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Multimodal Machine Learning Prediction of 12-Month Suicide Attempts in Bipolar Disorder

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ABSTRACT

Introduction: Bipolar disorder (BD) patients present an increased risk of suicide attempts. Most current machine learning (ML) studies predicting suicide attempts are cross-sectional, do not employ time-dependent variables, and do not assess more than one modality. Therefore, we aimed to predict 12-month suicide attempts in a sample of BD patients, using clinical and brain imaging data.

Methods: A sample of 163 BD patients were recruited and followed up for 12 months. Gray matter volumes and cortical thickness were extracted from the T1-weighted images. Based on previous literature, we extracted 56 clinical and demographic features from digital health records. Support Vector Machine was used to differentiate BD subjects who attempted suicide. First, we explored single modality prediction (clinical features, GM, and thickness). Second, we implemented a multimodal stacking-based data fusion framework.

Results: During the 12 months, 6.13% of patients attempted suicide. The unimodal classifier based on clinical data reached an area under the curve (AUC) of 0.83 and balanced accuracy (BAC) of 72.7%. The model based on GM reached an AUC of 0.86 and BAC of 76.4%. The multimodal classifier (clinical + GM) reached an AUC of 0.88 and BAC of 83.4%, significantly increasing the sensitivity. The most important features were related to suicide attempts history, medications, comorbidities, and depressive polarity. In the GM model, the most relevant features mapped in the frontal, temporal, and cerebellar regions.

Conclusions: By combining models, we increased the detection of suicide attempts, reaching a sensitivity of 80%. Combining more than one modality proved a valid method to overcome limitations from single-modality models and increasing overall accuracy.

1 | Introduction

Suicidal behaviors are a major global public health issue, challenging psychiatry and society, with more than 720.000 suicide-related deaths occurring annually in the general population [1] and with the global rate of suicide estimated to be 9.4 per 100,000 individuals (95% CI 8.5–10.3) [2]. An extensive range of factors has been reported to influence suicidal behavior rates, including gender, age, temporal factors, ethnic and socio-economic backgrounds, and medical history, particularly with regard to mental health [3].

Undoubtedly, psychiatric conditions are significant risk factors for suicidal behavior. Wide-ranging research indicates that

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almost 90% of the attempted and completed suicides have been committed by individuals suffering from at least one Axis I psychiatric disorder, often un- or misdiagnosed and treated [4–11].

Specifically, mood disorders are the most frequently reported diagnoses leading to suicidal behavior, with individuals diagnosed with bipolar disorder (BD) appearing at an even greater risk. In fact, it has been reported that 40% of individuals with BD attempt suicide at least once in their lifetime [12, 13], with the annual risk of suicide attempts among BD patients estimated to be 400–1400 per 100,000, or approximately 0.9%, which is 30–60 times higher than the rate observed in the general population [14–22]. Moreover, a recent review of the literature indicates that the standardized mortality ratio is approximately 20- to 30-fold higher compared to the general population, with the estimated suicide mortality rate among BD patients being roughly 0.2–0.4 per 100 person-year [6], indicating a higher lethality of suicide attempts within this population [23].

Several factors have been extensively studied and identified as potential contributors to suicidal behavior in individuals with BD. Sociodemographic variables such as male gender and age (particularly those under 35 or over 75), caucasian ethnicity, marital and familial status (e.g., being divorced, living alone, or having no children), and unemployment have been associated to an increased risk of suicide [4,6,24–30]. Furthermore, early adverse life events—including experiences of separation, emotional, physical, and sexual abuse—along with acute psychosocial stressors, like the death or separation from a significant other, loss of health, possessions, autonomy, employment, educational opportunities, or financial stability, and ongoing adverse life circumstances, have been implicated in precipitating suicidal behavior [4,6,24,27,31–34]. Additionally, as emphasized in Mann and colleagues' stress-diathesis model [35], a predisposition to suicide may also stem from genetic vulnerability, impaired serotonergic functioning, and specific temperamental traits, including aggressiveness, impulsivity, and hopelessness [11,27,28,30,35].

Nevertheless, the most critical determinants appear to be illness-related. These include a history of previous suicide attempts (especially with violent/highly lethal methods), a family history of suicide, and predominantly depressive episodes, particularly when accompanied by mixed affective states [29, 36–41]. Rapid cycling, a high number of previous episodes, early onset and early stage of the illness, a long duration of untreated illness and scarce adherence to treatment, and comorbid conditions such as anxiety disorders, substance abuse, or personality disorders have also been reported to further elevate risk [4, 6, 23, 42–45].

However, despite the identified risk factors, predicting and thereby preventing suicide in patients with bipolar disorder remains a considerable challenge in clinical practice, primarily due to the lack of reliable and verified biomarkers that can accurately and promptly signal the risk of suicidal behavior [46–48].

At the current state, the identification of at-risk patients still relies primarily on clinical assessments and patient history. However, studies have shown that traditional suicide risk factors have only limited clinical predictive value and present a relatively poor clinical utility in predicting suicide occurrence, even in high-risk populations, such as depressed patients [49, 50].

In this context, machine learning (ML) is emerging as a promising technology. By analyzing and integrating extensive datasets, including clinical, neuroimaging, behavioral, and genetic information, ML algorithms have been proven increasingly useful in uncovering complex patterns and correlations. Recent studies have demonstrated the use of ML in investigating BD, improving diagnostic accuracy [51, 52], and predicting depressive relapses [53] and adverse outcomes [54], including suicidal behavior [55].

Several ML studies also tried to predict suicide in different populations [56], reaching good prediction accuracies. The most common populations assessed are mood disorders, especially major depression and BD, but several studies predicted suicide behaviors in a transdiagnostic fashion, without stratifying the sample by diagnoses [56]. Nevertheless, the current literature on suicide risk in BD appears constrained by several limitations. First of all, most of the studies [57, 58] assessed suicide attempts in a cross-sectional fashion (e.g., prediction of lifetime suicide attempts), without defining prospectively a time window of analysis; second, most of the studies [59, 60] employed unimodal approaches, not exploiting the full potential of ML approaches that allow handling multimodal data; moreover, ML models usually implement time-fixed variables, even though it is clear that some features tend to vary across time (e.g., a suicide attempt few months ago might have a higher weight in the prediction of future attempts, when compared to a suicide attempt occurred 20 years ago), in the end failing to fully capture the dynamic and multifaceted nature of suicide risk.

To address these limitations, our study adopts a prospective design with a 12-month observation period, using a multimodal approach integrating clinical data with MRI features and incorporating time-variant variables, accounting for the varying influence of recent versus historical aspects of the disorder.

Specifically, our aims are to: (1) develop unimodal models for predicting 12-month suicide risk in patients with BD, utilizing clinical and MRI features; (2) evaluate the impact of time-dynamic features on prediction accuracy; and (3) investigate whether integrating multimodal features can improve the prediction of suicide attempts. We hypothesized that a multimodal approach could improve the prediction of suicide attempts, therefore fully exploiting ML potential, and that time-dynamic features would results among the most predictive.

By employing a prospective approach and leveraging advanced ML techniques, our research intends to enhance the accuracy of suicide risk prediction and to facilitate more timely and personalized interventions, potentially informing more effective prevention and treatment strategies in clinical settings, thereby improving patient outcomes.

2 | Materials and Methods

2.1 | Sample

One hundred and sixty-three subjects with BD (mean age 44.81 + −15.28; 88%/53.9% females) were recruited at the Department of Mental Health of the IRCCS Ca′ Granda,

Policlinico Hospital in Milan (Italy). The enrolment was approved by the Et125hical Committee of the IRCCS Fondazione Ca′ Granda Policlinico Hospital (Neuron-051, GR-2019-12369100, Cariplo2019–3415, GR-2016-02361283, Neuroinno, CANMAN). The diagnoses were confirmed by a trained psychiatrist, using the Structured Clinical Interview (SCID) from the DSM-IV [61].

All patients were enrolled during their admission to the acute ward, following hospitalization for either a depressive or manic episode. During this admission, all subjects underwent MRI scans, and baseline clinical information was collected.

After discharge, the subjects were followed up at territorial outpatient clinics with regular monthly visits in a naturalistic way. The visits were conducted by trained psychiatrists, assessing patients' well-being and treatments. To preserve a naturalistic framework, there was no specific intervention for the present study; therefore, the visits had the timing (monthly) and the structure of a regular outpatient clinic visit. For the purposes of this study, the follow-up period was set at 12 months, during which all suicide attempts were documented as the outcome of interest of the prediction model.

2.2 | Unimodal Classifiers

As presented in Figure 1, we aimed to create different unimodal classifiers based on clinical information, GM volumes, and cortical thickness (CT).

The clinical model was based on 56 features (see Supplementary for a full description of the features), informed by previous studies in the field of prediction of suicidal attempts [56]. In addition, to overcome previous studies' limitations of cross-sectional features [62] we created time-variant variables, allowing to better define the risk in the 12-month time-window. For example, along with "suicide attempts lifetime" and "number of suicide attempts lifetime", our features' pool included also "suicide attempts in the last 12 months", given that the weight of a recent attempt is likely to be greater than a suicide attempt many years ago. The features selected for the clinical model are presented in Table 2.

Moreover, we created a composite score based on intermediate visits at 1, 3, and 6 months after discharge, including information regarding treatment variations, admissions in the ER, or any other mental health service. All the information regarding an index case (e.g., ER admission due to suicide attempts) was not included in the score, so as not to create bias in the prediction. This score serves as a proxy for the patient's trajectory, mimicking the clinician's assessment (See Supplementary for a complete description).

Two separate models were then created, one including only baseline features and one also including the 3 timepoints composite scores.

A structural MRI model, based on GM volumes and CT features at baseline. Before extracting the morphological parameters, all T1-weighted images were segmented according to GM, white matter and cerebrospinal fluid, bone, soft tissue, and air/background. Second, the Dartel (Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra) (http://www.fil.ion.ucl.ac.uk/spm/) tools were then used to determine the nonlinear deformations for registering the GM and white matter images of all subjects. Finally, the resulting images were spatially normalized into the Montreal Neurological Institute (MNI) space and smoothed with an isotropic Gaussian kernel of

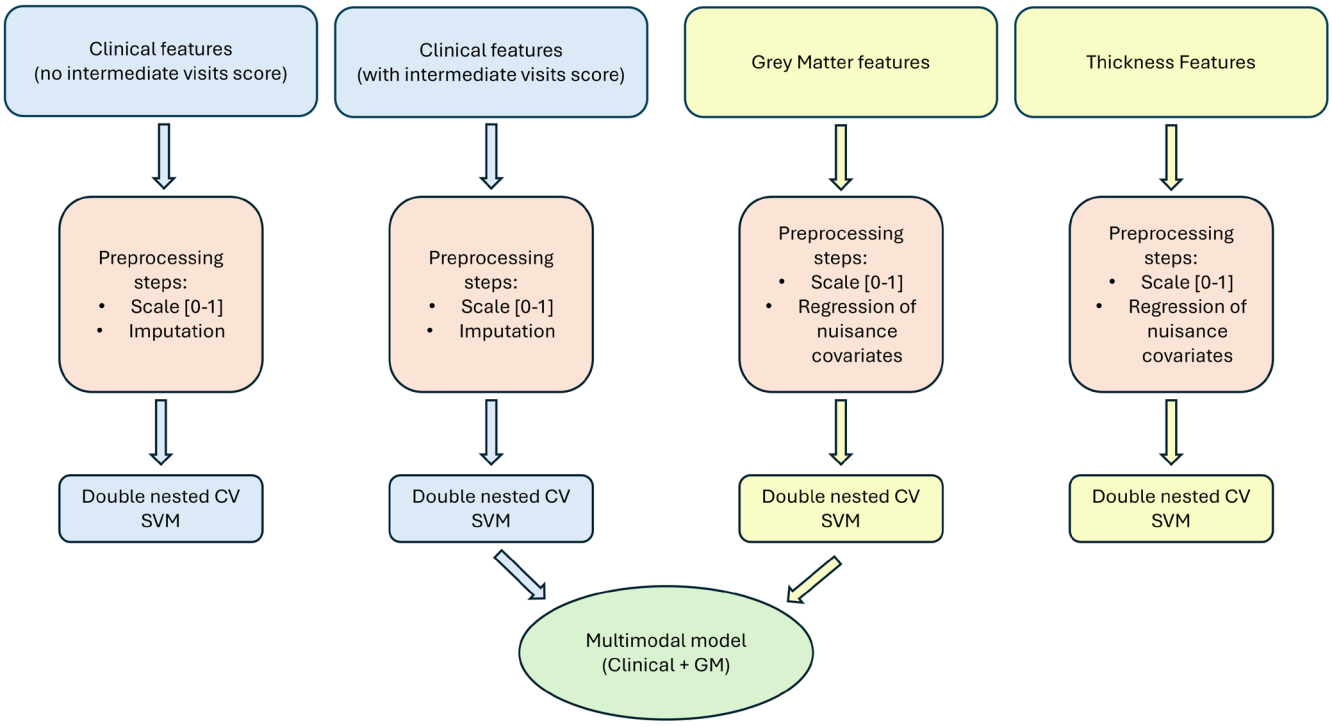

FIGURE 1 | General description of the analyses pipeline.

6 mm full width at half maximum Gaussian kernel to increase the signal-to-noise ratio and to account for subtle variations in anatomic structures. The total intracranial volume was also extracted using CAT12. Thus, smoothed, modulated, and normalized GM volumes were employed for the extraction of GMV and CT from brain regions defined according to probabilistic atlases. For each subject, mean GMV values were extracted for regions of the volume-based Neuromorphometrics ($n = 136$) atlas [63] whereas mean CT values were extracted for regions of the surface-based Desikan-Killiany ($n = 72$) atlas [64]. Among them, GMV features from 122 ROIs of the Neuromorphometrics atlas were extracted, after having excluded the ROIs with only white matter (WM). 68 ROIs of the Desikan-Killiany atlas were selected based on the availability of CT regional measures across subjects. The MRI acquisition parameters can be found in the Supporting Information.

2.3 | Machine Learning Pipelines

The overall analytic strategy (Figure 1) entailed initially quantifying the unimodal prognostic performance of each classifier (clinical, GM volumes, CT), and subsequently understanding whether integrating MRI information with the clinical model would improve prediction performance. Therefore, four unimodal models were created (two clinical models, with and without composite score, one with GM volumes as features, and one with CT as features). All the ML analyses were performed with Neurominer version 1.1 for Matlab (Nikolaos Koutsouleris, Munich, Germany; see https://github.com/neurominer-git).

The complete pipelines are presented in Supporting Information.

For both unimodal and multimodal models, a double-nested cross-validation (CV) scheme was created, in which k-fold CV (3 repetitions, 3 folds) at the inner and outer CV levels was created. The number of folds was determined based on the limited occurrence of events (suicide attempts) to ensure that each fold consistently included a sufficient number of patients who had attempted suicide.

2.3.1 | Features Preprocessing

Inside the CV scheme, the following feature engineering pipelines were applied to the clinical models:

- Since many machine learning algorithms are sensitive to differences in feature scales, each variable was scaled to a [0,1] range to remove these effects from the training sample matrices.
- Imputation was performed for missing data using Euclidean distance between the 7-nearest observations.

Our preprocessing pipeline for the structural MRI classifiers (same pipeline for GM and thickness) consists of the following steps:

- Each variable was scaled to a [0,1] range.

Covariates nuisance was removed using Pearson correlations. Specifically, age, sex, MRI group, and TIV (only for GM) were removed.

2.3.2 | ML Algorithm

A Support Vector Machine (SVM) was used as the algorithm of choice. SVM is considered among the best-performing algorithms in psychiatric complex problems [56, 65] and one of the easiest to interpret. Given the unbalance between the groups (suicide vs. non-suicide patients), the hyperplane was weighted for uneven group sizes, therefore minimizing the risk that the algorithm might predict only non-suicide patients (the larger group). The C parameter was optimized within a range (11 parameters, from 0.015625 to 16).

Permutations were used to define the significance of the model (See Supporting Informations and Figure S1).

To measure the discriminative utility of the input variables within each unimodal classifier, we computed the probability of being selected for classification purposes within the inner cross-validation loop for each feature [66].

2.4 | Multimodal Classifier

After training the individual classifiers, we implemented a stacking-based data fusion framework [67, 68] to assess whether the combination of these unimodal classifiers would generate superior predictive systems for suicide attempts compared to using each classifier individually.

To rule out any information leakage between the training and test samples, we employed the identical repeated k-fold CV scheme for unimodal and multimodal classification. The stacking procedure started by combining decision scores of the individual classifiers' committees within a given CV1 partition, standardizing the resulting matrices, and subsequently using them as new sets of predictive features, which replaced the original features in a given CV1 partition.

SVM was employed to find a parsimonious combination of decision scores maximizing BAC across the C parameter range. As for the unimodal classifiers described above, we determined an ensemble of optimized SVM models across the C range that conjointly maximized BAC in the given CV1 training and test data. Then, the CV2 validation predictions of the previously trained individual classifiers' SVM ensembles were combined and standardized. Each SVM ensemble was then applied to this standardized CV2 decision score matrix to generate probability estimates. Majority voting was used to predict the CV2 outcome targets, and this procedure was repeated until all CV2 cases had received a multimodal prediction.

The analyses and the results were reported following the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) guidelines [69]. See Table S2 for the TRIPOD Checklist.

3 | Results

During the 12 months of observation, 10 patients (6.13%) attempted suicide; luckily, none of the attempts were lethal. The demographic characteristics of the sample are described in Table 1. No significant differences between attempters and non-attempters were found in demographics (sex, ages, education), psychiatric family history, use of substances and clinical scales. The only significant difference was in chlorpromazine equivalents, with non-attempters having higher scores ($p = 0.009$).

3.1 | Unimodal Models

A complete description of the models is reported in Table 3; Figure 2.

Regarding clinical data, the unimodal classifier created without the composite score of the intermediate visits reached an area under the curve (AUC) of 0.71, with a BAC of 68%, sensitivity of 40%, and specificity of 97.4%. Instead, the second model including scores derived from the intermediate visits overcame the first classifier, reaching an AUC of 0.83, BAC of 72.7%, sensitivity of 50%, and specificity of 95.4%. This model was able to correctly individuate one additional subject compared to the first model. However, the ability to identify individuals at risk of suicide (represented here by the sensitivity) remained low (50%). The model was significant with $p < 0.01$ (see Supplementary Figures—Supporting Informations).

The model based on GM volumes data reached an AUC of 0.86, BAC 76.4%, sensitivity 60%, and specificity 92.8%. Also, in this case, the model was significant with $p < 0.01$ (see Supplementary Figures—Supporting Informations).

Finally, the model based on thickness features yielded fewer results in terms of suicide prediction, with an AUC of 0.61, BAC 62.2%, sensitivity 40%, and specificity 84.9%.

3.2 | Most Important Features in the Unimodal Classifiers

Regarding the clinical features' pool, in the Neurominer model, the most significant features by weight order were: 6 months composite score, lifetime suicide, suicide in the past 12 months, use of antiepileptics, suicide modality, *n*. of lifetime attempts, prevalent polarity, use of atypical antipsychotics, suicide ideation in the past 12 months, 3 months composite score, psychiatric family history, alcohol use (actual), chlorpromazine equivalents, compulsory treatment, and neurologic comorbidities. See Figures S2 and S3 for further details.

In the GM volumes model, the most relevant features for the prediction werethe left frontal pole, bilateral thalamus, right planum temporale, left cerebellum, right posterior orbital gyrus, left accumbens, right opercular part of the inferior frontal gyrus, bilateral ventral diencephalon, right cerebellum, right cuneus, right postcentral gyrus, and right planum polare. The most important areas are represented in Figure 3.

Given the low prediction accuracy, the features' weights of the thickness model were not calculated.

TABLE 1 | Demographic characteristics of our sample. The significance refers to the comparison between suicide and non-suicide groups.

	Total sample ($N = 163$), mean (SD)	Suicide ($N = 10$), mean (SD)	Non-suicide ($N = 153$), mean (SD)	Sign.
Age	44.81 (15.28)	40.10 (10.18)	45.13 (15.53)	0.144
Sex	75/87	3/7	72/80	0.286
Age at onset	27.22 (10.4)	25.40 (9.45)	27.34 (10.48)	0.983
GAF	34.89 (15.88)	30.13 (17.14)	35.27 (15.81)	0.965
HAMD	14.30 (9.45)	15.25 (8.06)	14.23 (9.61)	0.376
BPRS	41.64 (10.23)	34.5 (8.54)	42.10 (10.21)	0.671
YMRS	18.35 (10.97)	16 (13.24)	18.51 (10.92)	0.920
Duration of illness	17.49 (12.29)	14.40 (8.69)	17.70 (12.49)	0.125
Years of education	13.76 (3.57)	14.40 (3.2)	13.71 (3.6)	0.766
Chlor eq	413.10 (281.7)	300.50 (136.37)	420.66 (287.52)	0.009
n. of cigarettes	9.77 (11.27)	12.5 (11.84)	9.57 (11.25)	0.637
Family history	98	4	94	0.088
Cannabis	49	4	45	0.507
Other substances	13	3	10	0.037

Abbreviations: BPRS, Brief Psychiatric Rating Scale; Chlor eq, chlorpromazine equivalents of antipsychotics; GAF, global assessment of functioning; HAMD, Hamilton's Depression; SD, standard deviation; YMRS, Young's Mania Rating Scale.

TABLE 2 | Presentation and description of all the features used in the clinical model.

Feature	Type	Notes
Age	Continuous	
Sex	1/2	
Diagnosis	1/2	BD I or BD II
Age at onset	Continuous	
Psychosis lifetime	Dichotomous	
Psychosis in the last 12 months	Dichotomous	
GAF	Continuous	
Duration of illness	Continuous	Expressed in months
Cannabis use (present)	Dichotomous	
Alcohol abuse (present)	Dichotomous	
Other substances (present)	Dichotomous	
Substances use in the past (not present)	Dichotomous	
Suicide attempts lifetime	Dichotomous	
N. of suicides attempts lifetime	Continuous	
Suicide attempts modality	Categorial	1 = Prescription drugs
		2 = Cut
		3 = Defenestration
		4 = Hanging
		5 = Caustics
		6 = Other
Suicide attempts in the last 12 months	Dichotomous	
Suicide ideation in the last 12 months	Dichotomous	
N. admissions lifetime	Continuous	
N. admissions in the last 12 months	Continuous	
N. ER admissions in the last 12 months	Continuous	
Compulsory admission (actual)	Dichotomous	
Family history of psychiatric disorders	Dichotomous	
Family history of suicide		
N. of family members with psychiatric disorders	Continuous	
Years of education	Continuous	
Max education level reached	Continuous	
Job/employment	Categorial	1 Unemployed
		2 Retired
		3 Student
		4 Factory worker or equivalent
		5 White collar or equivalent
		6 Post-academic role
		7 Manager
		8 Others

(Continues)

TABLE 2 | (Continued)

Feature	Type	Notes
Mean income/months	Continuous	
Live with	Categorial	0 = Alone
		1 = Husband/Spouse/Children
		2 = Parents/Family of origin
		3 = Others (e.g., flatmates)
		4 = Homeless
Status	Categorial	0 = Single
		1 = Married/Living
		2 = Divorced
		3 = Widow
Tobacco use	Dichotomous	
N. cigarettes/day	Continuous	
Comorbidities	Dichotomous	
N. of comorbidities	Continuous	
Inflammatory comorbidites	Dichotomous	E.g., autoimmune disorders, inflammatory bowel disease
Neurologic comorbidites	Dichotomous	E.g., parkinson, MS
Tyroid comorbidites	Dichotomous	E.g., Hashimoto, hypothyroidism
Metabolic comorbidites	Dichotomous	E.g., diabetes, metabolic syndrome
Psychiatric comorbidities	Dichotomous	Other than BD, e.g., anxiety disorders, personality disorders
Antipsychotics	Dichotomous	
Typical antipsychotics	Dichotomous	
Atypical antipsychotics	Dichotomous	
Chlorpromazine equivalents	Continuous	Based on Leucht et al. [123]
LAI	Dichotomous	
Antidepressants	Dichotomous	
Stabilizers	Dichotomous	
Lithium	Dichotomous	
Antiepileptics	Dichotomous	
Benzodiazepines	Dichotomous	
BPRS total	Continuous	BPRS at the admission
HAMD total	Continuous	HAMD at the admission
YMRS total	Continuous	YMRS at the admission
N. of depressions	Continuous	
N. of manias	Continuous	
Prevalent polarity	Dichotomous	

Abbreviations: BD, bipolar disorder; BPRS, Brief Psychiatric Rating Scale; HAMD, hamilton scale for depression; LAI, long-acting antipsychotics; MS, multiple sclerosis; YMRS, Young Mania Rating Scale.

3.3 | Multimodal Classifier

Given the results of the unimodal classifiers, we implemented a stacking-based data fusion model combining clinical and GM predictive decision scores, as described in the Method section.

The multimodal classifier (clinical + GM) reached an AUC of 0.88, BAC 83.4%, sensitivity 80%, and specificity 86.8%. Interestingly, the combination of the 2 modalities allowed for the correct identification of 8 out of 10 suicide attempts, significantly increasing the sensitivity.

TABLE 3 | Comparison of models' primary metrics and their significance against the null model (permutation-based).

	True positive	True negative	False positive	False negative	Sensitivity	Specificity	BAC	AUC (95% CI)	Sign.
Clinical model (no intermediate score)	4	148	4	6	40.0	97.4	68.7	0.71 (0.53–0.90)	$p < 0.05$
Clinical model (with intermediate score)	5	145	7	5	50.0	95.4	72.7	0.83 (0.66–0.99)	$p < 0.01$
GM model	6	141	11	4	60.0	92.8	76.4	0.84 (0.68–0.99)	$p < 0.01$
Thickness model	4	129	23	6	40.0	84.9	62.4	0.61 (0.42–0.80)	NA
Multimodal model (clinical + GM)	8	132	20	2	80.0	86.8	83.4	0.88 (0.74–1.02)	$p < 0.01$

Abbreviations: AUC, area under the curve; BAC, balanced accuracy (= (sensitivity + specificity)/2); GM, gray matter.

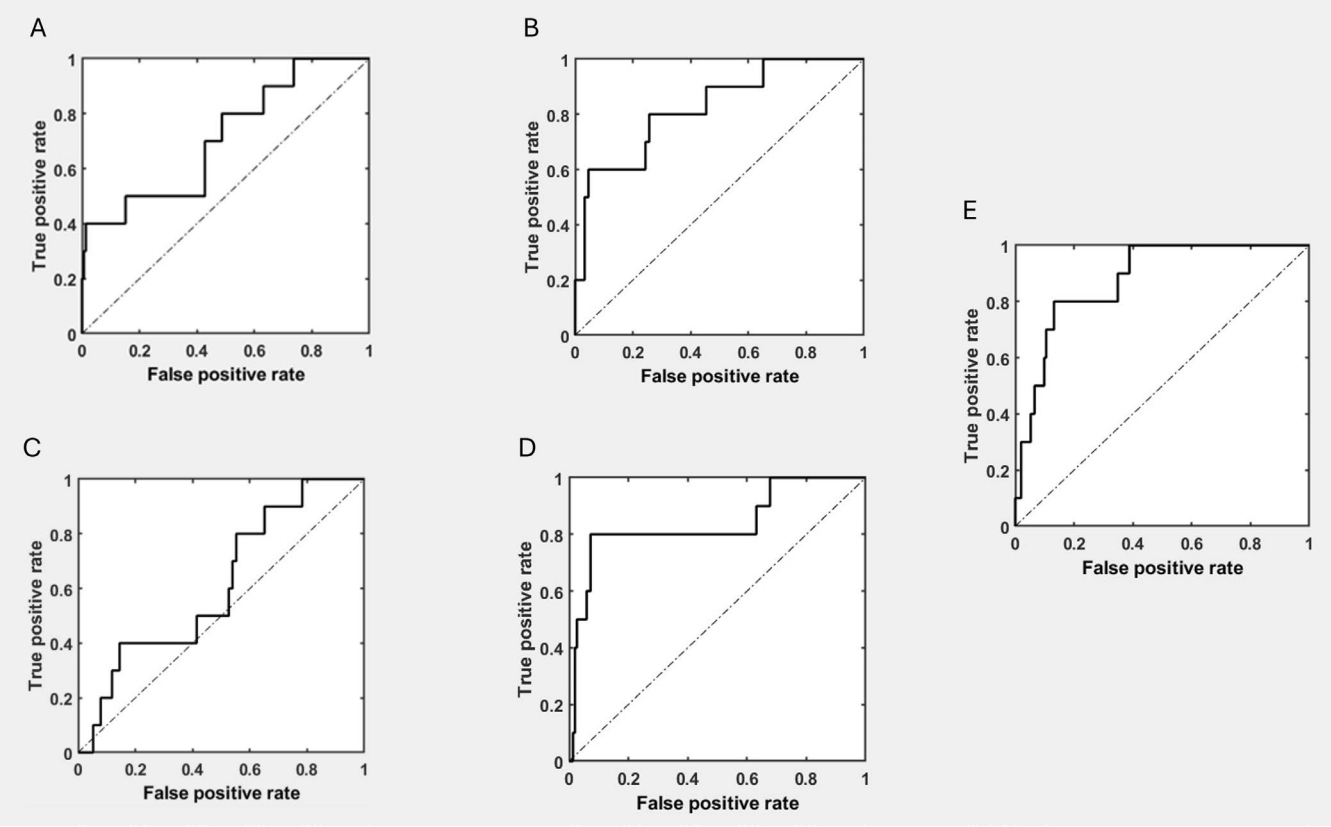

FIGURE 2 | AUCs of the different unimodal (A–D) and multimodal (E) models. A shows the AUC of the clinical model without the intermediate composite score; (B) shows the AUC of the clinical model, including the intermediate composite score among the features; (C) shows the AUC of the model based on thickness features; (D) shows the AUC of the model based on GM features. Finally, E shows the AUC of the multimodal (clinical + GM) model.

4 | Discussion

With our study, we aimed to employ different ML approaches combining different modalities to explore their ability to predict 12-month suicide attempts in BD patients. Firstly, we created unimodal models using either clinical or MRI features, which reached good accuracies, in line with other studies [70, 71]. Nevertheless, as could be expected in situations characterized by uneven group distributions, unimodal models persistently demonstrated a disproportionate relationship between sensitivity and specificity.

Taking this into consideration, we subsequently combined unimodal prediction into an integrated multimodal model to exploit the different predictive abilities of the two unimodal models. This approach resulted not only in improved overall accuracy but, crucially, in a significant enhancement of sensitivity, with

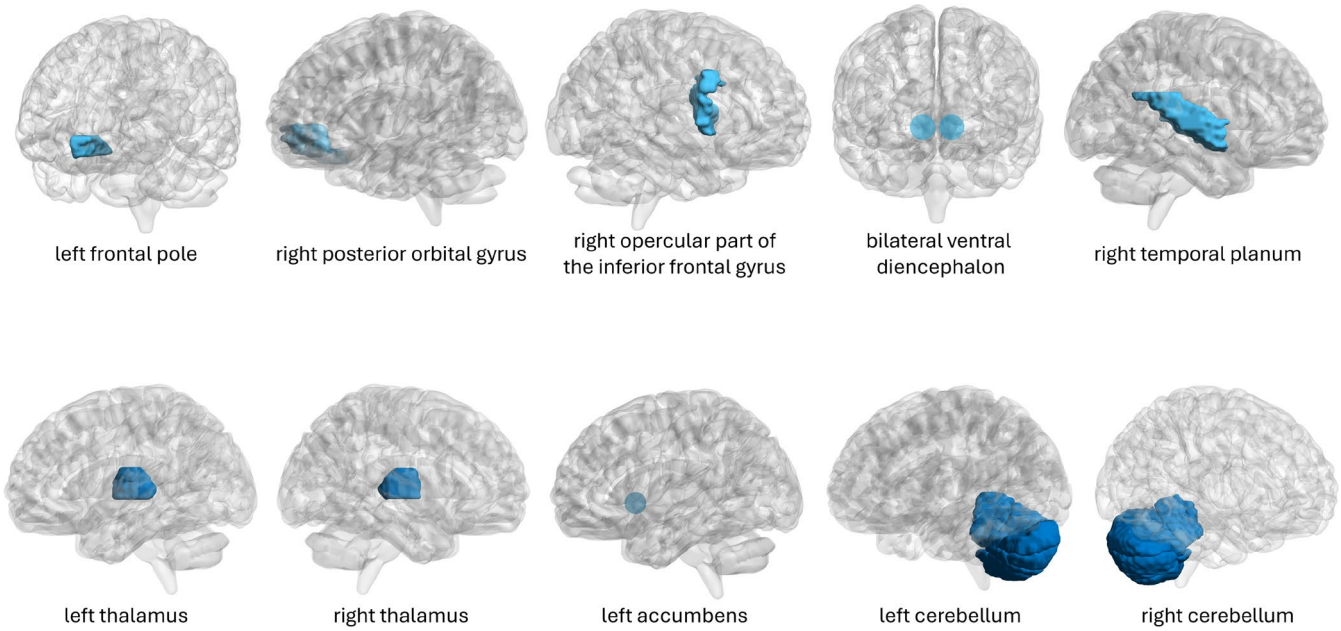

FIGURE 3 | The first 10 most relevant features based on the GM MRI prediction.

the algorithm correctly predicting 8 suicide attempts out of 10 within the designated time frame. The possibility to enhance the prediction ability by combining clinical and MRI data is in line with the recent study of Shao and colleagues [72], presenting how the addition of MRI may increase the overall classification of suicide attempts in mood disorders. Of note, our study is the first to evaluate this pipeline prospectively, overcoming one of the most common pitfalls of ML prediction of suicidal behaviors: a cross-over design.

Interestingly, our results support the hypothesis that time-variant features could be very predictive in the model. For example, among the most predictive features there were "suicide in the past 12 months" and "suicide ideation in the past 12 months", suggesting how the weight of features tends to vary according to different time windows. Furthermore, they encourage future research to employ, set up, or redefine ML algorithms for worse outcome prediction in a complex, superordinate, and multimodal, rather than unimodal perspective [67].

4.1 | Clinical Features

In the clinical model, the most significant features were those related to the history of suicide (suicide attempts lifetime, suicide attempts in the last 12 months, suicide modality, number of suicide attempts lifetime, and suicidal ideation in the last 12 months), to the severity trajectory (6 months composite score), to depressive polarity, to the prescribed treatment (especially use of antiepileptics), and to comorbidities, including alcohol abuse and neurological comorbidities.

From our results emerged a vulnerability based on a history of prior suicide attempts, with their significance likely escalating as the number of these attempts accumulates over a lifetime. This vulnerability appears to be further accentuated by the methods employed in suicide attempts, which may serve as an indicator of underlying intentionality. Indeed, as previously mentioned, among individuals with BD, the ratio of attempts to completed suicides is markedly lower than in the general population, revealing a proclivity for more violent and lethal means [23].

In this context, it is also worth highlighting, as Boudreaux and colleagues [62] suggested, that the features' weights may vary over time. From this perspective, suicide attempts and suicidal ideation within the past 12 months may contribute significantly more to suicidal risk susceptibility, emphasizing the critical importance of comprehensive clinical assessment and precise, timely monitoring.

Among the other salient clinical features, prevalent polarity is particularly noteworthy, affirming that a predominant depressive polarity (as well as mixed affective states) may significantly elevate the risk of suicidal behavior in individuals with BD [36, 39, 41]. Furthermore, it is pertinent to mention that a familial history of psychiatric disorders and suicidal behaviors may also influence suicide risk, implying a possible genetic predisposition [37, 40].

In our study, features related to the use of specific medications, such as antiepileptics and atypical antipsychotics (considered as dichotomous variables), as well as chlorpromazine equivalents (treated as a continuous variable), in conjunction with compulsory treatment, may be viewed as proxies for illness severity rather than as direct contributors to increased suicide risk. Intuitively, more severe episodes necessitating complex therapies and a compulsory treatment regimen are likely to be associated with a heightened risk of suicidal behavior.

However, the use of antiepileptics in BD has long been a point of contention, particularly in relation to suicide risk [73–77].

A recent review of the literature [78] confirmed valproate's therapeutic advantage over no treatment with respect to suicide

attempts and completions, though it emphasized the need for further data. However, compared to lithium, valproate has been associated with a higher risk of suicide attempts and completions. Other antiepileptics, such as lamotrigine and carbamazepine, have been noted as requiring further investigation regarding their association with suicide-related outcomes [78].

Similarly, research has explored the impact of atypical antipsychotics on suicide risk in BD [79]. Some studies have indicated the potential for these drugs to exacerbate suicide risk in certain patients when compared to mood stabilizers such as lithium or valproate [80, 81]. However, these findings remain inconsistent and often overlook the role of illness severit [82–89].

Given the widespread use of atypical antipsychotics in the treatment of BD, particularly in the management of acute phases where combination therapies with mood stabilizers are considered effective for severe cases, further investigation into the relationship between atypical antipsychotics and suicide risk appears essential [86].

Lastly, our findings have identified current alcohol use as a significant clinical feature in predicting suicidal behavior among individuals with BD [90]. As a matter of fact, literature has evidenced that alcohol consumption may exacerbate mood instability, increase impulsivity, and impair judgment, all of which may contribute to heightened vulnerability to suicidal thoughts and actions [91, 92]. Moreover, alcohol's depressant effects may worsen depressive episodes, deepening feelings of hopelessness [93]. Studies have demonstrated that comorbid alcohol use disorder in bipolar patients is associated with a higher incidence of suicide attempts, underscoring the critical need for addressing alcohol use in suicide prevention strategies [94, 95].

In conclusion, our results confirm some of the previously known risk factors, extensively documented in the literature, as significant contributors in the ML model prediction accuracy, particularly highlighting aspects related to illness severity and history of suicide attempts, either personal or familiar. These results underline the importance of a complete assessment of suicide potentially helping to identify individuals at heightened risk.

4.2 | MRI Features

The MRI features that mostly contributed to the prediction are mapped in the frontal (frontal pole, orbital gyrus, inferior frontal gyrus), temporal (planum temporale, and planum polare), and cerebellar regions.

With regards to frontal regions, these findings are not surprising as these areas are among the most implicated neural structures in suicidality [72, 96]. The ventral areas of the frontal lobe are essential for guiding goal-directed response selection, especially in unpredictable environments where actions must be adjusted flexibly based on both recent and past reinforcement histories [97]. Notably, in line with the GM loss in the suicide attempters reported by Shao and colleagues, the opercular part of the inferior frontal gyrus resulted among the most selected features. This region is heavily involved in making goal-directed decisions guided by adaptive reinforcement processing [98]. Additionally, these areas show extensive connections with the caudate nucleus [99], which plays a significant role in implementing instrumental processing and goal-directed behaviors [98, 100]. Therefore, our findings support the idea that taking the critical step toward suicide may result from a failure to choose the most beneficial (or least harmful) action in situations where difficulties appear to overshadow any positive outlook. This notion aligns with the proposed specialized function of the lateral orbitofrontal cortex and ventrolateral-prefrontal-insular systems in signaling and regulating responses to nonrewarding or aversive experiences, which is a key aspect of the broader top-down inhibitory control over emotions, cognition, and actions [101].

Consistent with our findings, structural alterations in temporal cortices were associated with suicide in a range of psychiatric disorders and related to high lethality attempts and higher impulsivity [96]. Specifically, alterations in middle and superior temporal gyrus volume were described in suicide attempters with primary psychotic disorders [102, 103], mood disorders [104], but also borderline personality disorders [105]. Reduced middle and superior temporal volumes were also associated with increased lethality [106] and higher impulsivity in individuals with suicidal behaviors with different mental disorders [107]. fMRI studies also pointed out the association between the superior temporal gyrus and suicidal behaviors. Specifically, suicidal ideation was associated with increased superior temporal activation during error processing in veterans with traumas [108], while lower perfusion in these temporal regions during rest was reported in mood disorders with suicidal ideation [109]. Moreover, the functional connectivity of the superior temporal gyrus was found to be associated with psychological risk factors, including loneliness and purpose in life, in a recent fMRI study [110].

Finally, the cerebellum is increasingly recognized for its involvement in emotional processes [111, 112]. Volumetric alterations of the cerebellum were reported in adults and adolescents with mood disorders and suicide behaviors [113]. Functionally, recent studies suggested an involvement of the cerebellum in the recollection of memories related to suicide attempts. In a recent publication [114], participants who had attempted suicide had greater fMRI task-related activation in visual areas and the cerebellum, with the number of suicide attempts associated with the difference in BOLD response. The cerebellum seems to be also relevant in emotional pain, which can lead to suicidal conduct especially in young individuals [115]. A recent review [116] proposed a model that integrates the previous notions of brain imaging in suicidal studies. In the model, two systems interplay in shaping suicide risk: the emotional pain circuit, including the cerebellum, hippocampus, and amygdala, and the social disconnect circuit, which comprises the lateral OFC and temporal gyri, as well as the connections between them (the frontotemporal system). Emotional pain can be caused by a combination of predisposition and stressful life events and can lead to suicidal ideation, especially in adolescents. If, in addition, the subject is experiencing social disconnect, this can lead to a suicide attempt.

In summary, the brain areas from frontal, temporal, and cerebellar regions that were selected in our model proved to have a role in the neurobiology of suicide, highlighting the relevance

of the ML algorithm's feature selection from both a clinical and neurobiological perspective. However, it is important to mention that MRI scans present some critical issues in psychiatry. First of all, MRI scans present an important cost compared to clinical-demographic variables, and they require a relevant amount of time. Moreover, it is likely that very severe patients in acute wards are not able to endure an MRI scan, possibly creating a bias in terms of sample selection. These are critical aspects that should be further investigated in the future. Nonetheless, our results support the idea that MRI features can improve the ability of the algorithm to recognize patients at increased risk for suicide; future studies need to assess whether this increase in algorithm performance is feasible in terms of cost and time, compared to a simpler model based on clinical and demographic features.

4.3 | Limitations and Future Directions

The above-exposed results should be regarded in light of some limitations. First, the sample size is small, although it is in line with similar ML studies [70, 117, 118]. This appears particularly relevant as machine learning needs an important amount of data to be trained properly; therefore, despite having performed a double-nested CV, the risk of overfitting cannot be completely ruled out. ML studies should find a tradeoff between very large databases, often not well characterized, and smaller studies. In our study, we preferred to have a well-characterized sample, although it might pose some problems regarding overfitting. Similarly, the index event (namely, suicide) is luckily a rare occurrence, and this reflects on a highly unbalanced sample, which is a common finding in suicide literature [56]. However, balanced samples (similar size for attempters and non-attempters) are something very far from reality, and we believe it should be avoided. To avoid this bias, we tried to assess this aspect by weighting the hyperplane for uneven groups and considering different metrics, such as sensitivity and specificity, given that accuracy in these cases could be misleading. Another important limitation is the absence of an external validation sample that would confirm the generalizability of our results.

Finally, it is important to mention that the selected features do not include all the possible risk factors for suicide. For example, we did not have data regarding traumas or adverse events available for our sample. These non-disease related factors are well documented in the literature [119, 120] and could add important value to ML prediction. Similarly, a more in-depth description of some clinical aspects of the disorder might be important. For example, recent studies suggested that specific sleep and circadian disturbance variables might confer unique risk for suicide in BD [121]. This highlights the importance of conducting a thorough sleep and circadian assessment in clinical practice and include such variables in ML models.

Bearing the above-exposed limitations in mind, we plan to design and conduct future studies including features designed to assess other domains (e.g., adverse life events and traumas), further broader validation samples of patients with BD, as well as transdiagnostic psychiatric cases, to test whether the prediction model's applicability extends across diverse diagnoses [122]. Finally, even though modalities such as cognitive functions or additional MRI sequences have not been implemented in our study, we believe that incorporating them in future research could significantly enhance the precision in defining suicide risk among BD patients.

5 | Conclusions

Incorporating ML models into clinical practice for predicting suicide risk in patients with BD appears promising, especially when using a multimodal, time-variant approach. As our findings have evidenced, integrating MRI features with clinical data may notably improve predictive accuracy for 12-month suicide risk in this population.

These advanced techniques have the potential to enhance predictive precision, assisting clinicians in obtaining a more nuanced evaluation of individual risk profiles and thereby facilitating earlier and more targeted interventions. Such advancements could significantly improve patient outcomes and further develop management strategies within mental health care.

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

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