Development and validation of a prediction model for rehospitalization among people with schizophrenia discharged from acute inpatient care

Akira Sato[1*], Toshihiro Moriyama [2], Norio Watanabe[3], Kazushi Maruo[4], Toshi A. Furukawa[1]

[1] Department of Health Promotion and Human Behavior, Kyoto University Graduate School of Medicine/School of Public Health, Kyoto, Japan.

[2] Isogaya Hospital, Ichihara, Japan.

[3] Department of Psychiatry, Soseikai General Hospital, Kyoto, Japan.

[4] Department of Biostatistics, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan.

*** Correspondence:**
Akira Sato
asatomatsu@gmail.com

Keywords: Schizophrenia spectrum disorder, Relapse, Prognosis, Individualized risk, Hospitalization, Psychoses.

Abstract

Objective: Relapses and rehospitalization prevent the recovery of individuals with schizophrenia or related psychoses. We aimed to build a model to predict the risk of rehospitalization among people with schizophrenia or related psychoses, including those with multiple episodes.

Methods: This retrospective cohort study included individuals aged 18 years or older, with schizophrenia or related psychoses, and discharged between January 2014 and December 2018 from one of three Japanese psychiatric hospital acute inpatient care wards. We collected nine predictors at the time of recruitment, followed up with the participants for 12 months, and observed whether psychotic relapse had occurred. Next, we applied the Cox regression model and used an elastic net to avoid overfitting. Then, we examined discrimination using bootstrapping, Steyerberg's method, and "leave-one-hospital-out" cross-validation. We also constructed a bias-corrected calibration plot.

Results: Data from a total of 805 individuals were analyzed. The significant predictors were the number of previous hospitalizations (HR 1.42, 95% CI 1.22–1.64) and the current length of stay in days (HR 1.31, 95% CI 1.04–1.64). In model development for relapse, Harrell's c-index was 0.59 (95% CI 0.55–0.63). The internal and internal-external validation for rehospitalization showed Harrell's c-index to be 0.64 (95% CI 0.59–0.69) and 0.66 (95% CI 0.57–0.74), respectively. The calibration plot was found to be adequate.

Conclusion: The model showed moderate discrimination of readmission after discharge. Carefully defining a research question by seeking needs among the population with chronic schizophrenia with multiple episodes may be key to building a useful model.

1 Introduction

The prognosis of patients with schizophrenia or related psychoses has not improved over the past few decades. A study by the world health Organization (WHO) showed that during a 15-year follow-up in the 1970s and 1990s, only 38% of those with schizophrenia and 55% of those with other psychoses reached a recovery phase lasting two years or longer (Harrison et al., 2001). Similarly, in recent years, only 13.5 to 38% of people with schizophrenia and related psychosis, including those with first-episode psychosis, recovered past two years (Jääskeläinen et al., 2013;Lally et al., 2017). While definitions may vary, poor recovery among people with psychotic disorders indicates a vast unmet need.

One important factor hindering the recovery process is relapse. More than 80% of people with first-episode schizophrenia experience relapse within five years of initial recovery (Robinson et al., 1999). Similarly, 63% of such individuals suffer from a relapse within two years after their discharge from the hospital, and most of those who relapse are rehospitalized (Schennach et al., 2019). Hospitalization is the most common method for measuring relapse in people with schizophrenia and first-episode psychosis. A systematic review found that 6 of 16 studies used readmission to measure relapse (Gleeson et al., 2010), and another showed that 47 of 87 manuscripts reported hospitalization to define relapse (Olivares et al., 2013). Therefore, hospitalization can be used as a quantifiable, easy-to-measure proxy for relapse, which mental health professionals may find easier to discuss with patients and their caregivers.

Multiple prognostic factors may well be related to relapses and rehospitalization. Several prognostic factors, such as adherence problems and expressed emotions, have been identified (Olivares et al., 2013;Lecomte et al., 2019). However, such separately reported prognostic factors do not allow us to predict individual patient prognoses. A prediction model that considers relevant predictors simultaneously and provides personalized risk for each patient is required.

Unfortunately, research on prediction modeling in psychiatry is scarce. A recent systematic review of prediction models in *Psychiatry* included only 89 articles (Salazar de Pablo et al., 2021). Of these, only seven studied schizophrenia, merely one of which focused on psychotic relapse (Fond et al., 2019). Moreover, the study used predictors that would not be assessable outside research-oriented academic centers. Another systematic review of prediction models in first-episode psychosis included 13 studies (Lee et al., 2022). Again, only two of the included studies had an outcome of rehospitalization (Bhattacharyya et al., 2021;Puntis et al., 2021). These articles used covariates that are easily obtained in routine practice; however, they focused on people in the first episode. Therefore, little is known about the personalized risk of relapse and psychiatric rehospitalization in clinical settings, including that in people with schizophrenia after multiple episodes.

To address this issue, we aimed to develop and validate a clinical prediction model that could estimate the risk of relapse, including hospitalization, among people with schizophrenia or related psychoses, including those with multiple episodes, at the time of discharge from acute inpatient care in psychiatric hospitals. Our primary interest is building a model with routinely collected data for people with such illnesses, regardless of their life trajectories.

2 Materials and methods

We have previously published our protocol for this study elsewhere (Sato et al., 2022). We adhered to the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) for developing and validating our prediction model (**Appendix 1**) (Moons et

al., 2015). This study was registered in the UMIN-CTR (UMIN000043345) on February 20, 2021. In this section, we briefly summarize our methods.

2.1 Study design and source of data

We conducted a retrospective cohort study to obtain datasets for our prediction model. We collected data from three psychiatric hospitals in Japan that differed in their physical venues and care levels. The Chiba Psychiatric Medical Center (CPMC) is a publicly owned tertiary care psychiatric facility that primarily treats psychosis. The Urawa Psychiatric Sanatorium Hospital (UPSH) and Isogaya Hospital (IH) are private secondary care psychiatric hospitals. We collected data only from the acute care wards of the participating hospitals. In Japan, acute care usually provides intensive treatment for people with acutely ill, first-episode, or relapsing psychotic disorders, with an average length of stay of 56.7 days from 2011 onwards (Sato;OECD, 2015).

2.2 Study population

By consecutively reviewing all inpatient records in the three psychiatric hospitals between 2014 and 2018, we recruited people with schizophrenia or related psychoses who were discharged from an acute inpatient ward. We reviewed the medical records of patients admitted to IH and USPH between January 1, 2014, and December 31, 2018. For CPMC, we could access such records between January 1, 2014, and December 31, 2016, excluding those in 2017 and 2018, for administrative reasons. We chose this 5-year period to avoid the influence of concurrent events of the major earthquake and COVID-19 pandemic in 2011 and 2019, respectively.

2.3 Eligibility criteria

We included individuals if they:

1. Were 18 years of age or older;

2. Had a diagnosis of schizophrenia or related psychoses, including schizotypal disorder, persistent delusional disorders, acute and transient psychotic disorders (ATPD), induced delusional disorder, schizoaffective disorders, other nonorganic psychotic disorders, and unspecified non-organic psychosis.

3. Received inpatient care primarily to treat psychosis; and

4. Were discharged from an acute inpatient care ward.

The International Classification of Diseases 10th revision (ICD-10) was used for diagnosis (World Health Organization, 1992). If an individual had several hospitalization episodes during the study period, we randomly selected data from one episode.

We excluded individuals who were diagnosed with substance or medication-induced psychotic disorders or psychotic disorders secondary to another medical condition. We excluded patients with a tentative diagnosis of schizophrenia or related psychoses without further evaluation for a definite diagnosis upon discharge. We also excluded individuals who were currently hospitalized for a non-psychotic episode, discharged from a non-acute ward, had an unclear diagnosis, were transferred to another psychiatric/medical facility, or had an immediate plan to return home overseas after

discharge. For hospitalization episodes excluded from our study, we recorded age, sex, and reasons for exclusion.

2.4 Study outcome

Our primary outcome was time to relapse as a composite outcome defined as the occurrence of any one of the following: (1) rehospitalization, (2) psychiatrist judgment that the patient requires hospitalization, (3) increasing doses of antipsychotics, or (4) suicidal or homicidal ideation or violent behavior resulting in injury to self or another person. All events should occur because of psychotic exacerbation. Our secondary outcome was time to rehospitalization due to psychotic exacerbation within 12 months of discharge. We followed up the discharged individuals by reviewing their outpatient medical records to observe whether they had such outcomes.

2.5 Selection of candidate predictors

Before collecting the data, we specified nine predictors based on existing literature and expert opinions. In the literature search, we used a search filter for the concept of prediction (Ingui and Rogers, 2001). The prespecified predictors were age at discharge, sex, number of previous hospitalizations, presence of any hospitalization in the previous year, current length of stay, presence of current substance use disorders, use of long-acting injections at discharge, number of psychosocial interventions during the current hospitalization, and receipt of benefits.

Briefly, previous hospitalizations included any psychiatric admissions in the past, regardless of the type of admission, length of stay, or reasons for hospitalization. We defined hospitalization in the previous year as any hospitalization intended to treat a psychotic episode in the past 12 months before the start of the current hospitalization episode. We counted the number of psychosocial interventions provided during the current hospitalization regardless of the duration of the intervention. Psychosocial interventions include psychoeducational, social skills training, and occupational therapeutic approaches. We excluded any interventions provided to family members because our data sources did not include those records.

We collected the predictors by reviewing inpatient records at the time of their discharge.

2.6 Data extraction and data cleaning

We first extracted data on predictors for the included individuals from inpatient records. Relapse data were collected from the outpatient records. All hospitals stored inpatient and outpatient medical records in physically different locations. Two data extractors independently reviewed the medical records of 30 individuals. For data extraction accuracy, we calculated percentage agreements and kappa statistics for binary variables, and an intraclass correlation coefficient (ICC) for continuous variables. We also kept the data extractors blinded to the outcome while extracting baseline data or to the baseline data while judging the outcome, and reported the proportion of data for which this blinding was broken.

For continuous variables of previous hospitalizations, current length of stay, and psychosocial interventions, we identified outliers above the 99th percentiles by creating box plots. We "winsorized" those outliers by shifting very high values to the 99th percentiles. We identified no predictors with a narrow or skewed distribution.

2.7 Sample size calculation

To estimate our sample size, we followed the criteria proposed by Riley et al. (Riley et al., 2019). We calculated the minimum sample size to be 754 to develop our model without overfitting predictor effects.

2.8 Model development

We applied a Cox regression model to predict outcomes. We treated both participants who dropped out before the end of the study and those who had no relapse at the 12-month follow-up as censored. From a clinical perspective, we assumed no interaction in our model. We assessed the linearity assumption by performing an overall test and including squared or higher-order polynomials in our model to observe any changes in model performance. Nonlinear terms were included in our model if the overall test p-value was less than 0.05, or if including nonlinear terms improved the performance. To avoid overfitting, we employed an elastic net for penalized estimation of the regression coefficients (Zou and Hastie, 2005). An elastic net allows for both the selection and penalization of the main effects by introducing two tuning parameters. It also considers the correlations between predictors. Ten-fold cross-validation allowed us to obtain optimal values for the two parameters.

2.9 Model performance

We calculated the Brier score for overall accuracy, that is, the extent to which the prediction model could explain the variability in outcomes (Brier, 1950;Steyerberg, 2019a). We estimated Harrell's C-statistic for discrimination (Harrell et al., 1984;Steyerberg, 2019a), which is the ability of a model to discriminate participants with the outcome from those without the outcome. For a graphical depiction of discrimination, we drew a grouped Kaplan-Meier plot (Steyerberg, 2019a). We divided the included individuals into three groups based on tertiles of predicted probabilities of no hospitalization and plotted Kaplan-Meier curves for time-to-observed hospitalization in each of the grouped cohorts. We also examined a calibration plot to determine the agreement between the observed and predicted outcomes (Harrell, 2015;Steyerberg, 2019a).

2.10 Model validation

We examined both internal and internal-external validity (Steyerberg, 2019d). Bootstrap validation with 500 repetitions was performed to assess model reproducibility. We also report the optimism-corrected performance described by Steyerberg (Steyerberg, 2019b). Geographical transportability was inspected by "leave-one hospital-out" cross-validation (Furukawa et al., 2020). In this internal-external validation, a dataset from one hospital out of the three was excluded to test the performance of the model. A dataset from the remaining two hospitals was used to construct the model. This process was repeated for each of the three hospitals. A bias-corrected calibration plot with 500 bootstraps was constructed for visual inspection of the results.

2.11 Sensitivity analyses

We performed sensitivity analyses to observe whether the performance of our model changed. We developed three prediction models for people with schizophrenia only, people with first-episode schizophrenia only, and people aged between 18 and 65 years.

2.12 Statistical software

We used R version 4.1.2 for our analyses (R Core Team, 2021). The packages we employed included *rms* version 6.3-0 (Harrell, 2022), *glmnet* version 4.1-4 (Friedman et al., 2010), and *glmnetUtils* version 1.1.8(Ooi, 2021).

2.13 Changes from the protocol (Sato et al., 2022)

From a clinical perspective and owing to the small sample size, we did not perform a statistical analysis for the additivity assumption, as initially planned in our protocol. To assess linearity, we introduced squared or higher-order polynomials as predictor variables, in addition to the overall test, as described in the protocol. As we found only four (0.5%) missing values in the baseline data, we did not use multiple imputations, as specified in the protocol. Instead, a complete case analysis was performed. We added a bias-corrected calibration plot. Because our model needed to perform better to be used in clinical practice, we neither performed decision curve analysis nor created a web-based application.

3 Results

3.1 Participants' characteristics

Data were collected between January 2021 and June 2022 and analyzed from August to October 2022. Inter-rater reliability showed moderate to excellent agreement for data extraction on predictors and the outcome, and the degree of unblinding during data collection was negligible (**Supplementary Table 2 and 3**). We did not find any patient overlap between the hospitals.

For the medical records between 2014 and 2018, we screened 3608 hospitalization episodes of discharged individuals. We excluded 2798 episodes for various reasons with the most frequent reason being diagnosis of non-psychotic disorder (n = 1530), randomly chose one episode for an individual with multiple episodes, and finally included 810 individuals (**Figure 1**).

Overall, the mean age was 45.1 years (SD 13.8 years), 58.9% were female, 19.0% were hospitalized in the previous year, 14.0% received benefits from their local government, 15.6% were medicated in the form of long-acting injections, and 1.5% were dually diagnosed with substance use disorders (**Table 1, Supplementary Table 4**). The median number of previous hospitalizations, current length of stay, and psychosocial intervention sessions during hospitalization were 1 (range, 0–9), 52 (range, 2–205), and 0 (range, 0–34), respectively. Of the cohort, 684 participants (84.0%) were diagnosed with schizophrenia, 57 (7.0%) with ATPD, 48 (5.9%) with schizoaffective disorders, 17 (2.1%) with delusional disorders, and 4 (0.5%) with other diagnoses (**Table 1, Supplementary Table 4**).

We excluded five individuals because of missing data. Of the remaining 805 individuals, 411 (51.1%) had no hospitalization episodes until the end of follow-up, 268 (33.3%) were lost to follow-up, and 131 (16.3%) were hospitalized (**Figure 1**). After inspecting the nonlinear terms, we included nine predictors in our final model, as specified in our protocol (**Supplementary Table 5**). The significant predictors of hospitalization within 12 months of discharge were the number of previous hospitalizations (HR 1.42, 95% CI 1.22–1.64) and the current length of stay in days (HR 1.31, 95% CI 1.04–1.64) (**Table 2**).

3.2 Model development and validation

In developing a model for relapse broadly defined as a composite outcome, we found that Harrell's c-index was 0.59 (95% CI 0.55–0.63) and did not proceed to further analysis. Hereafter, we describe the findings from the model of the secondary outcome of rehospitalization. In the model development, the overall accuracy in the Brier scores at fixed time points was 0.07, 0.12, and 0.16 on day 90, 180, and 360 after discharge, respectively. The Kaplan-Meier plot showed the proportion of individuals free of observed hospitalization in the three groups based on tertiles of predicted survival (i.e., no hospitalization) (**Figure 2**). In groups 1 and 2, 25 of 269 and 32 of 268 patients had hospitalization episodes, respectively. In contrast, 74 of 268 patients had hospitalization episodes in group 3, the group with the worst predicted survival. For regularization of coefficients in the nine predictors to avoid overfitting, the elastic net selected ridge regression over least absolute shrinkage and selection operator (LASSO) regression. In model validation, our model showed moderate discrimination. The internally validated Harrell's c-index from Steyerberg's optimism-corrected measure and the bootstrapping were 0.64 (95% CI 0.59–0.69) and 0.64 (95% CI 0.61–0.71), respectively. For the internal-external validation, the average of the three c-indices from the "leave-one hospital-out" cross-validation was 0.66 (95% CI 0.57–0.74). The bias-corrected calibration plot using bootstrapping indicated an adequate calibration of the predicted probabilities of no hospitalization against the observed proportions of non-hospitalization (**Figure 3**).

3.3 Sensitivity analysis

The sensitivity analysis included three different models: people with schizophrenia only (i.e., excluding those with other psychoses), people with the first episode of hospitalization, and those aged between 18 and 65 (i.e., excluding elderly patients). In model development, Harrell's c-index for each of the three prediction models showed results similar to those of the primary analyses (**Supplementary Table 6**).

4 Discussion

In this retrospective cohort study, we described the development and validation of a prediction model for readmission after hospital discharge in individuals with schizophrenia or related psychoses who had a history of no, single, or multiple hospitalizations. To use the model in everyday practice, we focused on nine routinely collected predictors at the time of discharge. Our final model showed moderate discrimination for rehospitalization, and the internally and internal-externally validated Harrell's c-index were 0.64 and 0.66, respectively.

When we built a model with relapse as a composite outcome instead of rehospitalization alone, the model's discrimination ability was close to no better at prediction of relapse compared to random chance (Harrel's c-index, 0.59). The difficulty in observing the components of our composite outcome in paper-based medical records may account for this poor discrimination. We found it difficult to follow relapse occurrences because handwritten documents were sometimes difficult to read, poorly organized, or even damaged. We also suspect that it was difficult to observe the broadly defined relapse outcome, because some physicians did not record a relapse other than hospitalization. For example, physicians may not record why they increased antipsychotic doses or how many days a patient used antipsychotics prescribed as needed. In addition, they may not record police or ambulance involvement, as such involvement is not strictly a psychiatric issue. However, we did not have such problems with collecting predictors and hospitalization because they were simply numbers or recorded as a single word. The relatively low agreement in inter-rater reliability for relapse compared to other variables may support this speculation (Cohen's kappa 0.71, **Supplementary Table 2**).

That said, the discrimination ability of our model may not increase even if we do not overlook any components of the composite outcome. We believe that all the components were measured subjectively and that many factors influence subjective judgment; for instance, a physician may increase the antipsychotic dose when a patient seems agitated. However, agitation may or may not result from psychotic exacerbations. Physicians may not have enough time to distinguish these differences but may increase the dosage if it is due to psychosis. In addition, we could not include factors that occurred during follow-up, which could have influenced the prognosis of individuals after discharge. These factors may include adherence to medication at home, psychological distress from a row with family members, and job loss during the index hospitalization. One or more of these factors may interact with a patient's life after discharge and influence one or more components of the composite outcome.

When we built the model for rehospitalization, its moderate discrimination (Harrel's c-index 0.66) was comparable to that of previous studies that included similar outcomes or populations. A model predicting readmission after hospital discharge in individuals with first-episode psychosis had a c-index of 0.66 (95% CI not shown) in the model validation (Bhattacharyya et al., 2021). Another model using LASSO, which predicted the occurrence of nonorganic psychotic disorders, 70% of which were schizophrenia, following ATPD, showed similar discrimination at 1-year follow-up (area under the curve [AUC] 0.678, 95% CI not shown) (Damiani et al., 2021). Furthermore, a model predicting transition to psychosis in individuals at clinical high risk reported a c-index of 0.665 (95% CI 0.627–0.682) (Malda et al., 2019). However, the discrimination ability of our model, among others, may hinder its use in clinical settings. Models that forecast the outcome of changes in psychotic conditions may require future research to improve their performance for use in clinical practice.

As for predictors, the hazard ratios of the two predictors were statistically significant, while the other seven showed otherwise. However, among those with negative findings, the upper confidence limits of the number of psychosocial interventions and the use of long-acting injections at discharge, for example, were close to one: Had we had a larger sample size, they may have shown significant effects. However, non-significant findings for each predictor do not necessarily exclude themselves from a model (Steyerberg, 2019c). Prediction models produce estimation rather than hypothesis testing. Negative, non-significant results do not imply a zero effect. We pre-specified predictors based on the literature. Including all the pre-defined predictors in our model still did not achieve clinically useful predictive power.

On the other hand, prediction models for the behavior of people with severe mental illnesses may be promising. A study using the same data source presented different prediction models for people with severe mental illness, 63% of which were schizophrenia. One model predicting violent offences within one year showed good discrimination ability (c-index 0.89, 95% CI 0.85–0.93) (Fazel et al., 2017). Another model for suicide within one year reported the measure of discrimination to a lesser extent (c-index 0.71, 95% CI 0.66–0.75) (Fazel et al., 2019). However, we should notice that when the former model was externally validated in another dataset, with a slightly different outcome, the AUC decreased to 0.67 (95% CI 0.61–0.73) (Lamsma et al., 2022). We consider that the generalizability of a model can still be challenging.

Our study has several limitations. First, we were not able to include some important prognostic factors. For example, the emotion expressed by a patient's family is an important predictor of relapse (Butzlaff and Hooley, 1998). We did not include adherence to antipsychotics; although we had

identified this factor as a candidate predictor in our literature search, we were obliged to discard it in the present study because our data sources did not record the variable. Another limitation is the possibility of underestimating the number of rehospitalizations. In total, 189 individuals were transferred to another mental health facility (**Figure 1**). Many of these mental health facilities do not provide inpatient care; when transferred patients experience psychotic relapse and need hospitalization, they may or may not be referred back to our hospital. When not referred back, these patients' relapses and rehospitalizations were not accounted for in our dataset.

By contrast, the strengths of this study lie in our endeavor to demonstrate its robustness. We performed a systematic literature search to pre-specify predictors and precisely defined outcomes, registered this study beforehand in the clinical trial registration system, and published our protocol in a peer-reviewed journal. The study period was carefully selected to avoid confounding due to concurrent events. We extracted data from the three different hospitals to examine their geographical transportability. We assessed the inter-rater reliability to ensure that the data extraction was trustworthy.

5 Conclusion

Here, we present a prediction model designed not only for first-episode admission, but also for the population of schizophrenia with multiple episodes. Our model, with routinely collected data from three psychiatric hospitals, showed moderate discrimination of psychotic readmission after hospital discharge. We speculate that depending on the complex nature of an outcome, it may be challenging to forecast such an outcome within a year, regardless of the predictors we choose. Carefully defining a research question by seeking needs among the population with chronic schizophrenia with multiple episodes, for example, using qualitative interviews, may be key to building a useful model.

6 Acknowledgements

We would like to thank Akira Kikuchi, Hiroshi Yamanaka, Toyomi Nemoto, and Goro Fukami for providing data sources.

7 Ethics approval and consent to participate

This study is conducted in accordance with the declaration of Helsinki and the Japanese Ethical Guidelines for Medical and Biological Research Involving Human Subjects (Eba and Nakamura, 2022). The study protocol was approved with a waiver of consent by the ethics committee of Kyoto University Graduate School and Faculty of Medicine (no. R2710-2) and the ethics committees of CPMC and IH. The ethics committee of Kyoto University Graduate School and Faculty of Medicine also approved the protocol on behalf of UPSH as UPSH did not hold such a committee.

8 Consent for publication

Not applicable.

9 Declaration of interest

AS declares no conflicts of interest. TAF reports personal fees from Boehringer-Ingelheim, DT Axis, Kyoto University Original, Shionogi and SONY, and a grant from Shionogi, outside the submitted work; In addition, TAF has patents 2020-548587 and 2022-082495 pending, and intellectual

properties for Kokoro-app licensed to Mitsubishi-Tanabe. KM, NW, and TM declare no conflicts of interest.

10 Role of the funding source

There was no external funding support for this study.

11 Availability of data and materials

The datasets to be used during the current study are not publicly available because individual privacy could be compromised.

12 Authors' contributions

AS, NW, and TAF contributed to the conception of this study. TAF was the principal investigator of this study protocol. AS, NW, and TAF designed the overall framework. AS wrote the manuscript in consultation with KM, NW, TAF, and TM. AS and TM independently collected data for assessing the reliability of data extraction. All authors read and approved the final manuscript.**Reference**

Bhattacharyya, S., Schoeler, T., Patel, R., Di Forti, M., Murray, R.M., and Mcguire, P. (2021). Individualized prediction of 2-year risk of relapse as indexed by psychiatric hospitalization following psychosis onset: Model development in two first episode samples. *Schizophr Res* 228**,** 483-492.

Brier, G.W. (1950). VERIFICATION OF FORECASTS EXPRESSED IN TERMS OF PROBABILITY. *Mon Weather Rev* 78**,** 1-3.

Butzlaff, R.L., and Hooley, J.M. (1998). Expressed emotion and psychiatric relapse - A meta-analysis. *Archives of General Psychiatry* 55**,** 547-552.

Damiani, S., Rutigliano, G., Fazia, T., Merlino, S., Berzuini, C., Bernardinelli, L., Politi, P., and Fusar-Poli, P. (2021). Developing and Validating an Individualized Clinical Prediction Model to Forecast Psychotic Recurrence in Acute and Transient Psychotic Disorders: Electronic Health Record Cohort Study. *Schizophr Bull* 47**,** 1695-1705.

Eba, J., and Nakamura, K. (2022). Overview of the ethical guidelines for medical and biological research involving human subjects in Japan. *Jpn J Clin Oncol* 52**,** 539-544.

Fazel, S., Wolf, A., Larsson, H., Lichtenstein, P., Mallett, S., and Fanshawe, T.R. (2017). Identification of low risk of violent crime in severe mental illness with a clinical prediction tool (Oxford Mental Illness and Violence tool [OxMIV]): a derivation and validation study. *Lancet Psychiatry* 4**,** 461-468.

Fazel, S., Wolf, A., Larsson, H., Mallett, S., and Fanshawe, T.R. (2019). The prediction of suicide in severe mental illness: development and validation of a clinical prediction rule (OxMIS). *Transl Psychiatry* 9**,** 98.

Fond, G., Bulzacka, E., Boucekine, M., Schürhoff, F., Berna, F., Godin, O., Aouizerate, B., Capdevielle, D., Chereau, I., D'amato, T., Dubertret, C., Dubreucq, J., Faget, C., Leignier, S., Lançon, C., Mallet, J., Misdrahi, D., Passerieux, C., Rey, R., Schandrin, A., Urbach, M., Vidailhet, P., Leboyer, M., Boyer, L., and Llorca, P.M. (2019). Machine learning for predicting psychotic relapse at 2 years in schizophrenia in the national FACE-SZ cohort. *Prog Neuropsychopharmacol Biol*

Psychiatry 92**,** 8-18.
Friedman, J., Hastie, T., and Tibshirani, R. (2010). Regularization Paths for Generalized Linear Models via Coordinate Descent. *J Stat Softw* 33**,** 1-22.
Furukawa, T.A., Debray, T.P.A., Akechi, T., Yamada, M., Kato, T., Seo, M., and Efthimiou, O. (2020). Can personalized treatment prediction improve the outcomes, compared with the group average approach, in a randomized trial? Developing and validating a multivariable prediction model in a pragmatic megatrial of acute treatment for major depression. *J Affect Disord* 274**,** 690-697.
Gleeson, J.F., Alvarez-Jimenez, M., Cotton, S.M., Parker, A.G., and Hetrick, S. (2010). A systematic review of relapse measurement in randomized controlled trials of relapse prevention in first-episode psychosis. *Schizophr Res* 119**,** 79-88.
Harrell, F.E. (2015). "Cox Proportional Hazards Regression Model," in *Regression Modeling Strategies: With Applications to Linear Models, Logistic and Ordinal Regression, and Survival Analysis*. (Cham: Springer International Publishing), 475-519.
Harrell, F.E., Jr. (2022). "rms: Regression Modeling Strategies. R package version 6.3-0.".).
Harrell, F.E., Jr., Lee, K.L., Califf, R.M., Pryor, D.B., and Rosati, R.A. (1984). Regression modelling strategies for improved prognostic prediction. *Stat Med* 3**,** 143-152.
Harrison, G., Hopper, K., Craig, T., Laska, E., Siegel, C., Wanderling, J., Dube, K.C., Ganev, K., Giel, R., An Der Heiden, W., Holmberg, S.K., Janca, A., Lee, P.W., Leon, C.A., Malhotra, S., Marsella, A.J., Nakane, Y., Sartorius, N., Shen, Y., Skoda, C., Thara, R., Tsirkin, S.J., Varma, V.K., Walsh, D., and Wiersma, D. (2001). Recovery from psychotic illness: a 15- and 25-year international follow-up study. *Br J Psychiatry* 178**,** 506-517.
Ingui, B.J., and Rogers, M.A. (2001). Searching for clinical prediction rules in MEDLINE. *J Am Med Inform Assoc* 8**,** 391-397.
Jääskeläinen, E., Juola, P., Hirvonen, N., Mcgrath, J.J., Saha, S., Isohanni, M., Veijola, J., and Miettunen, J. (2013). A systematic review and meta-analysis of recovery in schizophrenia. *Schizophr Bull* 39**,** 1296-1306.
Lally, J., Ajnakina, O., Stubbs, B., Cullinane, M., Murphy, K.C., Gaughran, F., and Murray, R.M. (2017). Remission and recovery from first-episode psychosis in adults: systematic review and meta-analysis of long-term outcome studies. *Br J Psychiatry* 211**,** 350-358.
Lamsma, J., Yu, R., and Fazel, S. (2022). Validation and recalibration of OxMIV in predicting violent behaviour in patients with schizophrenia spectrum disorders. *Sci Rep* 12**,** 461.
Lecomte, T., Potvin, S., Samson, C., Francoeur, A., Hache-Labelle, C., Gagné, S., Boucher, J., Bouchard, M., and Mueser, K.T. (2019). Predicting and preventing symptom onset and relapse in schizophrenia-A metareview of current empirical evidence. *J Abnorm Psychol* 128**,** 840-854.
Lee, R., Leighton, S.P., Thomas, L., Gkoutos, G.V., Wood, S.J., Fenton, S.H., Deligianni, F., Cavanagh, J., and Mallikarjun, P.K. (2022). Prediction models in first-episode psychosis: systematic review and critical appraisal. *Br J Psychiatry* 220**,** 1-13.
Malda, A., Boonstra, N., Barf, H., De Jong, S., Aleman, A., Addington, J., Pruessner, M., Nieman, D., De Haan, L., Morrison, A., Riecher-Rössler, A., Studerus, E., Ruhrmann, S., Schultze-Lutter, F., An, S.K., Koike, S., Kasai, K., Nelson, B.,

Mcgorry, P., Wood, S., Lin, A., Yung, A.Y., Kotlicka-Antczak, M., Armando, M., Vicari, S., Katsura, M., Matsumoto, K., Durston, S., Ziermans, T., Wunderink, L., Ising, H., Van Der Gaag, M., Fusar-Poli, P., and Pijnenborg, G.H.M. (2019). Individualized Prediction of Transition to Psychosis in 1,676 Individuals at Clinical High Risk: Development and Validation of a Multivariable Prediction Model Based on Individual Patient Data Meta-Analysis. *Front Psychiatry* 10**,** 345.

Moons, K.G., Altman, D.G., Reitsma, J.B., Ioannidis, J.P., Macaskill, P., Steyerberg, E.W., Vickers, A.J., Ransohoff, D.F., and Collins, G.S. (2015). Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): explanation and elaboration. *Ann Intern Med* 162**,** W1-73.

Oecd (2015). "Quality of mental health care in Japan," in *OECD Reviews of Health Care Quality: Japan 2015: Raising Standards*. (Paris: OECD Publishing), 163-204.

Olivares, J.M., Sermon, J., Hemels, M., and Schreiner, A. (2013). Definitions and drivers of relapse in patients with schizophrenia: a systematic literature review. *Ann Gen Psychiatry* 12**,** 32.

Ooi, H. (2021). "glmnetUtils: Utilities for 'Glmnet'. R package version 1.1.8.".).

Puntis, S., Whiting, D., Pappa, S., and Lennox, B. (2021). Development and external validation of an admission risk prediction model after treatment from early intervention in psychosis services. *Transl Psychiatry* 11**,** 35.

R Core Team (2021). "R: A language and environment for statistical computing.". (Vienna, Austria: R Foundation for Statistical Computing).

Riley, R.D., Snell, K.I., Ensor, J., Burke, D.L., Harrell, F.E., Jr., Moons, K.G., and Collins, G.S. (2019). Minimum sample size for developing a multivariable prediction model: PART II - binary and time-to-event outcomes. *Stat Med* 38**,** 1276-1296.

Robinson, D., Woerner, M.G., Alvir, J.M., Bilder, R., Goldman, R., Geisler, S., Koreen, A., Sheitman, B., Chakos, M., Mayerhoff, D., and Lieberman, J.A. (1999). Predictors of relapse following response from a first episode of schizophrenia or schizoaffective disorder. *Arch Gen Psychiatry* 56**,** 241-247.

Salazar De Pablo, G., Studerus, E., Vaquerizo-Serrano, J., Irving, J., Catalan, A., Oliver, D., Baldwin, H., Danese, A., Fazel, S., Steyerberg, E.W., Stahl, D., and Fusar-Poli, P. (2021). Implementing Precision Psychiatry: A Systematic Review of Individualized Prediction Models for Clinical Practice. *Schizophr Bull* 47**,** 284-297.

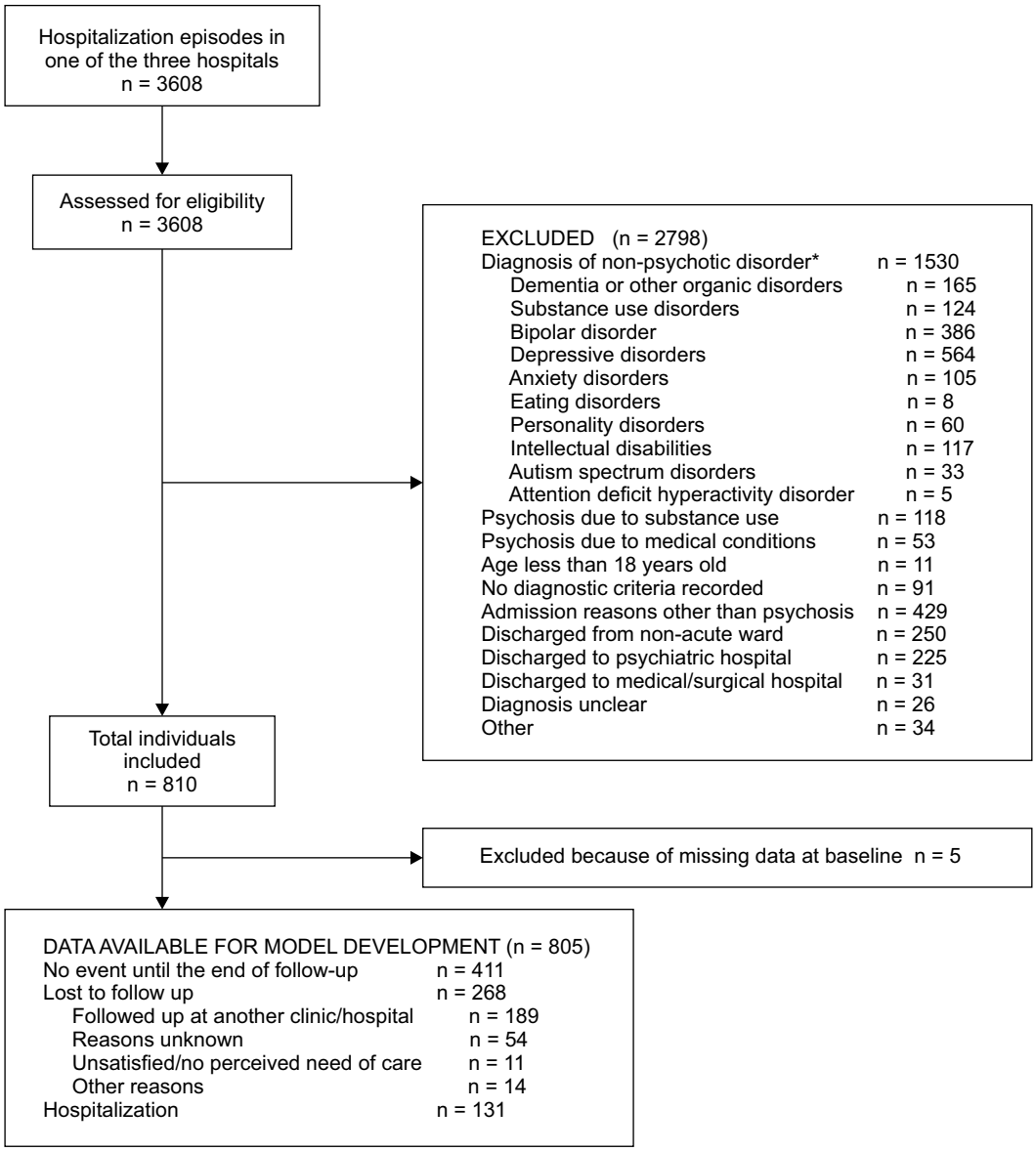
Sato, A., Watanabe, N., Maruo, K., Moriyama, T., and Furukawa, T.A. (2022). Psychotic relapse in people with schizophrenia within 12 months of discharge from acute inpatient care: protocol for development and validation of a prediction model based on a retrospective cohort study in three psychiatric hospitals in Japan. *Diagn Progn Res* 6**,** 20.

Sato, G. *Report on the Questionnaire about the Reduced Number of Psychiatric Emergency Ward Beds* [Online]. Available: https://skk-mamoru.org/results/ [Accessed December 2 2021].

Schennach, R., Riedel, M., Obermeier, M., Jäger, M., Schmauss, M., Laux, G., Pfeiffer, H., Naber, D., Schmidt, L.G., Gaebel, W., Klosterkötter, J., Heuser, I., Maier, W., Lemke, M.R., Rüther, E., Klingberg, S., Gastpar, M., Seemüller, F., Spellmann, I., Musil, R., and Möller, H.J. (2019). What happens with schizophrenia patients after their discharge from hospital? Results on outcome and treatment from a

"real-world" 2-year follow-up trial. *Eur Arch Psychiatry Clin Neurosci*.
Steyerberg, E.W. (2019a). "Evaluation of Performance," in *Clinical Prediction Models: A Practical Approach to Development, Validation, and Updating*. (Cham, Switzerland: Springer International Publishing), 277-308.
Steyerberg, E.W. (2019b). "Overfitting and Optimism in Prediction Models," in *Clinical Prediction Models: A Practical Approach to Development, Validation, and Updating*. (Cham, Switzerland: Springer International Publishing), 95-112.
Steyerberg, E.W. (2019c). "Selection of Main Effects," in *Clinical Prediction Models: A Practical Approach to Development, Validation, and Updating*. (Cham: Springer International Publishing), 207-225.
Steyerberg, E.W. (2019d). "Validation of Prediction Models," in *Clinical Prediction Models: A Practical Approach to Development, Validation, and Updating*. (Cham: Springer International Publishing), 329-344.
World Health Organization (1992). *The ICD-10 classification of mental and behavioural disorders : clinical descriptions and diagnostic guidelines*. Geneva: World Health Organization.
Zou, H., and Hastie, T. (2005). Regularization and Variable Selection via the Elastic Net. *Journal of the Royal Statistical Society. Series B (Statistical Methodology)* 67**,** 301-320.

Figure 1. Flow chart of individuals in the model development

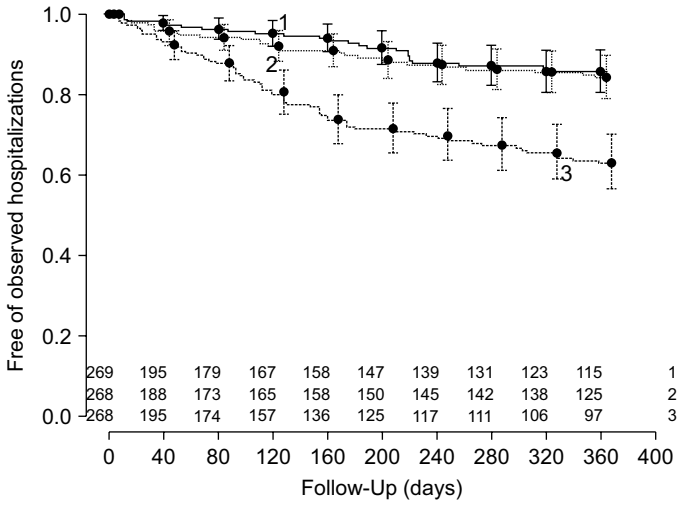


511 * Subcategories do not equal 1530 because some patients had a dual diagnosis.

512 * Subcategories do not equal 1530 because some patients had a dual diagnosis.

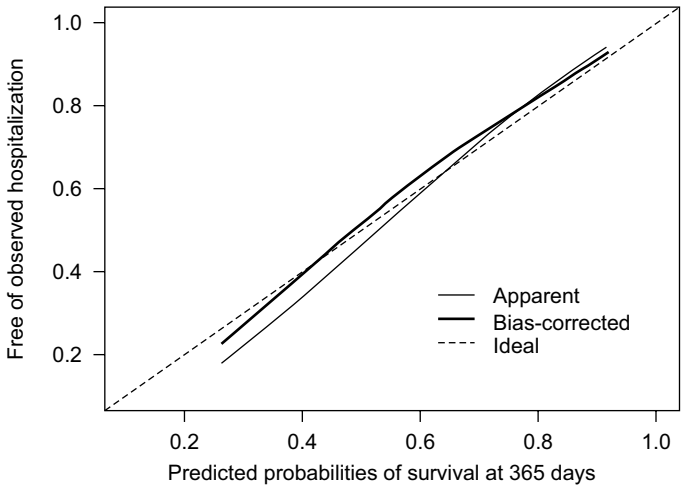
513

514 Figure 2. Fractions of individuals free of observed hospitalizations in three groups according to
515 tertiles of predicted probabilities of no hospitalization in the model development



516

517 Figure 3. Calibration plots for the predicted probabilities of no hospitalization against proportions of
518 individuals free of observed hospitalization



519

Table 1 Baseline characteristics of individuals (n = 810)

Characteristic	Number (%)
Age at discharge, mean (SD), y	45.1 (13.8)
Female sex	477 (58.9)
Psychiatric diagnoses (ICD-10 code)	
Schizophrenia (F20)	684 (84.4)
ATPD (F23)	57 (7.04)

Schizoaffective disorder (F25)	48 (5.93)
Delusional disorder (F22)	17 (2.10)
Others (F21, F24, F28, F29)	4 (0.50)
Receipt of benefits	114 (14.1)
Number of previous hospitalizations, median (range)	1 (0 to 15)
Hospitalization in the previous year	153 (19.0)
Current length of stay in days, median (range)	52 (2 to 207)
Use of long-acting injections at discharge	126 (15.6)
Current substance use disorder	12 (1.48)
Number of psychosocial interventions, median (range)	0 (0 to 34)

520 ATPD, acute and transient psychotic disorders.

521

Table 2 Association between pre-specified predictors and hospitalization from the ridge regression in the complete-case analysis (n = 805)

Variable	Hazard ratio (95% CI)
Age at discharge	0.87 (0.69–1.12)
Female sex	0.89 (0.63–1.27)
Receipt of benefits	1.20 (0.75–1.90)
Number of previous hospitalizations	1.42 (1.22–1.64)
Current length of stay	1.31 (1.04–1.64)
Current substance use disorders	0.70 (0.10–5.15)

Number of psychosocial interventions	0.95	(0.87–1.03)
Use of long-acting injections at discharge	0.63	(0.34–1.04)
Hospitalization in the previous year	1.23	(0.80–1.89)

522

Supplementary Material

Development and validation of a prediction model for rehospitalization among people with schizophrenia discharged from acute inpatient care

523 **Akira Sato*, Toshihiro Moriyama , Norio Watanabe, Kazushi Maruo, Toshi A. Furukawa**

524 *** Correspondence:** Corresponding Author: asatomatsu@gmail.com

525 14 Supplementary Tables

526 **Supplementary Table 1.** TRIPOD Checklist: Prediction Model Development and Validation.

Section/Topic	Item		Checklist Item	Page
Title and abstract				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	1
Introduction				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	2
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	2
Methods				
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	2
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	2
Participants	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	2
	5b	D;V	Describe eligibility criteria for participants.	2, 3
	5c	D;V	Give details of treatments received, if relevant.	n/a
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	3
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted.	3
Predictors	7a	D;V	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	3

	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors.	3
Sample size	8	D;V	Explain how the study size was arrived at.	3
Missing data	9	D;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	4
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	3
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	3, 4
	10c	V	For validation, describe how the predictions were calculated.	3
	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	3, 4
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	n/a
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	n/a
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	3, 4
Results				
Participants	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	4, Fig 1
	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	4, Table 1
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	Supplementary Table 4
Model development	14a	D	Specify the number of participants and outcome events in each analysis.	4, Fig 1
	14b	D	If done, report the unadjusted association between each candidate predictor and outcome.	n/a
Model specification	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	Supplementary Table 5
	15b	D	Explain how to the use the prediction model.	n/a
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	4
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	n/a
Discussion				
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	7

Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	6
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	5-7
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	6, 7
Other information				
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	2, 8
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	See below

Funding: No funding support was received for this study. Reference: Sato, A., Watanabe, N., Maruo, K. et al. Psychotic relapse in people with schizophrenia within 12 months of discharge from acute inpatient care: protocol for development and validation of a prediction model based on a retrospective cohort study in three psychiatric hospitals in Japan. Diagn Progn Res 6, 20 (2022). https://doi.org/10.1186/s41512-022-00134-w

Supplementary Table 2. Inter-rater reliability of predictors and relapse for the 30 consecutive participants.

	ICC	Cohen's Kappa	Percentage agreement
Eligibility criteria		0.814	93.3
Age at discharge	0.999		
Sex		0.930	96.7
Receipt of benefit		0.902	96.7
Total number of past hospitalizations	0.847		
Current length of stay	0.986		
Current SUD use		0	96.7
Total psychosocial sessions	1.000		
Current LAI use		0.701	86.7
Hospitalization in the previous year		0.933	96.7
Relapse		0.714	86.7

ICC, intraclass correlation coefficient. LAI, long-acting injections. SUD, substance use disorders.

536

537 **Supplementary Table 3.** Proportions of unblinded data during data collection (n=810).

	Number (%)
Unblinded at baseline (i.e., the data extractor knew the outcome)	67 (8.3)
Unblinded during the follow-up (i.e., the data extractor knew the condition of at least one of nine predictors)	38 (4.7)

538

Supplementary Table 4. Baseline characteristics of individuals in each hospital*.

Characteristic	All hospitals (n = 810) (%)	CPMC (n = 370)(%)	IH (n = 161) (%)	UPSH (n = 279) (%)
Age at discharge, mean (SD), y	45.1 (13.8)	41.9 (12.3)	47.3 (14.8)	48.1 (14.3)
Female sex	477 (58.9)	222 (60.0)	90 (55.9)	165 (59.1)
Psychiatric diagnoses (ICD-10 code)				
Schizophrenia (F20)	684 (84.4)	316 (85.4)	127 (78.9)	241 (86.4)
ATPD (F23)	57 (7.04)	27 (7.3)	10 (6.2)	20 (7.2)
Schizoaffective disorder (F25)	48 (5.93)	21 (5.7)	15 (9.3)	12 (4.3)
Delusional disorder (F22)	17 (2.10)	6 (1.6)	9 (5.6)	2 (0.7)
Others (F21, F24, F28, F29)	4 (0.50)	0 (0.0)	0 (0.0)	4 (1.4)
Receipt of benefits	114 (14.1)	33 (8.9)	22 (13.7)	59 (21.2)
Number of previous hospitalizations, median (range)	1 (0 to 15)	1 (0 to 15)	1 (0 to 15)	1 (0 to 15)
Hospitalization in the previous year	153 (19.0)	49 (13.2)	31 (19.3)	73 (26.5)
Current length of stay in days, median (range)	52 (2 to 207)	45 (2 to 207)	65 (5 to 207)	61 (6 to 207)

Use of long-acting injections at discharge	126 (15.6)	56 (15.1)	59 (36.7)	11 (3.9)
Current substance use disorder	12 (1.48)	5 (1.35)	2 (1.24)	5 (1.80)
Number of psychosocial interventions, median (range)	0 (0 to 34)	0 (0 to 19)	0 (0 to 34)	4 (0 to 34)

* For continuous variables of previous hospitalizations, current length of stay, and psychosocial interventions, we "winsorized" those outliers by shifting very high values to the 99th percentiles. ATPD, acute and transient psychotic disorders. CPMC, Chiba Psychiatric Medical Center. IH, Isogaya Hospital. UPSH, Urawa Psychiatric Sanatorium Hospital.

Supplementary Table 5. Presenting the final ridge model, including the baseline survival, for a specific time point*.

	Beta coefficient
Age at discharge	-0.007158979
Sex	-0.109747286
Number of previous hospitalizations	0.113617134
Presence of any hospitalization in the previous year	0.210998992
Current length of stay	0.005070876
Presence of current substance use disorders	-0.340880953
Use of long-acting injections at discharge	-0.453464154
Number of psychosocial interventions during the current hospitalization	-0.017031005
Receipt of benefits	0.175664749

* $S_0(365) = 0.7817099$ (365-day baseline survival).

Supplementary Table 6. Sensitivity analysis comparing three different models for hospitalization with the original model in the model development.

	n	Events	Harrell's c-index (95% CI)
Original model	805	131	0.667 (0.618–0.716)
Model including individuals aged < 65	734	122	0.669 (0.618–0.720)
Model including individuals with first episode of hospitalization only	315	26	0.662 (0.568–0.755)
Model including individuals with schizophrenia only	679	114	0.650 (0.597–0.704)