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Predicting Diagnostic Conversion From Major Depressive Disorder to Bipolar Disorder: An EHR Based Study From Colombia

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ABSTRACT

Objectives: Most bipolar disorder (BD) patients initially present with depressive symptoms, resulting in a delayed diagnosis of BD and poor clinical outcomes. This study aims to identify features predictive of the conversion from Major Depressive Disorder (MDD) to BD by leveraging electronic health record (EHR) data from the Clínica San Juan de Dios Manizales in Colombia.

Methods: We employed a multivariable Cox regression model to identify important predictors of conversion from MDD to BD.

Results: Analyzing 15 years of EHR data from 13,607 patients diagnosed with MDD, a total of 1610 (11.8%) transitioned to BD. Predictive features of the conversion to BD included severity of the initial MDD episode, presence of psychosis and hospitalization at first episode, family history of BD, and female gender. Additionally, we observed associations with medication classes (positive associations with prescriptions of mood stabilizers, antipsychotics, and negative associations with antidepressants) and a positive association with suicidality, a feature derived from natural language processing (NLP) of clinical notes. Together, these risk factors predicted BD conversion within 5 years of the initial MDD diagnosis, with a recall of 72% and a precision of 38%.

Conclusions: Our study confirms previously identified risk factors identified through registry-based studies (female gender and psychotic depression at the index MDD episode) and identifies novel ones (suicidality extracted from clinical notes). These results simultaneously demonstrate the validity of using EHR data for predicting BD conversion and underscore its potential for the identification of novel risk factors, thereby improving early diagnosis.

1 | Introduction

Bipolar Disorder (BD) is a common, highly heritable, chronic disorder characterized by episodes of depression and (hypo)mania [1]. The diagnosis of BD is challenging in clinical practice, with a mean delay between illness onset and diagnosis of 7 years [2]. It may take a long time to reach a BD diagnosis because illness onset is often marked by a depressive episode [3–5], resulting in

an initial diagnosis of unipolar major depression (MDD) in 60% of BD patients. The delayed diagnosis of these BD patients has many potentially detrimental consequences, including prescription of antidepressants in the absence of mood-stabilizing drugs, which in some cases can lead to mania, poor clinical outcomes and high health care costs [1]. Reducing the time to a BD diagnosis would thus be of great benefit to patients, their families, and society.

Several studies have tried to determine factors that are predictive of conversion from MDD to BD. The meta-analysis of Kessing et al. [6] examined 31 different studies and could not identify risk factors that acted consistently across studies; they attributed their lack of consistent findings to methodological differences among studies. Another meta-analysis [7] examined 56 studies (19 overlapping with [6]) and found family history of BD, an earlier age of onset of depression, and presence of psychotic symptoms all to be significant predictors of conversion to BD. However, most existing studies are based on small cohorts, include few predictors, and/or rely on patient recall.

Two analyses from Denmark [8] and Finland [9] are notable for their large samples of consistently ascertained and evaluated individuals using national registries. An analyses of registry data from 91,587 Danish residents with a diagnosis of MDD [8] found family history of BD, psychotic depression, prior diagnoses of non-affective psychosis, inpatient or emergency room treatment at the first MDD episode, previous diagnosis of alcohol abuse, female sex, and depression severity, all to be significant predictors of conversion to BD. Analysis of 43,495 Finnish residents hospitalized with unipolar depression [9] also found female sex, the type and severity of first MDD episode, and the age of the first MDD episode to all be predictive of BD conversion.

National registry data [8, 9], are extremely valuable because they represent complete information from an entire country, uniformly recorded and longitudinal in nature. While national registries are only available in a select few upper income countries, electronic health records (EHR) have become widely available in recent decades, including in lower-middle income countries (LMIC). EHR data share characteristics of registry data: they are systematic records of health care utilization and longitudinal in nature. In settings where all members of a population have equal access to health care, and catchment areas are well-defined, EHR data may approach registry data in terms of their potential for large epidemiologic investigations that include a time component. Moreover, the breadth and granularity of EHR data provides information beyond data available in registries: for example, EHR include clinical notes describing the progression of clinical features recorded at every visit, and daily during a hospital stay. Features extracted from these notes provide additional layers of information above the structured data types commonly available in registries.

The Clínica San Juan de Dios Manizales (CSJDM) in Manizales, Colombia, is the primary psychiatric hospital for the entire department (state) of Caldas (population 1 million). EHR data have been available since 2005, and treatment is available to all residents regardless of insurance status [10]. We previously validated information related to diagnoses in the records and established a Natural Language Processing (NLP) pipeline for the reliable and precise extraction of symptoms and behaviors from the clinical notes [11].

Here, we aim to identify factors associated with the diagnostic switch from MDD to BD using a multivariable Cox regression model based on features extracted from the CSJDM EHR. In doing so, we use both features extracted from structured information (including gender, age, diagnostic history and medication use) and NLP-derived features extracted from clinical notes (suicidality and psychotic features). We further test the ability of our model to predict which patients newly diagnosed with MDD will convert to BD within 5 years.

2 | Methods

2.1 | Sample

Participants in this study were identified through electronic health records (EHR) at the CSJDM in Manizales, the capital of the department (state) of Caldas, Colombia. The CSJDM is the primary mental health care facility in Caldas; it serves all inhabitants, regardless of health insurance status. CSJDM has maintained EHR on all inpatient and outpatient visits since 2005. We used EHR information entered in the system from implementation in 2005 through December 31, 2021, in our analyses.

We extracted from the EHR information on patients, who at some point, had an inpatient or outpatient International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) code indicating a diagnosis of major depressive disorder (MDD: F32 or F33). If patients received both an MDD and a BD (BD: F31) diagnosis through their time course, we included only patients whose MDD diagnoses preceded their BD diagnosis. Patients that transitioned from MDD to BD were included if they did not transition back to an MDD diagnosis later in their time course. Patients with an ICD-10 diagnoses of schizophrenia (SCZ) or schizoaffective disorder (at any point in their time course) were excluded, as were patients whose first MDD diagnosis was before age eight. This minimum age limit was selected as some of the risk factors included in our model are not applicable to very young children. We employed sensitivity analyses to assess the impact of these exclusion criteria. To be included in the analysis, patients had at least 1 day of follow-up after their initial MDD diagnosis.

Ethical approval for this study was granted by The Institutional Review Board, Medical Institutional Review Board 3, at UCLA; the Comité de Ética del Instituto de Investigaciones Médicas, at Universidad de Antioquia; and the Comité de Bioética de Clinica San Juan de Dios, at CSJDM.

2.2 | Data Extraction

The EHR data at CSJDM are composed of both structured and unstructured information and are contained in two different databases. The structured fields include demographics such as age and sex, vitals, medications, diagnostic codes (ICD-10), health system utilization data such as the duration and type

of encounters (inpatient, outpatient, emergency room), among others. From the structured data, any field considered to be Protected Health Information by HIPAA [12] was removed from the records. In addition, names and numbers exceeding 5-digits (potential ID numbers) were stripped from the text using regular expressions.

The unstructured part of the EHR is composed of diverse types of notes, as described in De La Hoz et al. [11]. We extracted information on symptoms, behaviors, substance use, and family history of psychiatric disorders from the unstructured part of the EHR using Named Entity Recognition (NER) [11].

2.3 | Predictors

Predictors were based on data extracted on or before the first visit to the CJSDM with an MDD diagnosis, and can be grouped into broad categories of demographic, family history of psychiatric disorders, severity of the first MDD diagnosis, psychiatric diagnostic history, substance use, prescription medication use, and symptoms/behaviors. Many predictors were coded as dummy variables (see below); individuals without the indicated conditions served as the reference category for these variables. Demographic variables included the age at the first MDD diagnosis, sex, and residence. Residence was coded using two dummy variables: residence in Manizales or residence in the outlying municipality of Aranzazu, a community 55 km from Manizales shown to have a high incidence of BD [10]. We coded information on family history of psychiatric disorders into four dummy variables: history of BD, SCZ, MDD, or psychosis. Two indicator dummy variables captured aspects of the severity of the first MDD episode: hospitalized at the first MDD diagnosis and seen in the emergency room at the first MDD diagnosis (without subsequently being hospitalized). The type of first MDD episode (as indicated by the three-digit ICD-10 code) was categorized into two dummy variables: Severe No Psychosis, Severe with Psychosis. Data on patient psychiatric history was coded by two dummy variables with any psychiatric diagnosis before the first MDD diagnosis, and an indicator if the first psychiatric visit of any type was while the patient was a minor. Substance use was coded as five dummy variables that recorded any use (not necessarily current use) of tobacco, alcohol, marijuana, cocaine, or other recreational drugs, up to and including the time of the first MDD diagnosis. We condensed use of prescription medications into five dummy variables: use of any antidepressant, use of any antipsychotic, use of any mood stabilizer, use of any hypnotic/antianxiety, and use of any hypothyroid medication, up to and including the time of the first MDD diagnosis. We focused on two symptoms/behaviors that were reliably extracted in De La Hoz et al. [11]: suicidality (defined as a recorded suicide attempt or suicidal ideation), and presence of delusions. Each was coded as a dummy variable, and recorded presence/absence of these symptoms/behaviors at any point up to and including the time of the first MDD diagnosis.

2.4 | Outcome Measures

For each patient we recorded the time, in days, from their first MDD diagnosis to their conversion to a BD diagnosis. If the patient did not convert to BD before December 31, 2021, they were considered to be censored for the outcome, and we record the time, in days, from their first MDD diagnosis to the last known visit in the EHR.

2.5 | Statistical Analysis

Analyses were conducted in R version 3.6.1. We divided our data into a training set (70%) and a testing set (30%), preserving the ratio of censored observations to BD conversions in the division. We performed analyses in the training data and evaluated model predictions in the test data. We used multivariable Cox regression (implemented in the survival package, [13]) to estimate the hazard ratio for each predictor. To evaluate the Cox regression assumption of proportional hazards we performed a generalized linear regression of the scaled Schoenfeld residuals on functions of time, using the cox.zph() function in the survival package. A non-zero slope is an indication of a violation of the proportional hazard assumption. To account for multiple testing, we applied a Bonferroni correction for the number of predictors in the multivariable model and used a significance threshold of $0.05/26 = 0.0019$.

In the held-out test data, we used the hazard ratios estimated from the multivariable model (developed in the training data) to calculate the probability of converting to BD within 5 years (hereafter abbreviated as PrC5) of the first MDD diagnosis for each patient. In this analysis, the model developed in the training data used the full follow-up time for each person, and we then evaluated the probability to convert to BD at 5 years, using the model output and observed risk factors in the held-out test data. We chose 5 years as our primary evaluation time, as we observed 85% of observed conversions to occur within this time frame and a 5-year follow-up is a common time frame in survival analysis. We also evaluated model performance one and 2 years after the first MDD diagnosis, as these were the times of median and mean, respectively, observed conversions. For each threshold, we evaluated the probability of conversion using the Breslow non-parametric estimator of the baseline hazard function as implemented by the survfit() function in the R survival package [13].

We can apply a decision threshold to the PrC5 to assign a label (converter/non-converter) to the patients in the held-out test data. The chosen threshold determines the balance between the number of false positives and false negatives resulting from our classification. The area under the ROC curve (AUC) is a measure of the performance of these conversion probabilities to classify new observations. The AUC is equal to the probability that a randomly chosen BD converter will have a higher PrC5 than will a randomly chosen non-converter.

Key to evaluating performance of the PrC5 from our Cox model in correctly classifying new observations is knowing the true status of our patients (converter or non-converter). We cannot know this with certainty for censored observations, we only know that the patient had not converted at the last observation time. We use the PrC5 in a nearest-neighbor weighted Kaplan–Meier approach [14] to estimate the ROC curve, as implemented in the package survivalROC [15]. We evaluated the variability

in estimates of recall, precision, and AUC using 1000 different splits of our data into training/test data sets.

2.6 | Post Hoc Analyses

While our primary model used data on predictor variables collected on or before the first MDD episode (termed our baseline model), we performed a secondary analysis using covariate data collected during interim visits to the clinic, after the first MDD diagnosis but before conversion to BD (or censoring). This secondary analysis employed time-dependent covariates in a Cox model. We compared hazard ratios estimated in the training data in the time-dependent analysis to those estimated in the baseline model to evaluate the possible gain in predictive power by using data collected on interim visits.

3 | Results

3.1 | Sample Characteristics

The EHR contained records on 73,785 patients seen between 2005 and December 31, 2021. After we applied inclusion and exclusion criteria described in Section 2, our final sample for analysis was comprised of 13,607 patients (Figure S1). The sample was followed for a total of 21,573.8 person-years; length of follow-up ranged from 1 day to 15 years (mean: 1.6 years; SD: 2.4 years; Figure 1A). A total of 1610 patients (11.8%) converted to BD during follow-up; on average they converted within 2.1 years of their MDD diagnosis (SD = 2.7 years) and 49% converted within 1 year of diagnosis. The Kaplan–Meier estimate of the survival curve indicated the highest incidence of conversion to BD within the first year of the MDD diagnosis (Figure S2).

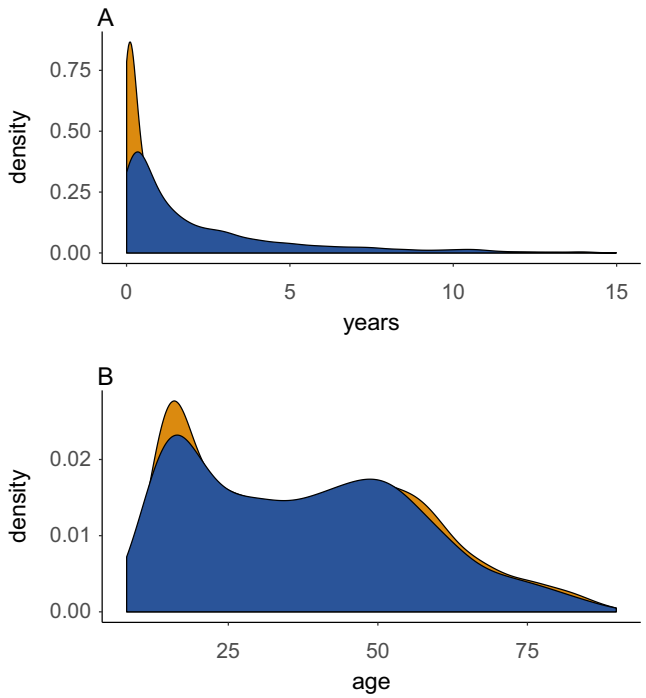

FIGURE 1 | (A) Distribution of time to conversion or censoring. (B) Distribution of age at first MDD. Converters ($n = 1610$) are orange, censored observations ($n = 11{,}997$) are blue.

The sample was majority female (66%) and primarily from Manizales (68%). Most patients (72%) were on antidepressants on or before their first MDD visit. The distribution of the age of patients at their first MDD diagnosis was bimodal (Figure 1B), with peaks in the late teens and at mid-life. A full description of the prevalence and distribution of predictor variables for the sample can be found in Table 1.

3.2 | Cox Model on Training Data

We tested the assumption of proportional hazards in the training data for each of the 26 predictor variables. Correcting for multiple testing, we found one variable (use of mood-stabilizing drugs) to be significant at the 0.05 level. Inspection of the residual plot, however, showed the deviation to be very modest (Figure S3).

The baseline Cox regression model used 9525 patients in the training data: 1127 converted to BD and 8398 were censored (Figure 2, Table S1). Males had a reduced rate of conversion to BD compared to females. Suicidality was associated with increased the rate of conversion to BD and while delusions recorded in the text had similar effect size to suicidality, this association did not survive correction for multiple testing. Use of antipsychotics or mood stabilizers on or before the first MDD diagnosis was associated with an increased rate of conversion to BD, while use of antidepressants was associated with a decreased the rate of conversion. Family history of BD increased the rate of conversion to BD while having a family history of SCZ, MDD, or psychosis was not strongly associated to BD conversion rate (Figure 2). Of the substance use variables, alcohol use was associated with an increased rate of BD conversion and marijuana use was associated with a decreased rate of BD conversion, however these associations did not survive correction for multiple testing. Age at the first MDD diagnosis was not associated with conversion to BD, and while a visit to the psychiatric hospital as a minor (not necessarily for MDD) was nominally associated with increased rate of conversion to BD, it was not significant after multiple testing correction. Patients who visited the ER at their first MDD diagnosis, were hospitalized at the time of their first MDD diagnosis, or received a diagnosis of Severe MDD with psychosis, had significantly increased BD conversion risk. We observed no significant associations with geographic location variables included in our model (living in Manizales or Aranzazu).

Our finding that the of use of antidepressants was associated with a decrease in the rate of conversion to BD appears in contrast with previous work, where antidepressant use in the absence of a mood stabilizer was shown to potentially induce manic episodes [16]. In our sample, participants prescribed antidepressants at the time of their first MDD episode were also less likely to have been hospitalized at that first episode, less likely to have had a severe MDD diagnosis (psychotic and/or non-psychotic), less likely to have had suicidality, and less likely to have experienced delusions (summarized in Table S2) than are participants that were not prescribed antidepressants; they were more likely, however, to have had a family history of MDD. When we stratify the training sample by severity (presence of

TABLE 1 | Sample characteristics of censored ($n = 11{,}997$) and uncensored ($n = 1610$) observations in the full sample.

Category	Variable	Censored	Uncensored (convert to BD)
(A) Binary variables. Presented is the proportion of patients with the indicated covariate			
Demographics	Male	0.35	0.28
	Manizales	0.68	0.68
	Aranzazu	0.01	0.02
Family history	Bipolar	0.03	0.09
	Schizophrenia	0.02	0.03
	MDD	0.13	0.17
	Psychosis	0.00	0.01
Psych history	First Psych visit as minor	0.22	0.22
	Previous Psych visit	0.21	0.23
Symptoms	Delusions	0.05	0.09
	Suicidality	0.37	0.36
Medications	Antipsychotics	0.05	0.11
	Antidepressants	0.74	0.63
	Mood stabilizers	0.11	0.24
	Hypnotics/antianxiety	0.54	0.56
	Hypothyroidism	0.01	0.01
Substance use	Marijuana	0.08	0.07
	Tabacco	0.27	0.24
	Alcohol	0.19	0.19
	Cocaine	0.04	0.04
	Other drugs	0.30	0.24
Characteristics first MDD	Treatment setting: ER	0.04	0.05
	Treatment setting: inpatient	0.39	0.40
	Severe, no psychosis	0.30	0.26
	Severe, with psychosis	0.04	0.09
		Mean (SD)	**Range**
(B) Continuous variables			
Days of follow-up after the first MDD diagnosis			
Censored		552 (861)	1–5471
Uncensored		756 (974)	1–5243
Age (in years) at first MDD diagnosis			
Censored		38 (19)	8–90
Uncensored		37 (19)	8–87

a severe MDD diagnosis, suicidality, hospitalization/ER visit), however, we find that the hazard ratio for antidepressant use was very similar in the two groups (data not shown), so it does not appear that reduced severity was driving the protective effect of antidepressant use.

3.3 | Prediction in Held-Out Data

Next, we test how well our multivariable model predicted conversion to BD. We applied the results of the baseline Cox model developed in the training data to 4082 patients (483 converters,

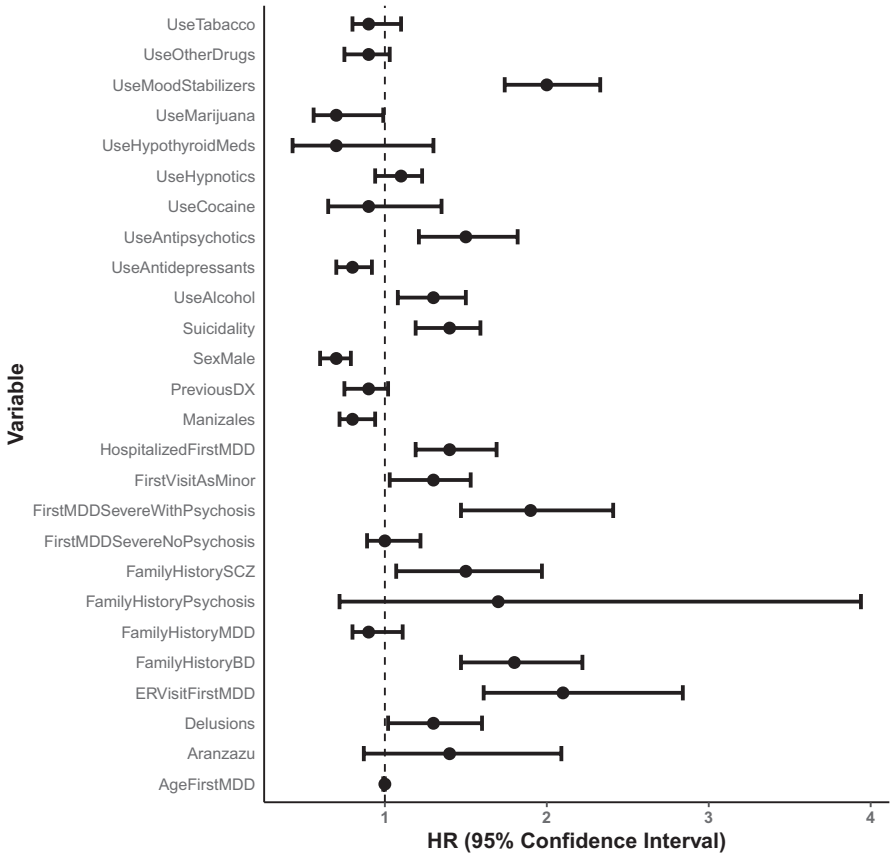

FIGURE 2 | Hazard ratios and 95% confidence intervals from the baseline multivariable Cox model used on the training data.

3599 censored) held-out as a test data set, and estimated the probability of converting to BD 5 years after their initial MDD diagnosis (PrC5). We find that the PrC5 was higher in patients where we observed conversion to BD than in censored patients (Figure 3A). The cases in the top 10% of the PrC5 have ~2.4× the number of observed converters than did the cases in the bottom 10% (83 vs. 35, respectively). We binned the PrC5 estimated in the test data into quartiles, and plotted Kaplan–Meier survival curves for each quartile (Figure 3B). Among the 483 converters in the test data, the median time to conversion decreased with increasing PrC5 (Figure S4). The area under the ROC curve was 0.65 (95% CI 0.62–0.68) and the area under the precision-recall curve was 0.39 (95% CI 0.36–0.45) (Figure S5). That is, the probability that a converter has a higher likelihood of converting based on our model was 65%.

The optimal probability threshold for classification was determined as the point on the ROC curve maximally distant from the diagonal [17], this threshold (24% in this case) gives equal weight to maximizing sensitivity and specificity. At this point, recall of conversion to BD within 5 years of the first MDD diagnosis was 0.72 (95% CI 0.5–0.74) and precision was 0.38 (95% CI 0.34–0.45). That is, we would capture 72% of patients that truly convert to BD within 5 years and 38% of patients labeled as converters are observed to convert.

Using this threshold, we labeled our 4082 patients in the test data as predicted converters/non-converters and compared this label to their observed status at each time point: converted to BD, not converted to BD, and unknown/censored (Table 2A). While these tables provide a useful visual of model performance in the test data, note that calculating recall and the false positive rate from this confusion matrix by discarding the unknown/censored observations would result in a biased estimate of these parameters [18]. Instead, the recall estimates we report that were obtained from the weighted nearest-neighbor Kaplan–Meier approach correctly handle the censored data.

Evaluating the ability of the model to identify converters after one or two, rather than 5 years resulted in a similar AUC (0.62 at 1 year, 0.64 at 2 years, 0.65 at 5 years), and recall (0.76 at 1 year, 0.77 at 2 years, compared to 0.72 at 5 years) and a substantially decreased precision (0.12 at 1 year, 0.20 at 2 years, compared to 0.38 at 5 years).

3.4 | Sensitivity Analyses

We assessed the sensitivity of our results to excluding participants who (1) had a BD diagnosis before their first MDD diagnosis (total $N = 13{,}659$ with 1662 conversions) (2) had a SCZ diagnosis at any time in their medical history (total $N = 13{,}799$ with 1667 conversions) and (3) who received their first MDD diagnosis before age eight (total $N = 13{,}686$ with 1625 conversions). Estimates of AUC, recall, and precision and the Cox regression parameter estimates were similar to what we see in our primary analysis (Table S3, Figure S6).

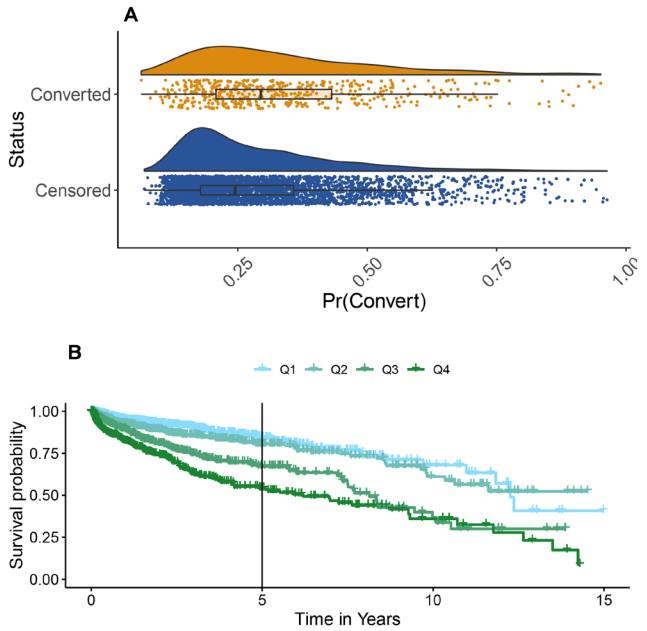

FIGURE 3 | We estimated the probability to convert to BD within 5 years of the initial MDD diagnosis in 4082 patients in the test data, using hazard ratios estimated in the training data. (A) Distribution of the probability to convert to BD in 483 converters and 3599 censored patients in the test data. (B) Kaplan–Meier survival plots for 4082 patients in the test data. Patients were split into quartiles based on the distribution of their probability to convert to BD within 5 years, using hazard ratios estimated in the training data. Q1, first quartile; Q2, second quartile; Q3, third quartile; Q4, fourth quartile.

TABLE 2 | Predicted status 5 years after the first MDD episode versus true status in 4082 patients held out in a test data set.

	True status		
	Convert	Not convert	Unknown
(A) Predicted status generated using results from a Cox model with mood stabilizers as a predictor			
Predicted			
Convert	280	149	1748
Not convert	135	226	1544
(B) Predicted Status generated using results from a Cox model without mood stabilizers as a predictor			
Predicted			
Convert	239	111	1546
Not convert	176	264	1746

3.5 | Outliers in PrC5 in Test Data

As shown above, a higher probability of conversions was associated with an increase in the observed conversion rate in test data. However, there were patients who, despite having a high probability to convert (PrC5 > 50%, about twice the level we use to classify someone as a converter), did not convert. We hypothesized that they may still convert but do not have sufficient follow-up time in the EHR (Figure S4). Indeed, among the 3599 patients in the held-out test data that did not convert, 339 have PrC5 > 50%: for these patients, the mean follow-up time is 165 days shorter than those with PrC5 < 50%. More generally, for every 10% increase in PrC5, we observe 88 days shorter follow-up time in non-converters (SE = 9.5 days, $p < 2e\text{-}16$), thus indicating that while patients did not convert during the follow-up time, they may still convert in the future, possibly contributing to a modest AUC.

3.6 | The Role of Use of Mood Stabilizers in Prediction

Our finding that prescription of mood stabilizers was a strong predictor of the rate of conversion to BD is not surprising, as this medication class is commonly used in patients with BD, and in the test data, participants using mood stabilizer had a higher PrC5 (Figure S7). Given that some patients were prescribed mood stabilizers before their conversion to BD may indicate that the clinician suspected BD. In the full data with $n = 1610$ conversions, those on mood stabilizers converted an average of 208 days (0.6 years) earlier than did those not on mood stabilizers (mean 2.3 years [SD = 2.7 years] vs. mean 1.7 years [SD = 2.4 years]). We ran a secondary analysis, omitting from the training data 1199 patients (282 converters and 917 censored patients) that were on mood stabilizers on or before the time of their first MDD diagnosis. The Cox model assumption of proportional hazards was met in this secondary analysis. We find that for most coefficients, the magnitude of the HR in the two analyses was very similar (Figure S8); however, the smaller sample size reduced significance.

In our sample, prescribed mood stabilizers were either valproic acid or lithium. In a sensitivity analysis we decomposed mood stabilizer use to two indicators: use of lithium only and use of other mood stabilizers. We find both indicators were significant risk factors for conversion to BD, indicating that our finding was not specific to the type of medication.

Using the HR estimated from a Cox model without mood stabilizer use as a predictor (but including the 1199 patients on mood stabilizers), we evaluated the PrC5 in the held-out test data. The 4082 patients in the held-out test data included 509 participants that were on mood stabilizers at the first visit (98 converters, 411 censored). Compared to a model with mood stabilizer we found the AUC was unchanged at 0.65. At that model's optimal cut-point for classification (30%), recall and precision were 0.60 and 0.43, respectively (compared to the original 0.72 and 0.38).

While it is not a formal clinical predictor for conversion to BD, we treated a prescription of mood stabilizers prior to conversion as a proxy for such a predictor and compared it to the performance of our model that did not include the use mood stabilizers. We observe that the overall performance of this univariate prediction model was worse than our model excluding mood stabilizers (AUC is 0.54, precision is 0.38 and recall is 0.18) indicating that the other variables contributed meaningfully to the prediction.

3.7 | Value of Data From Interim Clinic Visits

HRs estimated from the Cox model using time-dependent covariates were similar in magnitude to those estimated using only predictor data gathered on or before the first MDD diagnosis in the baseline model (Figure S9). A notable exception is the HR estimated for use of mood stabilizers, where the HR has increased to 3.8 (95% CI 3.32–4.39) and the confidence intervals from the two models did not overlap: patients who begin taking mood stabilizers after their first MDD diagnosis had a greatly increased risk of conversion to BD.

Having shown previously that distance to the hospital has an effect of treatment-seeking behavior for outpatients, specifically those with MDD [10], we evaluated a model including only patients residing in Manizales, where the hospital is located. This model resulted in similar effect size estimates as well as predictive power (data not shown).

3.8 | Post Hoc Analyses Using Random Survival Forests

To assess additional predictive power using non-linear models we performed a post hoc analyses using random survival forests. Using this model did not improve performance compared to our Cox model (AUC = 0.59, recall = 0.35, precision = 0.43; details not shown).

4 | Discussion

We show that by using data that could be collected at the time of the first MDD episode, we can identify 72% of patients that go on to convert to BD within 5 years. Our study, which relied entirely on EHR data from a psychiatric hospital, confirmed many previously identified risk factors identified through registry-based studies (such as female gender and psychotic depression at the index MDD episode), and also identified novel ones (specifically, suicidality extracted from clinical notes). We studied the effect of mood stabilizers on our predictive models and quantified how risk factors identified *after* the index MDD visit but *before* conversion to BD differentially affect risk of converting to BD.

As in other studies [2, 6–9], we found the highest incidence of conversion to BD within the first year of the MDD diagnosis; however, the conversion rates we observe were higher. Conversion rates in the first year after MDD diagnosis have been estimated to be ~1.5% [8] to ~4% [6] our rate was 9.6% in the first year. We hypothesize that the rates are elevated in our sample because patients with mild MDD, who are less likely to convert to BD, may not be seen in a psychiatric hospital. Song et al. [10] showed a decrease in incidence of MDD with increasing distance from CSJDM for outpatients, but not inpatients, supporting this view. Note that while other studies [8, 9] are able to report a 15-year cumulative incidence of conversion, the short mean follow-up time (especially in censored individuals), and smaller numbers, in our data, prevent us from estimating a non-inflated cumulative incidence.

Our EHR-based Cox model identified many of the same predictors found in registry-based studies performed in the Northern European countries of Denmark [8] and Finland [9]. For example, as in previous work [8, 9], we found gender and severity of the first MDD episode to be significantly related to conversion. The HR estimates of these consistently identified risk factors also very similar: males had lower rates of conversion to BD than did female (HR: 0.70–0.80); psychotic depression at the first episode increased rates of conversion (HR: 1.7–2.0). As in Musliner and Ostergaard [8], we further identify family history of BD, presence of psychosis at the first MDD, ER treatment or hospitalization at the first MDD to be significantly associated with the rate of conversion to BD. These similarities highlight the validity of using EHR for identifying risk factors of diagnostic changes. Contrary to most [9, 19, 20] though not all [8], reports in the literature, we did not find age at onset to be predictive of conversion to BD. While somewhat unexpected, it may be partly attributed to differing definitions of age at onset in the literature [3], and barriers to seeking care for milder patients with MDD [10], who also tend to be older [21]. Further research is needed to explore this hypothesis and to understand the complex interactions between age at onset, severity, and conversion to BD.

Our study further builds on existing registry-based approaches quantifying the cumulative effect of the identified risk factors and their ability to predict conversion in a pre-defined time frame, highlighting that EHR data can be used to predict disease trajectories. A study using insurance claims data [20] observed similar predictive performance to our model; however, in their framework the prediction window was 1 year, and analyses were restricted to patients with complete follow-up and without a prior history of antipsychotic, antidepressant, lithium or mood-stabilizing drugs.

Predictive modeling from the complete EHR further allowed the inclusion of additional features not commonly integrated with registry or claims data, such as symptoms and behaviors derived from clinical notes. While suicidal behavior has been identified as a predictor in previous work [20], to the best of our knowledge, we are the first to test and identify suicidality reported in clinical notes as risk factors for conversion to BD. These variables were identified as risk factors even when controlling for hospitalization at the index MDD visit. In addition, from available prescription data, we found the use of antipsychotic medications and mood-stabilizing medications increased the rate of conversion to BD, when controlling for diagnostic codes; conversely, in our data, antidepressant use was protective factor.

Antipsychotic use was also identified in Pradier et al. [22], a study that estimated risk factors for transition to BD within 90 days of the first prescription for an antidepressant. Unlike our study, which relies on data from a psychiatric clinic and includes only patients treated by specialists, their work focused on general health care institutions. Indeed, the strongest risk factor observed in their study was being seen by a psychiatric provider (about 9% of their total sample), which increased the transition rate to BD compared to general care 3.5-fold.

Our finding that antidepressant use was associated with lower probability of conversion to BD may appear unexpected, given the known risk of antidepressant-induced mania without concurrent mood stabilization therapy [16]. In a predictive setting, the association between antidepressant use and conversion to BD has not been extensively studied and based on the few

studies that exist, there is no clear consensus in the literature [23–25], and work in acute BD-II depression has shown that treatment with second-generation antidepressant monotherapy does not increase the rate of conversion to BD-I [26]. When evaluating our finding further, we observed that participants prescribed antidepressants at the time of their first MDD episode were less severe: they were less likely to have been hospitalized at that first episode, less likely to have had a severe MDD diagnosis, less likely to have suicidality, and less likely to have experienced delusions. However, this confounding by severity does not account for the observed protective effect, as the effect size of AD use was similar when stratified by severity, further underscoring the probable lack of a causal relationship between medication use and conversion to BD.

Another novelty of our study is our in-depth analyses of the association of prescriptions of mood stabilizers in conversion to BD. We do not suggest this association to be causal, instead we believe the association indicated that the attending physicians were cognizant of an increased risk of mania in these patients. Controlling for all the predictors used in our Cox model, the odds of being prescribed a mood stabilizer for patients with a family history of BD was 1.48× the odds for patients without a family history of BD, which could indicate that that physicians were using this information in developing their treatment plan. When we exclude the use of mood-stabilizing medications at the time of their first MDD as a predictor in our Cox regression model, we found that the model was still predictive of conversion to BD in the held-out data, with recall of 60% and AUC of 65%.

Evaluation of data from interim clinic visits, for patients who had multiple visits before conversion/censoring, indicated that HR were very similar for all predictors except for mood-stabilizer use. Patients who were not on mood stabilizers at their initial MDD visit, but subsequently were prescribed them, were identified as being at increased risk for conversion. Mood stabilizer use, however, was clearly well-known to physicians, who are likely already aware of the risk for conversion to BD for these patients. Other risk factors identified in our model had similar HR when using data from interim clinic visits as when using data from the first MDD episode, suggesting that accuracy of prediction of conversion was similar in the two approaches and conversion risk can be well estimated using data available at the time of the first MDD episode.

5 | Limitations

A limitation of using EHR as opposed to registry data is incomplete information: even in a setting such as here, when a catchment area is well-defined, one can never know whether absence of recorded visits mean people left the region, stopped needing/using treatment, or passed away. Second, EHR have the issue of censoring; it is possible that patients converted to BD before the records started or after the follow-up time. Interestingly, we show that for every 10% increase in predicted probability of conversion, we observed 88 days shorter follow-up time in non-converters, thus indicating that while patients did not convert during the follow-up time, they may still convert in the future, likely contributing to a modest AUC. Finally, while our EHR data are very detailed and complete, we are unable to link data recorded in the hospital with data from primary care providers. While we do not have access to complete registries or data from primary care providers, in future work we may be able to include aggregated community-level socio-demographic descriptors [27] into our models.

6 | Conclusions

We showed that EHRs can be used to predict conversion from unipolar depression to bipolar disorder using data from a psychiatric hospital in Colombia. We replicated several risk factors of conversion to BD previously identified in patient registries and EHRs from upper income countries, and also identified novel such features: namely, suicidality at or before the index depressive episode. Using our multivariable model, we can identify patients at increased risk of conversion from MDD to BD. While our predictions are not yet at the level of clinical utility, we hypothesize that future work including expanded NLP libraries, genetic risk factors, socio-demographic features, and more complex temporal modeling will improve prediction.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The datasets generated and/or analyzed during the current study are not publicly available due to privacy protection concerns. The local IRB committee prohibits making the dataset publicly available or available to other researchers. All model information is publicly available can be found in the Supporting Information.

References

1. R. S. McIntyre, M. Berk, E. Brietzke, et al., "Bipolar disorders," *Lancet* 396, no. 10265 (2020): 1841–1856, https://doi.org/10.1016/S0140-6736(20)31544-0.

2. J. Scott, A. Graham, A. Yung, C. Morgan, F. Bellivier, and B. Etain, "A Systematic Review and Meta-Analysis of Delayed Help-Seeking, Delayed Diagnosis and Duration of Untreated Illness in Bipolar Disorders," *Acta Psychiatrica Scandinavica* 146, no. 5 (2022): 389–405, https://doi.org/10.1111/acps.13490.

3. J. L. Kalman, L. M. Olde Loohuis, A. Vreeker, et al., "Characterisation of Age and Polarity at Onset in Bipolar Disorder," *British Journal of Psychiatry* 219, no. 6 (2021): 659–669, https://doi.org/10.1192/bjp.2021.102.

4. C. Daban, F. Colom, J. Sanchez-Moreno, M. Garcia-Amador, and E. Vieta, "Clinical Correlates of First-Episode Polarity in Bipolar Disorder," *Comprehensive Psychiatry* 47, no. 6 (2006): 433–437, https://doi.org/10.1016/j.comppsych.2006.03.009.

5. J. Angst and R. Sellaro, "Historical Perspectives and Natural History of Bipolar Disorder," *Biological Psychiatry* 48, no. 6 (2000): 445–457, https://doi.org/10.1016/s0006-3223(00)00909-4.

6. L. V. Kessing, I. Willer, P. K. Andersen, and J. D. Bukh, "Rate and Predictors of Conversion From Unipolar to Bipolar Disorder: A Systematic

Review and Meta-Analysis," *Bipolar Disorders* 19, no. 5 (2017): 324–335, https://doi.org/10.1111/bdi.12513.

7. A. Ratheesh, C. Davey, S. Hetrick, et al., "A Systematic Review and Meta-Analysis of Prospective Transition From Major Depression to Bipolar Disorder," *Acta Psychiatrica Scandinavica* 135, no. 4 (2017): 273–284, https://doi.org/10.1111/acps.12686.

8. K. L. Musliner and S. D. Ostergaard, "Patterns and Predictors of Conversion to Bipolar Disorder in 91587 Individuals Diagnosed With Unipolar Depression," *Acta Psychiatrica Scandinavica* 137, no. 5 (2018): 422–432, https://doi.org/10.1111/acps.12869.

9. I. Baryshnikov, R. Sund, M. Marttunen, et al., "Diagnostic Conversion From Unipolar Depression to Bipolar Disorder, Schizophrenia, or Schizoaffective Disorder: A Nationwide Prospective 15-Year Register Study on 43495 Inpatients," *Bipolar Disorders* 22, no. 6 (2020): 582–592, https://doi.org/10.1111/bdi.12929.

10. J. Song, M. C. Ramírez, J. Okano, et al., "Geospatial Analysis Reveals Distinct Hotspots of Severe Mental Illness," *Communications Medicine* 4 (2024): 26.

11. J. De La Hoz, A. Arias, S. K. Service, et al., "Analysis of Diagnosis Instability in Electronic Health Records Reveals Diverse Disease Trajectories of Severe Mental Illness," *medRxiv*, 2022:2022.08.20.22279007, https://doi.org/10.1101/2022.08.20.22279007.

12. Office for Civil Rights UDoHaHS, "Health Information Privacy," https://www.hhs.gov/hipaa/for-professionals/index.html.

13. "A Package for Survival Analysis in R," R Package version 3.2-3, 2022, https://CRAN.R-project.org/package=survival.

14. P. J. Heagerty, T. Lumley, and M. S. Pepe, "Time-Dependent ROC Curves for Censored Survival Data and a Diagnostic Marker," *Biometrics* 56, no. 2 (2000): 337–344, https://doi.org/10.1111/j.0006-341x.2000.00337.x.

15. "survivalROC: Time-Dependent ROC Curve Estimation From Censored Survival Data," R Package Version 1.0.3, 2022, https://CRAN.R-project.org/package=survivalROC.

16. A. Viktorin, P. Lichtenstein, M. E. Thase, et al., "The Risk of Switch to Mania in Patients With Bipolar Disorder During Treatment With an Antidepressant Alone and in Combination With a Mood Stabilizer," *American Journal of Psychiatry* 171, no. 10 (2014): 1067–1073, https://doi.org/10.1176/appi.ajp.2014.13111501.

17. W. J. Youden, "Index for rating diagnostic tests," *Cancer* 3, no. 1 (1950): 32–35.

18. P. Blanche, J. F. Dartigues, and H. Jacqmin-Gadda, "Review and comparison of ROC curve estimators for a time-dependent outcome with marker-dependent censoring," *Biometrical journal* 55, no. 5 (2013): 687–704, https://doi.org/10.1002/bimj.201200045.

19. S. E. Gilman, J. M. Dupuy, and R. H. Perlis, "Risks for the Transition From Major Depressive Disorder to Bipolar Disorder in the National Epidemiologic Survey on Alcohol and Related Conditions," *Journal of Clinical Psychiatry* 73, no. 6 (2012): 829–836, https://doi.org/10.4088/JCP.11m06912.

20. A. Nestsiarovich, J. M. Reps, M. E. Matheny, et al., "Predictors of Diagnostic Transition From Major Depressive Disorder to Bipolar Disorder: A Retrospective Observational Network Study," *Translational Psychiatry* 11, no. 1 (2021): 642, https://doi.org/10.1038/s41398-021-01760-6.

21. S. Zisook, I. Lesser, J. W. Stewart, et al., "Effect of Age at Onset on the Course of Major Depressive Disorder," *American Journal of Psychiatry* 164, no. 10 (2007): 1539–1546, https://doi.org/10.1176/appi.ajp.2007.06101757.

22. M. F. Pradier, M. C. Hughes, T. H. McCoy, Jr., S. A. Barroilhet, F. Doshi-Velez, and R. H. Perlis, "Predicting Change in Diagnosis From Major Depression to Bipolar Disorder After Antidepressant Initiation," *Neuropsychopharmacology* 46, no. 2 (2021): 455–461, https://doi.org/10.1038/s41386-020-00838-x.

23. H. Kim, Y. Kim, J. H. Baek, et al., "Predictive Factors of Diagnostic Conversion From Major Depressive Disorder to Bipolar Disorder in Young Adults Ages 19–34: A Nationwide Population Study in South Korea," *Journal of Affective Disorders* 265 (2020): 52–58, https://doi.org/10.1016/j.jad.2020.01.009.

24. Y. T. Jo, S. W. Joo, H. Kim, et al., "Diagnostic Conversion From Unipolar to Bipolar Affective Disorder—A Population-Based Study," *Journal of Affective Disorders* 301 (2022): 448–453, https://doi.org/10.1016/j.jad.2022.01.082.

25. I. Pacchiarotti, D. J. Bond, R. J. Baldessarini, et al., "The International Society for Bipolar Disorders (ISBD) Task Force Report on Antidepressant Use in Bipolar Disorders," *American Journal of Psychiatry* 170, no. 11 (2013): 1249–1262, https://doi.org/10.1176/appi.ajp.2013.13020185.

26. J. H. Park, N. A. Nunez, M. Gardea-Resendez, et al., "Short Term Second-Generation Antidepressant Monotherapy in Acute Depressive Episodes of Bipolar II Disorder: A Systematic Review and Meta-Analysis," *Psychopharmacology Bulletin* 52, no. 2 (2022): 45–72.

27. Departamento Administrativo Nacional de Estadística (DANE), "National Statistical System (NSS)—General Aspects," accessed August 14, 2024, https://www.dane.gov.co/index.php/en/national-statistical-system-nss/statistical-planning/general-aspects.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.