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Research paper

Predicting early psychiatric readmission among people with major depressive disorder: A machine learning analysis from the prospective multicentre DEEP READ study

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ABSTRACT

Background: Major depressive disorder (MDD) is associated with high relapse rates, with around 20% of inpatients experiencing readmission within 90 days after discharge. Routinely collected clinical information may help identify individuals at higher risk of readmission. Machine learning (ML) models could complement more traditional statistical approaches by exploring complex relationships among multiple vulnerability factors.
Methods: The DEEP READ study is a prospective, multicentre cohort study conducted across 13 Italian provinces, enrolling adults aged 18–65 years with a DSM-5-TR MDD diagnosis between January 2024 and December 2025.

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Rehospitalisation
Risk stratification

The primary outcome was unplanned psychiatric readmission within 90 days. Sociodemographic and clinical features (including Hamilton Depression Rating Scale scores and DSM-5 specifiers), comorbidities, and pharmacological treatment at discharge were recorded. A Random Forest classifier was trained on 22 predictors and internally evaluated using stratified 5-fold cross-validation.

Results: The sample included 322 individuals (mean age 43.0 years; 38.5% men), of whom 15.5% ($n = 50$) were readmitted within 90 days. The model achieved a mean test AUC of 0.74 (range: 0.59–0.87). Suicide attempts, prior hospitalisations, anticonvulsant prescription, cluster B personality disorder, female sex, and anxious distress ranked among the leading predictors. Although exploratory, lithium prescription showed a negative SHapley Additive exPlanations (SHAP) pattern.

Conclusions: A ML model based on routinely collected data showed moderate discrimination for 90-day readmission in MDD. These findings suggest that standard clinical variables may hold predictive value for early readmission. However, external validation, assessment of model calibration, and clinical utility are needed prior to clinical implementation.

1. Introduction

Major depressive disorder (MDD) is characterized by depressed mood, anhedonia, loss of energy, and recurrent thoughts of death (Marx et al., 2023), with increasing prevalence rates and relevant burden worldwide (Yan et al., 2024). Consistent with its recurrent course, approximately half of adults with MDD experience a clinical relapse within 5 years (Desai Boström et al., 2025), leading to significant functional impairment, suicidal behaviours, and physical health problems (Lye et al., 2020). While relapses are key determinants of hospital admissions in people with MDD, early rehospitalisation is associated with several individual, social, and contextual factors (Innes et al., 2015), possibly reflecting inadequate post-discharge stabilization and contributing to subsequent higher healthcare costs (Citrome et al., 2019). In particular, hospital readmission within 90 days of discharge is commonly used as an indicator of clinical vulnerability, affecting approximately 20% of individuals with MDD (Eseaton et al., 2023). In the United States, for example, early readmissions for MDD were estimated to cost nearly 300 million US dollars and 254,746 hospital days in 2018 (Eseaton et al., 2023). The identification of individuals at higher risk of early hospital readmission after discharge is thus an important clinical priority. This risk may involve different variables including sociodemographic characteristics, clinical features, and treatments (Citrome et al., 2019; Parami et al., 2021; Teigland et al., 2024), that are generally easy to collect, cost-effective, and readily available in clinical practice. However, traditional approaches, such as regression-based analyses, may be limited in capturing the complex interconnections across these factors. Machine learning (ML) methods, offering a complementary framework that can flexibly model interactions and non-linear associations across multiple variables, may be useful to predict the clinical course of MDD (Teutenberg et al., 2025). While ML approaches have shown promise in studies integrating complex information on genetics, neuroimaging, and biological biomarkers (e.g., Jiang et al., 2026; Winter et al., 2024), their performance using routinely collected variables in real-world clinical settings remains less established. To our knowledge, no prospective multicentre study has specifically evaluated the predictive contribution of variables routinely collected during hospitalisation, such as sociodemographic characteristics, clinical history, clinical features, and pharmacological treatments, using a ML framework for early readmission in MDD. In this study, we therefore evaluated the predictive performance of an exploratory ML model for 90-day unplanned readmission in a prospective cohort of inpatients with MDD consecutively admitted to psychiatric inpatient units across Italy. In addition, we assessed feature importance to provide a descriptive evaluation of the relative contribution of individual predictors to the likelihood of readmission.

2. Methods

2.1. Study design and setting

The DEEP READ (DEprEssion-related Predictors of hospital READmission) study is a prospective multicentre cohort study conducted across several psychiatric inpatient units affiliated with university and hospital centres in 13 different Italian provinces (Supplementary Fig. S1). The study was approved by the ethics committee of the coordinating centre (Comitato Etico Territoriale Lombardia 3 – ID 4371) in January 2024 and by relevant local ethics committees. It was carried out in accordance with the Declaration of Helsinki and reported following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (von Elm et al., 2008). Where applicable, prediction model reporting was additionally guided by the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis with Artificial Intelligence (TRIPOD+AI) principles (Collins et al., 2024).

2.2. Participants

We included individuals aged 18–65 years consecutively admitted with a diagnosis of current major depressive episode according to DSM-5-TR criteria (American Psychiatric Association, 2022), residing in the catchment area of the enrolling psychiatric inpatient unit. Participants were enrolled between January 2024 and December 2025, with the last observation at follow-up for the study outcome completed in March 2026. Subjects were excluded if they had a DSM-5-TR diagnosis of bipolar disorder or other severe mental illness, a depressive disorder induced by alcohol or substance use (while comorbid alcohol/substance use disorder was retained as a clinical predictor variable), depressive symptoms secondary to a general medical condition or other organic cause (American Psychiatric Association, 2022), or were unable to provide written informed consent.

2.3. Hospital readmission

The outcome was defined as an unplanned psychiatric readmission within 90 days after the index discharge, ascertained through hospital records or clinical charts at each participating centre. The 90-day timeframe was selected on the basis of evidence indicating that this period captures the peak of post-discharge clinical vulnerability in MDD (e.g., Eseaton et al., 2023; Zhu et al., 2022). We changed our primary outcome from a 1-month to a 3-month readmission window prior to formal ML analysis, based on the recognition that the number of 30-day readmission events would be insufficient for reliable model development.

2.4. Variables and measures

Data were collected during the index admission using standard

clinical interviews, chart review, and individual clinical records. Information included sociodemographic characteristics, participants' clinical history, clinical features, and prescribed pharmacological treatment at discharge. Sociodemographic variables included age, sex, and marital and living status. Clinical history included information on length of stay of the index hospitalisation, previous psychiatric hospitalisations, lifetime history of suicide attempts, and previous contacts with Adult and/or Child & Adolescent Psychiatry services. In terms of clinical features, we considered symptom severity, as measured by the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960), including a specific evaluation of current suicidal ideation according to HDRS item 3. We also assessed whether DSM-5 criteria for depressive episode specifiers, including anxious distress (Bartoli et al., 2024) and melancholic features (Valerio et al., 2023), were met. Information on comorbid conditions, such as personality clusters and alcohol/substance use disorders, was also collected. Finally, we recorded prescribed pharmacological treatments by class at discharge, including selective serotonin reuptake inhibitors (SSRIs), serotonin and noradrenaline reuptake inhibitors (SNRIs), other antidepressants (including bupropion, mirtazapine, trazodone, and vortioxetine), atypical and typical antipsychotics, lithium, and anticonvulsants.

2.5. Data analysis

A Random Forest classifier, combining predictions from multiple decision trees, was trained to predict 90-day hospital readmission (binary outcome). Model performance was evaluated using stratified 5-fold cross-validation (i.e., the sample is divided into five folds with each fold used once for testing and the remaining folds for model development), preserving the original class distribution across folds. Class imbalance was addressed through a combination of class weighting and Synthetic Minority Over-sampling Technique (SMOTE), applied within each training fold. To prevent data leakage, all preprocessing steps, including imputation to address missingness, were conducted within each cross-validation fold, with parameters estimated on the training set and applied to the corresponding test data. Model performance was primarily evaluated using the area under the receiver operating characteristic curve (AUC-ROC), averaged across folds, with related range and 95% confidence interval (CI). Additional threshold-dependent metrics (sensitivity, specificity, positive predictive value [PPV], negative predictive value [NPV], and F1-score – defined as the harmonic mean of precision and sensitivity [or recall]) were also examined. Precision-Recall analysis was carried out as a complementary evaluation of model performance, relative to the baseline determined by the prevalence of the positive class. We also expanded the evaluation of model performance including an assessment of calibration, by estimating the Brier score and generating the internal calibration plot. ROC curves were used to describe the performance of the full model and the incremental contribution of variable domains (sociodemographic characteristics, clinical history, clinical features, and prescribed pharmacological treatments). Feature importance scores were derived from the final model and interpreted as exploratory outputs, without formal inferential testing and a priori hypotheses. Model interpretability was further explored using SHapley Additive exPlanations (SHAP) values to quantify the direction and magnitude of individual feature contributions to model predictions. For each feature value (e.g., blue = 0 and red = 1 for categorical variables), positive SHAP values indicate a contribution toward a higher predicted risk of readmission, whereas negative SHAP values indicate a contribution toward a lower predicted risk. These associations were interpreted as descriptive rather than causal, acknowledging potential instability in the presence of correlated features. All analyses were conducted in Python (release 3.13.12).

3. Results

3.1. Sample characteristics

We included 322 participants (mean age: 43.0 ± 15.7 years; men: 38.5%) with a diagnosis of MDD. Table 1 shows full sample characteristics. Among them, 15.5% (n = 50) experienced an unplanned psychiatric readmission within 90 days of the index discharge, with approximately half (n = 27/50) experiencing rehospitalisation within 30 days.

3.2. Machine-learning model performance

The Random Forest classifier was evaluated on a set of 22 variables. DSM-5 depressive episode specifiers with low prevalence (<10%) – including psychotic, mixed, atypical, and catatonic features – were excluded to reduce instability associated with sparse predictors. The model achieved a mean test AUC of 0.74 (range: 0.59–0.87; 95%CI: 0.67–0.82), with specificity of 0.62 (range:0.52–0.70; 95%CI: 0.57–0.68), sensitivity of 0.72 (range: 0.50–0.90; 95%CI: 0.60–0.84), PPV of 0.26 (range: 0.17–0.33; 95%CI: 0.22–0.31), NPV of 0.92 (range: 0.86–0.97; 95%CI: 0.89–0.95), and F1-score of 0.38 (range: 0.26–0.49; 95%CI: 0.33–0.45). The mean ROC curve across folds is shown in Fig. 1.

Precision-Recall analysis indicated performance above the no-skill baseline, although variability across folds was observed (pooled Average Precision = 0.42, fold range 0.37–0.56; Supplementary Fig. S2). The Brier score was 0.14 (range: 0.12–0.16; 95%CI: 0.13–0.15; calibration intercept −0.88 and slope 1.20) and the calibration plot (Supplementary Fig. S3) suggested a possible overestimation of readmission

Table 1
Sample characteristics.

Sociodemographic characteristics	
Age (years), mean ± SD	43.0 ± 15.7
Male sex, n (%)	124 (38.5%)
Single, n (%)	151 (47.0%)
Living alone, n (%)	68 (21.4%)
Clinical history	
Length of stay (days), mean ± SD	14.0 ± 11.5
Prior contacts with adult mental health services, n (%)	238 (73.9%)
Prior contacts with CAP services, n (%)	37 (11.5%)
Prior psychiatric hospitalisations, n (%)	163 (50.6%)
Lifetime suicide attempts, n (%)	155 (48.1%)
Clinical features	
Cluster B personality disorder, n (%)	106 (32.9%)
Alcohol/substance use disorder, n (%)	50 (15.6%)
Anxious distress, n (%)	145 (45.0%)
Melancholic features, n (%)	41 (12.7%)
Psychotic features, n (%)	22 (6.8%)
Catatonic features, n (%)	4 (1.2%)
Mixed features, n (%)	7 (2.2%)
Atypical features, n (%)	5 (1.6%)
HDRS total score, mean ± SD	20.9 ± 7.3
HDRS item 3 (suicidal ideation), mean ± SD	2.0 ± 1.4
Pharmacological treatment at discharge	
SSRIs, n (%)	162 (50.3%)
SNRIs, n (%)	51 (15.8%)
Other antidepressants, n (%)	98 (30.4%)
Atypical antipsychotics, n (%)	234 (72.7%)
Typical antipsychotics, n (%)	24 (7.5%)
Anticonvulsants, n (%)	113 (35.1%)
Lithium, n (%)	79 (24.5%)

Missing values: single n = 1; living alone n = 4; alcohol/substance use disorders n = 2; HDRS total score n = 2; HDRS item 3 n = 2.
Abbreviations: CAP = Child & Adolescent Psychiatry; HDRS = Hamilton Depression Rating Scale; SNRI = Serotonin and Noradrenaline Reuptake Inhibitors; SSRI = Selective Serotonin Reuptake Inhibitors.

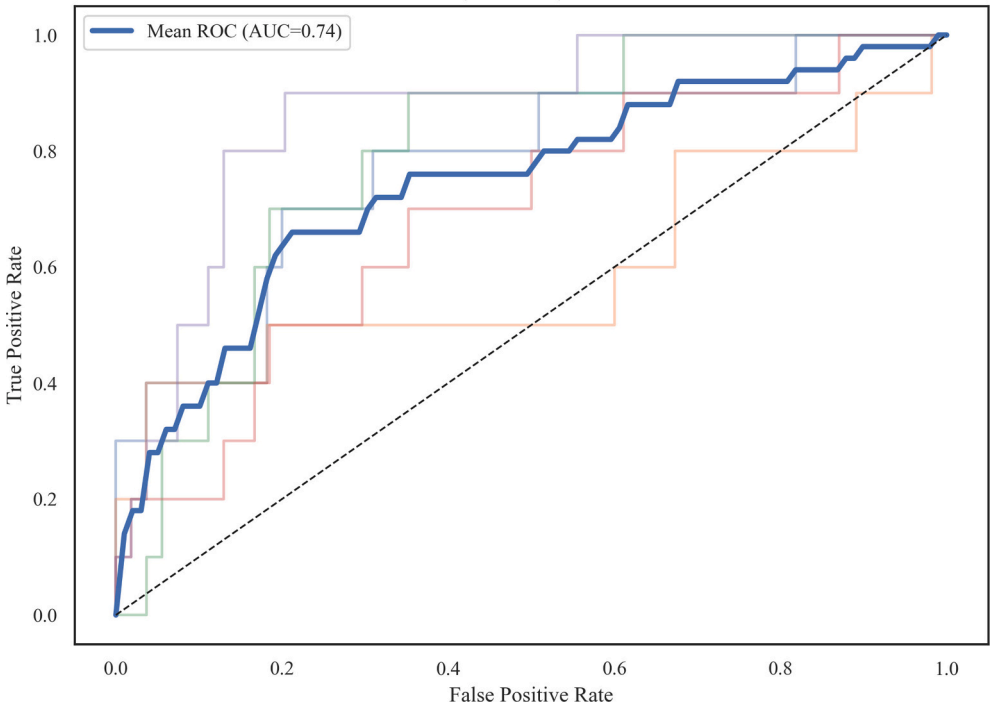


Fig. 1. Receiver operating characteristic (ROC) curves from 5-fold cross-validation of the Random Forest model.

risk, particularly at intermediate-to-higher predicted probabilities, while calibration was closer to the ideal line in the lower-risk range.

The incremental contribution of variable domains is shown in Fig. 2.

The full feature importance ranking and SHAP values – providing a descriptive indication of the relative contribution and direction of individual predictors within the model – are shown in Figs. 3 and 4, respectively. Lifetime suicide attempts, prior psychiatric hospitalisations, and cluster B personality disorder (mainly borderline personality disorder) ranked among the most influential predictors in the model, followed by sex and anxious distress. In particular, while lifetime suicide attempts, previous psychiatric hospitalisations, cluster B personality disorder, and anxious distress showed patterns consistent with higher model-predicted readmission risk, male sex (in red in Fig. 4) was predominantly associated with negative SHAP values, indicating that, within the fitted model and conditional on the other included features, male sex tended to shift predictions toward a lower probability of 90-day readmission. Among pharmacological variables, anticonvulsant prescription at discharge was associated with higher feature importance values. In contrast, antidepressant class variables and antipsychotics consistently ranked in the lowest third of the feature importance distribution. Lithium at discharge showed an intermediate level of pharmacological importance and a negative SHAP value pattern. This result should be interpreted as a model-specific, non-causal association.

4. Discussion

4.1. Summary and interpretation of findings

In this prospective multicentre study we evaluated a ML model for predicting 90-day psychiatric rehospitalisations in 322 inpatients with MDD across different psychiatric hospital units in Italy. Specific clinical and sociodemographic features achieved an internally validated AUC of 0.74, with moderate sensitivity and specificity. Overall, these results suggest preliminary discriminatory ability, warranting additional clinical evaluation. Our findings support the use of ML approaches to investigate the complex interplay between the numerous clinical and individual factors in the course of MDD (Teutenberg et al., 2025). To better contextualize these results, it is worth noting that they are consistent with those reported in previous studies using similar approaches, though comparisons should be interpreted cautiously. For instance, a multimodal panel achieved an AUC of 0.68 when predicting hospital readmissions in people with a major depressive episode, despite investigating a longer period of up to two years after discharge (Cearns et al., 2019). Moreover, in a large, although retrospective, dataset comprising 13,177 individuals, the model showed an AUC slightly higher (0.80; 95%CI: 0.75–0.85) for hospital readmissions within 90 days (Zhu et al., 2022). However, direct comparison with such studies is limited by substantial methodological differences (follow-up duration, predictor sets, and modelling frameworks). Nonetheless, while multimodal data may provide additional value under specific modelling and validation conditions, our findings suggest that routinely collected features of MDD may already capture a substantial proportion of the predictive signal. While not yet establishing clinical readiness, this may have practical implications for feasibility and scalability, as it suggests that acceptable predictive performance may be achievable without relying exclusively on more resource-intensive, less accessible multimodal assessments in daily clinical practice. However, this apparent comparability should be interpreted with caution, as it does not imply that these approaches are interchangeable.

Analyses identified lifetime history of suicide attempts, prior psychiatric hospitalisations, co-occurring personality disorders, and anxious distress among the most influential predictors of early readmission. In our study, individuals with MDD at higher predicted risk were thus more likely to present markers of recurrent illness course and suicidality, possibly driven by personality vulnerability and a prominent anxiety component. This pattern is broadly consistent with theoretical models suggesting bidirectional relationships between anxiety and depressive features (Jacobson and Newman, 2017), as well as their interconnections with both suicidality and relapses (Doering et al., 2024). In addition, the importance of previous hospitalisations among influential predictors aligns with available evidence showing that service utilisation may be a key determinant of rehospitalisation in severe mental disorders (e.g., Bartoli et al., 2020; Berardelli et al., 2022), including MDD (Lin et al., 2007). Sex ranked among the top predictors in

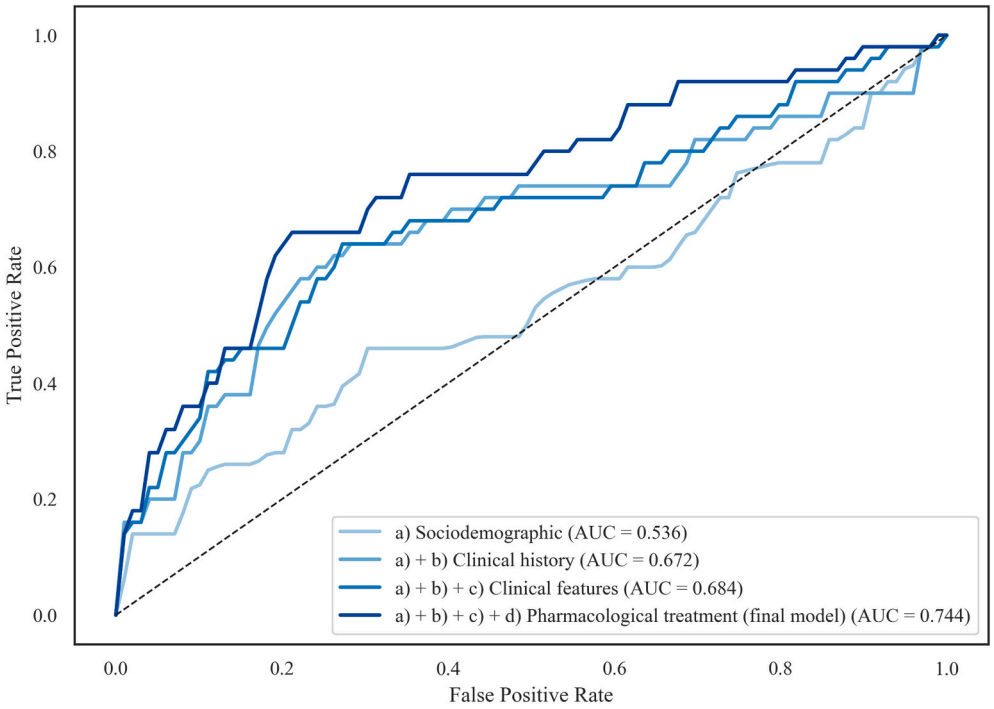


Fig. 2. ROC curves by variable domain.

our model, indicating a lower model-predicted probability of readmission within 90 days among men. This is consistent with prior studies reporting higher psychiatric rehospitalisation rates in women with depressive disorders (Zhu et al., 2022), especially among younger subjects (Seizer et al., 2025). Indeed, research consistently suggests that mood disorders represent a more frequent reason for rehospitalisation in women than in men (Vigod et al., 2016), and that the risk of recurrence after a major depressive episode is higher in women compared with men (Bertschy et al., 2016).

An additional point concerns the role of anticonvulsants within the model for hospital readmission. While systematic cross-national data on anticonvulsant use in unipolar depression are limited, the relatively high prevalence of anticonvulsant prescription in our sample may reflect confounding by indication, as a treatment with anticonvulsants may represent a proxy for underlying clinical severity of complex depressive presentations for which standard antidepressant monotherapy was insufficient. Indeed, anticonvulsants, such as carbamazepine, lamotrigine, and valproate, generally prescribed for individuals with bipolar disorder (Bowden, 2009), are often used also for patients with recurrent MDD and high levels of irritability or agitation (Vigo and Baldessarini, 2009). Moreover, the use of anticonvulsants, such as gabapentin and pregabalin, is common in the treatment of anxiety symptoms (Greenblatt and Greenblatt, 2018; Hong et al., 2022), which are among the most significant predictors of readmission in our study. However, this interpretation remains speculative and cannot be inferred from feature importance alone, as the prescription of antipsychotics – often useful augmentation strategies for difficult-to-treat depression (Kishimoto et al., 2022) – ranked lower in the feature importance distribution, suggesting a more limited contribution within the model. Moreover, lithium at discharge was associated with lower model-predicted probabilities of hospital readmission. Although this pattern is compatible with the established role of lithium in recurrence and suicide prevention (Ercis et al., 2023), it should be interpreted cautiously in the context of the present analysis. Within the context of a clinician-mediated prescription at discharge, this may reflect residual confounding related to adherence, illness profile or severity, centre-specific practices, or other unmeasured factors. Therefore, the SHAP pattern should be considered hypothesis-generating and interpreted in an exploratory rather than causal framework.

Overall, our study, based on a multicentre sample across different psychiatric units in Italy, provides support for the promising yet challenging usefulness of ML-based tools for predicting hospital readmission. This approach may have potential clinical relevance, for instance by supporting clinicians in identifying patients who would most benefit from transitional care interventions in the critical post-discharge period (Mitchell et al., 2022). Meta-analytic evidence shows that post-discharge transitional interventions, regardless of the specific intervention strategy, may reduce the risk of readmission during follow-up (Holzinger et al., 2017). However, the translation of ML models into clinical decision support tools remains challenging, particularly when methodological, ethical, and implementation issues must be carefully addressed (Crocamo, 2026). In particular, further work is needed to assess model calibration, clinical utility, and robustness across independent populations. Prospective validation, external replication, and careful consideration of implementation barriers in routine psychiatric care are essential prerequisites for clinical translation (Chekroud et al., 2021; Koutsouleris et al., 2022).

4.2. Limitations

Findings of this study should be interpreted with caution due to several limitations. First, while the multicentre design enhances the diversity of the sample, it does not ensure full representativeness of inpatients with MDD and cannot be considered a substitute for external validation. In particular, heterogeneity across catchment areas should be acknowledged. It is likely that local factors, such as available mental health care resources, the number of hospital beds, and different clinical approaches, may influence the readmission rates. However, given the limited sample size and number of outcome events within individual centres, centre-specific effects could not be reliably assessed, and leave-one-centre-out validation would have yielded unstable performance estimates. Second, while the preliminary protocol aimed at investigating 1-month readmissions, the analysis focused on the 3-month window to ensure an adequate number of outcome events for model development.

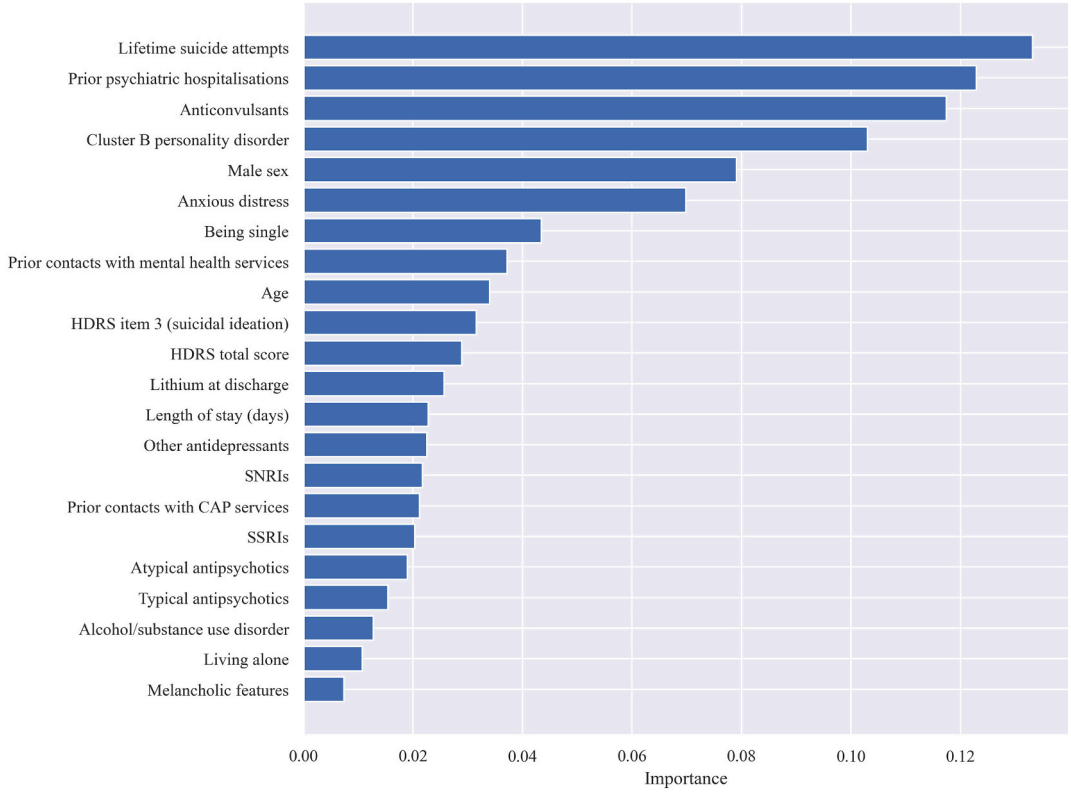


Fig. 3. Feature importance.

While this timeframe is supported by previous evidence of a peak in post-discharge vulnerability among people with MDD (Eseaton et al., 2023; Zhu et al., 2022), it represents a deviation from the original protocol; this decision was not data-driven and preceded ML analysis. Another limitation is the possibility that some readmissions occurred at facilities outside the enrolling network and were not captured, potentially underestimating the true readmission rate. This may also include rehabilitation or residential admissions occurring between the index discharge and the 90-day endpoint. However, given the territorial, catchment-based organisation of Italian psychiatric services (Ruggeri et al., 2008), the likelihood of undetected out-of-network readmissions may be relatively limited. Moreover, from a methodological standpoint, this analysis is shaped by challenges related to the curse of dimensionality. The relatively small sample size, combined with the number of predictors and the low outcome prevalence, may increase susceptibility to overfitting and instability in model estimates, while correlated clinical variables may further affect interpretability and generalisability. Consistent with this, the observed gap between training and test performance suggests partial capture of sample-specific patterns, warranting cautious interpretation. However, to mitigate these issues, stratified cross-validation was used to preserve class balance, and synthetic oversampling (SMOTE) was applied within each training fold to improve representation of the minority class. Model complexity was further constrained by specifying hyperparameters a priori (e.g., limited tree depth) to reduce the risk of overfitting and improve model robustness. This modelling choice was supported by the results of a nested cross-validation analysis. In addition, feature importance and SHAP patterns need to be considered for their explorative value and do not imply causal relationships. Future studies should adopt a prospective, hypothesis-driven design to investigate the contribution of the specific variables identified in our study and seek to confirm these findings in independent cohorts.

5. Conclusions

Using a prospective design and multicentre recruitment, study found that a ML model achieved moderate discrimination for 90-day readmission in individuals with MDD. Routinely collected, patient-level clinical profiles at discharge may carry meaningful predictive information for early readmission. However, external validation, calibration assessment, clinical utility analyses, and broader pharmacological characterization will be important next steps toward clinical risk stratification. Our findings should therefore be interpreted as hypothesis-generating for confirmatory prospective studies in larger samples.

CRediT authorship contribution statement

Francesco Bartoli: Writing – original draft, Visualization, Resources, Project administration, Methodology, Investigation, Conceptualization. **Mario Luciano:** Writing – review & editing, Resources, Project administration, Investigation, Conceptualization. **Cristina Crocamo:** Writing – review & editing, Visualization, Validation, Software, Resources, Methodology, Formal analysis. **Carlo Bassetti:** Writing – review & editing, Resources, Investigation, Formal analysis, Data curation. **Daniele Cavaleri:** Writing – review & editing, Resources, Formal analysis, Data curation. **Andrea Aguglia:** Writing – review & editing, Resources, Investigation. **Anna-Rita Atti:** Writing – review & editing, Resources, Investigation. **Isabella Berardelli:** Writing – review & editing, Resources, Investigation. **Angela Chiara Cecere:** Writing – review & editing, Resources, Investigation. **Salvatore Cipolla:** Writing – review & editing, Resources, Investigation. **Pasquale De Fazio:** Writing – review & editing, Resources, Investigation. **Renato de Filippis:** Writing – review & editing, Resources, Investigation. **Daniele De Francesco:** Writing – review & editing, Resources, Investigation. **Carla Gramaglia:** Writing – review & editing, Resources, Investigation. **Valeria Latorre:** Writing – review & editing, Resources, Investigation. **Giulia Lucca:** Writing – review & editing, Resources, Investigation. **Massimo**



Fig. 4. SHAP (SHapley Additive exPlanations) summary plot.

Pasquini: Writing – review & editing, Resources, Investigation. **Nicola Poloni:** Writing – review & editing, Resources, Investigation. **Maurizio Pompili:** Writing – review & editing, Resources, Investigation. **Alessandro Rodolico:** Writing – review & editing, Resources, Investigation. **Gianluca Rosso:** Writing – review & editing, Resources, Investigation. **Gianluca Serafini:** Writing – review & editing, Resources, Investigation. **Maria Salvina Signorelli:** Writing – review & editing, Resources, Investigation. **Lorenzo Tarsitani:** Writing – review & editing, Resources, Investigation. **Antonio Ventriglio:** Writing – review & editing, Resources, Investigation. **Umberto Volpe:** Writing – review & editing, Resources, Investigation. **Patrizia Zeppegno:** Writing – review & editing, Resources, Investigation. **Giuseppe Carrà:** Writing – review & editing, Validation, Supervision, Resources, Conceptualization. **Andrea Fiorillo:** Writing – review & editing, Validation, Supervision, Resources, Conceptualization.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used Claude (Anthropic) in order to support text revision and language editing. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2026.122502.

Data availability

Data supporting the findings of this study are available from the corresponding author upon reasonable request.

References

American Psychiatric Association, 2022. Diagnostic and statistical manual of mental disorders: DSM-5-TR, 5th ed. rev. American Psychiatric Association Publishing, Washington, DC.

Bartoli, F., Cavaleri, D., Moretti, F., Bachi, B., Calabrese, A., Callovini, T., Cioni, R.M., Riboldi, I., Nacinovich, R., Crocamo, C., Carrà, G., 2020. Pre-discharge predictors of 1-year rehospitalization in adolescents and young adults with severe mental disorders: a retrospective cohort study. Medicina (Kaunas) 56, 613. https://doi.org/10.3390/medicina56110613.

Bartoli, F., Bachi, B., Callovini, T., Palpella, D., Piacenti, S., Morreale, M., Di Lella, M.E., Crocamo, C., Carrà, G., NOMIAC Investigators, 2024. Anxious distress in people with major depressive episodes: a cross-sectional analysis of clinical correlates. CNS Spectr. 29, 49–53. https://doi.org/10.1017/S1092852923002377.

Berardelli, I., Sarubbi, S., Rogante, E., Erbuto, D., Cifrodelli, M., Giuliani, C., Calabrò, G., Lester, D., Innamorati, M., Pompili, M., 2022. Exploring risk factors for re-hospitalization in a psychiatric inpatient setting: a retrospective naturalistic study. BMC Psych. 22, 821. https://doi.org/10.1186/s12888-022-04472-3.

Bertschy, G., Velten, M., Weibel, S., 2016. Major depression: does gender influence the risk of recurrence? A systematic review. Eur. J. Psych. 30, 7–27.

Bowden, C.L., 2009. Anticonvulsants in bipolar disorders: current research and practice and future directions. Bipolar Disord. 11, 20–33. https://doi.org/10.1111/j.1399-5618.2009.00708.x.

Cearns, M., Opel, N., Clark, S., Kaehler, C., Thalamuthu, A., Heindel, W., Winter, T., Teismann, H., Minnerup, H., Dannlowski, U., Berger, K., Baune, B.T., 2019. Predicting rehospitalization within 2 years of initial patient admission for a major depressive episode: a multimodal machine learning approach. Transl. Psychiatry 2019, 285. https://doi.org/10.1038/s41398-019-0615-2.

Chekroud, A.M., Bondar, J., Delgadillo, J., Doherty, G., Wasil, A., Fokkema, M., Cohen, Z., Belgrave, D., DeRubeis, R., Iniesta, R., Dwyer, D., Choi, K., 2021. The promise of machine learning in predicting treatment outcomes in psychiatry. World Psychiatry 20, 154–170. https://doi.org/10.1002/wps.20882.

Citrome, L., Jain, R., Tung, A., Landsman-Blumberg, P.B., Kramer, K., Ali, S., 2019. Prevalence, treatment patterns, and stay characteristics associated with hospitalizations for major depressive disorder. J. Affect. Disord. 249, 378–384. https://doi.org/10.1016/j.jad.2019.01.044.

Collins, G.S., Moons, K.G.M., Dhiman, P., Riley, R.D., Beam, A.L., Van Calster, B., Ghassemi, M., Liu, X., Reitsma, J.B., van Smeden, M., Boulesteix, A.L., Camaradou, J. C., Celi, L.A., Denaxas, S., Denniston, A.K., Glocker, B., Golub, R.M., Harvey, H., Heinze, G., Hoffman, M.M., Kegne, A.P., Lam, E., Lee, N., Loder, E.W., Maier-Hein, L., Mateen, B.A., McCradden, M.D., Oakden-Rayner, L., Ordish, J., Parnell, R., Rose, S., Singh, K., Wynants, L., Logullo, P., 2024. TRIPOD+AI statement: updated guidance for reporting clinical prediction models that use regression or machine learning methods. BMJ (Clin. Res. Ed.) 385, e078378. https://doi.org/10.1136/bmj-2023-078378.

Crocamo, C., 2026. Rethinking artificial intelligence in psychiatry and mental healthcare: distinct needs, converging goals. BJPsych Adv. 32, 176–179. https://doi.org/10.1192/bja.2025.10191.

Desai Boström, A.E., Cars, T., Hellner, C., Lundberg, J., 2025. Recovery and recurrence from major depression in adolescence and adulthood. Acta Psychiatr. Scand. 151, 625–633. https://doi.org/10.1111/acps.13785.

Doering, S., Probert-Lindström, S., Ehnvall, A., Wiktorsson, S., Palmqvist Öberg, N., Bergqvist, E., Stefenson, A., Fransson, J., Westrin, Å., Waern, M., 2024. Anxiety symptoms preceding suicide: a Swedish nationwide record review. J. Affect. Disord. 355, 317–324. https://doi.org/10.1016/j.jad.2024.03.118.

von Elm, E., Altman, D.G., Egger, M., Pocock, S.J., Gøtzsche, P.C., Vandenbroucke, J.P., STROBE Initiative, 2008. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. J. Clin. Epidemiol. 61, 344–349. https://doi.org/10.1016/j.jclinepi.2007.11.008.

Ercis, M., Ozerdem, A., Singh, B., 2023. When and how to use lithium augmentation for treating major depressive disorder. J. Clin. Psych. 84, 23ac14813. https://doi.org/10.4088/JCP.23ac14813.

Eseaton, P.O., Enosolease, A.U., Ijioma, O., Ugoh, A.C., Onyeaka, H., Oladunjoye, A.F., Anugwom, G., Osiezagha, K., Edigin, E., 2023. Severe major depressive disorder readmissions: a national United States population study. J. Affect. Disord. 333, 177–180. https://doi.org/10.1016/j.jad.2023.04.070.

Greenblatt, H.K., Greenblatt, D.J., 2018. Gabapentin and pregabalin for the treatment of anxiety disorders. Clin. Pharmacol. Drug Dev. 7, 228–232. https://doi.org/10.1002/cpdd.446.

Hamilton, M., 1960. A rating scale for depression. J. Neurol. Neurosurg. Psychiatry 23, 56–62. https://doi.org/10.1136/jnnp.23.1.56.

Holzinger, F., Fahrenkrog, S., Roll, S., Kleefeld, F., Adli, M., Heintze, C., 2017. Discharge management strategies and post-discharge care interventions for depression - Systematic review and meta-analysis. J. Affect. Disord. 223, 82–94. https://doi.org/10.1016/j.jad.2017.07.026.

Hong, J.S.W., Atkinson, L.Z., Al-Juffali, N., Awad, A., Geddes, J.R., Tunbridge, E.M., Harrison, P.J., Cipriani, A., 2022. Gabapentin and pregabalin in bipolar disorder, anxiety states, and insomnia: Systematic review, meta-analysis, and rationale. Mol. Psychiatry 27, 1339–1349. https://doi.org/10.1038/s41380-021-01386-6.

Innes, H., Lewsey, J., Smith, D.J., 2015. Predictors of admission and readmission to hospital for major depression: A community cohort study of 52,990 individuals. J. Affect. Disord. 183, 10–14. https://doi.org/10.1016/j.jad.2015.04.019.

Jacobson, N.C., Newman, M.G., 2017. Anxiety and depression as bidirectional risk factors for one another: A meta-analysis of longitudinal studies. Psychol. Bull. 143, 1155–1200. https://doi.org/10.1037/bul0000111.

Jiang, J.C., Brianceau, C., Delzant, E., Colle, R., Bottemanne, H., Corruble, E., Wray, N. R., Colliot, O., Shah, S., Couvy-Duchesne, B., 2026. Applying machine-learning and deep-learning to predict depression from brain MRI and identify depression-related brain biology. Transl. Psychiatry 16, 171. https://doi.org/10.1038/s41398-026-03889-8.

Kishimoto, T., Hagi, K., Kurokawa, S., Kane, J.M., Correll, C.U., 2022. Efficacy and safety of antipsychotic augmentation of antidepressants in treatment-resistant depression: a systematic review and meta-analysis. Psychol. Med. 53, 4064–4082. https://doi.org/10.1017/S0033291722000745.

Koutsouleris, N., Hauser, T.U., Skvortsova, V., De Choudhury, M., 2022. From promise to practice: towards the realisation of AI-informed mental health care. Lancet Digit. Health 4, e829–e840. https://doi.org/10.1016/S2589-7500(22)00153-4.

Lin, C.H., Chen, Y.S., Lin, C.H., Lin, K.S., 2007. Factors affecting time to rehospitalization for patients with major depressive disorder. Psychiatry Clin. Neurosci. 61, 249–254. https://doi.org/10.1111/j.1440-1819.2007.01662.x.

Lye, M.S., Tey, Y.Y., Tor, Y.S., Shahabudin, A.F., Ibrahim, N., Ling, K.H., Stanslas, J., Loh, S.P., Rosli, R., Lokman, K.A., Badamasi, I.M., Faris-Aldoghachi, A., Abdul Razak, N.A., 2020. Predictors of recurrence of major depressive disorder. PLoS One 15, e0230363. https://doi.org/10.1371/journal.pone.0230363.

Marx, W., Penninx, B.W.J.H., Solmi, M., Furukawa, T.A., Firth, J., Carvalho, A.F., Berk, M., 2023. Major depressive disorder. Nat. Rev. Dis. Primers 9, 44. https://doi.org/10.1038/s41572-023-00454-1.

Mitchell, S.E., Reichert, M., Howard, J.M., Krizman, K., Bragg, A., Huffaker, M., Parker, K., Cawley, M., Roberts, H.W., Sung, Y., Brown, J., Culpepper, L., Cabral, H. J., Jack, B.W., 2022. Reducing readmission of hospitalized patients with depressive symptoms: a randomized trial. Ann. Fam. Med. 20, 246–254. https://doi.org/10.1370/afm.2801.

Parami, S., Tapak, L., Poorolajal, J., Moghimbeigi, A., Ghaleiha, A., 2021. Identifying factors associated with the hospital readmission rate among patients with major depressive disorder. BMC Psych. 21, 542. https://doi.org/10.1186/s12888-021-03559-7.

Ruggeri, M., Lora, A., Semisa, D., SIEP-DIRECT'S Group, 2008. The SIEP-DIRECT'S project on the discrepancy between routine practice and evidence. An outline of main findings and practical implications for the future of community based mental health services. Epidemiol. Psichiatr. Soc. 17, 358–368.

Seizer, L., Renner, T.J., Löchner, J., 2025. Prevalence and predictors of rehospitalization in youth depression patients: a 10-year longitudinal study. J. Affect. Disord. 390, 119800. https://doi.org/10.1016/j.jad.2025.119800.

Teigland, C., Mohammadi, I., Agatep, B.C., Boskovic, D.H., Velligan, D., 2024. Relationship between social determinants of health and hospitalizations and costs in patients with major depressive disorder. J. Manag. Care Spec. Pharm. 30, 978–990. https://doi.org/10.18553/jmcp.2024.30.9.978.

Teutenberg, L., Stein, F., Thomas-Odenthal, F., Usemann, P., Brosch, K., Winter, N., Goltermann, J., Leenings, R., Konowski, M., Barkhau, C., Fisch, L., Meinert, S., Flinkenflügel, K., Schürmeyer, N., Bonnekoh, L., Thiel, K., Kraus, A., Alexander, N., Jansen, A., Nenadić, I., Straube, B., Hahn, T., Dannlowski, U., Jamalabadi, H., Kircher, T., 2025. Machine learning-based prediction of illness course in major depression: the relevance of risk factors. J. Affect. Disord. 374, 513–522. https://doi.org/10.1016/j.jad.2025.01.060.

Valerio, M.P., Lomastro, J., Igoa, A., Martino, D.J., 2023. Clinical characteristics of melancholic and nonmelancholic depressions. J. Nerv. Ment. Dis. 211, 248–252. https://doi.org/10.1097/NMD.0000000000001616.

Vigo, D.V., Baldessarini, R.J., 2009. Anticonvulsants in the treatment of major depressive disorder: an overview. Harv. Rev. Psych. 17, 231–241. https://doi.org/10.1080/10673220903129814.

Vigod, S.N., Kurdyak, P., Fung, K., Gruneir, A., Herrmann, N., Hussain-Shamsy, N., Isen, M., Lin, E., Rochon, P., Taylor, V.H., Seitz, D., 2016. Psychiatric hospitalizations: a comparison by gender, sociodemographics, clinical profile, and postdischarge outcomes. Psychiatr. Serv. 67, 1376–1379. https://doi.org/10.1176/appi.ps.201500547.

Winter, N.R., Blanke, J., Leenings, R., Ernsting, J., Fisch, L., Sarink, K., Barkhau, C., Emden, D., Thiel, K., Flinkenflügel, K., Winter, A., Goltermann, J., Meinert, S., Dohm, K., Repple, J., Gruber, M., Leehr, E.J., Opel, N., Grotegerd, D., Redlich, R., Nitsch, R., Bauer, J., Heindel, W., Gross, J., Risse, B., Andlauer, T.F.M., Forstner, A. J., Nöthen, M.M., Rietschel, M., Hofmann, S.G., Pfarr, J.K., Teutenberg, L., Usemann, P., Thomas-Odenthal, F., Wroblewski, A., Brosch, K., Stein, F., Jansen, A., Jamalabadi, H., Alexander, N., Straube, B., Nenadic, I., Kircher, T., Dannlowski, U., Hahn, T., 2024. A systematic evaluation of machine learning-based biomarkers for major depressive disorder. JAMA Psych. 81, 386–395. https://doi.org/10.1001/jamapsychiatry.2023.5083.

Yan, G., Zhang, Y., Wang, S., Yan, Y., Liu, M., Tian, M., Tian, W., 2024. Global, regional, and national temporal trend in burden of major depressive disorder from 1990 to 2019: an analysis of the global burden of disease study. Psychiatry Res. 337, 115958. https://doi.org/10.1016/j.psychres.2024.115958.

Zhu, T., Jiang, J., Hu, Y., Zhang, W., 2022. Individualized prediction of psychiatric readmissions for patients with major depressive disorder: a 10-year retrospective cohort study. Transl. Psychiatry 12, 170. https://doi.org/10.1038/s41398-022-01937-7.