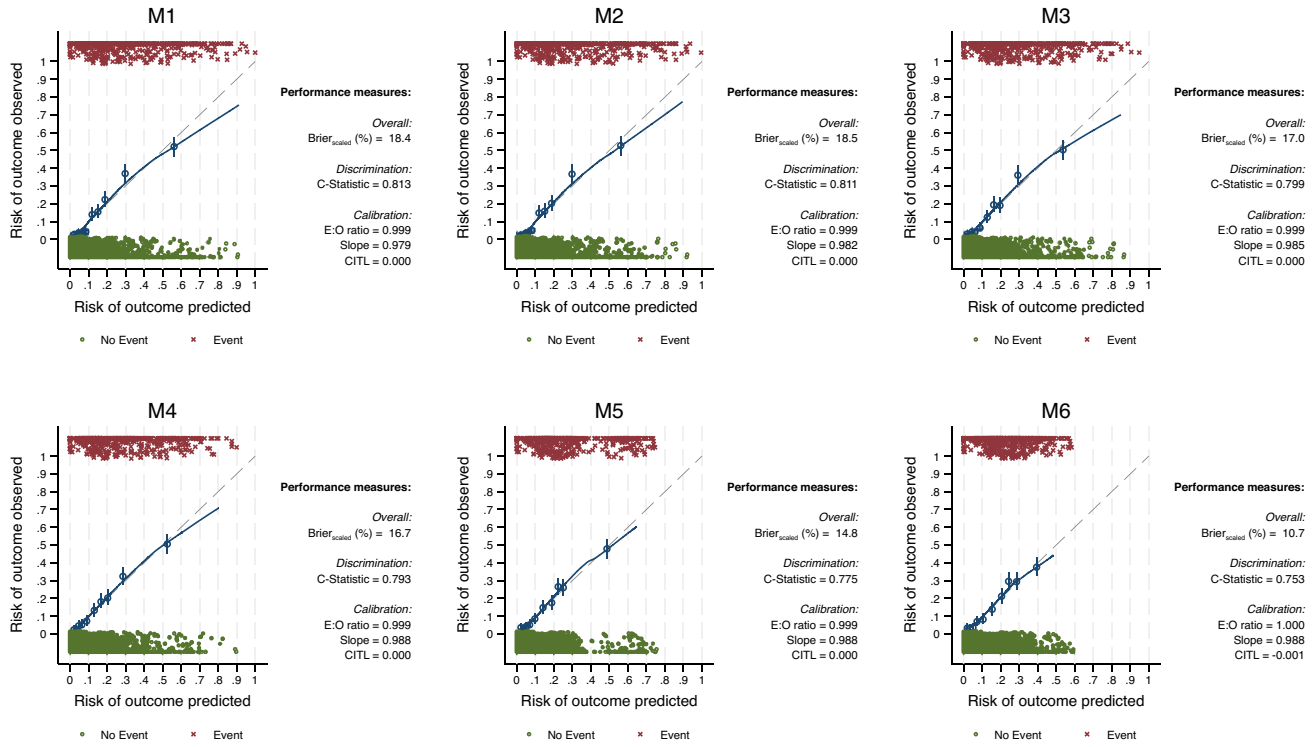

Fig. 1 Calibration plots of the multivariable logistic regression model the for the prediction of the probability of 1-year readmission for acute alcohol intoxication. See Table 3 for the underlying equations

defined according to the criteria listed under "Participants". This, however, implies that we might be underestimating the true probability of AAI. Another limitation, already discussed in the main study [2], is that there may be instances where the ICD codes were improperly applied, leading to an incorrect classification of the outcome and some predictors. Given that we have not performed an internal validation of the ICD coding system in this cohort, the proportion of such misclassification remains unknown [2]. Another limitation is that a patient may have had an AUD or SUD when they were admitted to the ED, but this was not yet known or recorded in the ED electronic registry. It is therefore possible that Models M1, M2 and M3 (Table 3) might be actually built on an underestimated prevalence of AUD or SUD. Another limitation is that, although our internal validation was done according to current standards and gave satisfactory results (Table 3), we did not perform an external validation. An external validation of any diagnostic or prognostic model is however essential because it is the first step to determine its clinical utility [20]. Our case-mix of patients together with how healthcare is provided under the Italian National Health System is likely to prevent the generalizability of our prediction model to other countries. However, we expect that it will work in similar contexts. Importantly, the external validation of our model is not expected to be onerous because it uses commonly collected data to make the prediction.

The model that we propose for external validation uses sex, age, at least one previous admission for trauma, mental or behavioral disease, and homelessness as predictors. In the present study, sex and age were independent predictors of AAI. This was not the case in our previous study [4], which used however an univariable selection of predictors instead of a direct multivariable modeling like we did in the present study [21]. Moreover, in the present study, the logit of age had a non-linear relationship with AAI that could only be captured by a second-degree fractional polynomial. However, the most likely reason for this difference is that, in our previous study [4], we did not have enough events to model all the predictors of interest with enough precision [6, 12]. We were not surprised to find at least one previous admission for trauma among the predictors of AAI, not only because of the findings of our previous study [4], but also because of the substantial evidence base linking trauma recidivism to alcohol abuse [22]. The same holds true for the strong linkage between alcohol consumption and psychological and behavioral disorders [3], as we also observed in our previous study [4]. Lastly, there is ample literature showing that homelessness is a risk factor for alcohol abuse [22].

In conclusion, a multivariable prediction model could be used to estimate the probability of 1-year readmission to ED for AAI based on sex, age, at least one previous admission for trauma, mental or behavioral disease, and homelessness.

This model should be externally validated to prove its clinical usefulness. More than the model equation, which may require recalibration, evidence that readily available predictors such as at least one previous admission for trauma, mental or behavioral disease, or homelessness are independent predictors of the probability of a 1-year readmission should be looked at more closely.

Provided that our model is proven to be useful by external validation, it should be evaluated in a randomized controlled trial to see if the calculation of the probability of readmission for AAI at 1-year has practical consequences for AAI patients, such as a sooner approach to specialized care [20].

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11739-023-03490-7.

Data availability Anonymized data may be made available upon reasonable request.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Human and animal rights The study was approved by the Ethical Committee of the Emilia-Romagna Region (CEAVEC, number of approval 302/2020/Oss/AOUBo).

Informed consent Written informed consent was waived in view of the retrospective nature of the study.

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