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Program of algorithm for pharmacological treatment of major depressive disorder in China: Benefits or not?

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ABSTRACT

Background: This research was designed to investigate Algorithm Guided Treatment (AGT) and clinical traits for the prediction of antidepressant treatment outcomes in Chinese patients with major depressive disorder (MDD).

Methods: This study included 581 patients who had reached treatment response and 406 patients remained non-responded observed after three months of treatment. Sociodemographic factors, clinical traits, and psychiatric rating scales for evaluating therapeutic responses between the two groups were compared. Logistic regression analysis was adopted to determine the risk factors of unresponsive to antidepressant (URA) in MDD. Kaplan-Meier survival analysis was utilized to compare the therapeutic response between AGT and treatment as usual (TAU).

Results: Compared to the MDD responsive to antidepressant (RA) group, the URA group had significantly lower rates of the following clinical traits: married status, anxious distress, moderate to severe depressive symptoms, and higher rates of comorbidity (*p-value* < 0.05). Logistic Regression Analysis showed that eight clinical traits from psychiatric rating scales, such as anxious characteristics, were correlated positively with URA, while the other eight symptoms, such as autonomic symptoms, were negatively correlated. Time to symptomatic remission was longer in TAU without statistically significant (*p-value* $= 0.11$) by log-rank testing.

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Conclusions: The factors may affect the therapeutic responses and compliance of patients, increasing the non-response risk for antidepressants. Therapeutic responses might be improved by increasing the clarification and elucidation of different symptom clusters of patients. Benefits on treatment response to AGT were not found in our study, indicating a one-size-fits-all approach may not work.

Trial Registration: We registered as a clinical trial at the International Clinical Trials Registry Platform (No. NCT01764867) and obtained ethical approval 2012-42 from SMHC.

1. Introduction

Currently, antidepressants are listed in the main treatment strategy for major depressive disorder (MDD). Second-generation antidepressants are being recommended to be the first-line medication with high safety and efficacy [1]. However, the treatment outcome of depression was not optimistic in general. In the Sequenced Treatment Alternatives to Relieve Depression (STAR * D) study, 50 % of the patients did not respond to the initial trial [2]. Meanwhile, the efficacy of treatment decreases with its frequency. The final remission rate was only 70 %, even with the completion of potential sequenced treatment steps [3]. Approximately the remaining 30 % patients would experience treatment-resistant depression (TRD) [4].

Although monoaminergic antidepressants have been under development for half of a century, there is no strong evidence of sequenced treatment alternatives for implementing pharmacological strategies (monotherapy, combination, polypharmaceutical or augmentation strategies) [5], as well as the effectiveness between any treatments at any treatment level [6]. Moreover, there is no significant difference between the different psychopharmacological classes used as augmenters in terms of symptom severity and treatment response [7]. Therefore, the identification of risk factors for TRD may be useful to guide an initial trial, avoid inefficient trial-and-error, and improve proper care for MDD [2,8]. Patients with MDD often experience side effects, inadequate responses, and residual symptoms that interfere with compliance [9], all of which can lead to treatment discontinuation [10].

Antidepressant agents should be considered over evidence-based strategies [11], however, many physicians mostly rely on their clinical experience for treatment decisions so that the treatment strategies are doomed to be different. Some physicians believe that they cannot follow the guidelines for practical reasons. Compared with sequenced treatment, it is more important to adjust medication to patient compliance for a better prognosis [12]. It may lead to inadequate or prolonged treatment (such as frequent changes among different strategies), reducing the patient's possibility of clinical cure.

On the other hand, choosing the most effective strategy to alleviate symptoms is an urgent direction of clinical researches on MDD. Algorithm Guided Treatment (AGT) involves sequential progression and appropriate decision-making based on the results of clinical evaluation, which may help improve treatment outcome, efficacy, and cost-effectiveness [13]. Therefore, the AGT was worth being investigated by comparing with the treatment as usual (TAU), as a potential prognostic factor.

A multiple-treatments meta-analysis (117 studies, $n = 25{,}928$) showed escitalopram, mirtazapine, venlafaxine, and sertraline are more efficacious than other second-generation antidepressants and escitalopram was suggested the best profile of acceptability, leading to significantly fewer discontinuations [14]. A systematic review and network meta-analysis was updated (522 studies, $n = 116{,}477$), indicating escitalopram, mirtazapine, paroxetine, venlafaxine, agomelatine, amitriptyline, and vortioxetine are more effective than other antidepressants [15]. Meanwhile, mirtazapine showed optimal acceptability in the lower range of their licensed dose (about 30 mg), as well as selective serotonin reuptake inhibitors (SSRIs) with the lower licensed range between 20 mg and 40 mg fluoxetine equivalents [16]. Considering the most favorable balance between benefits, acceptability, acquisition cost and mechanism-based targeting of receptor for antidepressant, we chose escitalopram and mirtazapine as the antidepressant agents in AGT. Although no advantage of treatment outcome was shown in head-to-head studies between the two antidepressants [15], mirtazapine was more effective in improving weight, poor appetite and biological rhythm symptoms of MDD [17].

Some studies suggested that baseline features and early symptoms could predict whether patients will respond to treatment [18,19]. Before evaluating symptoms by clinical rating scales, the potential multicollinearity among them should be considered. In the study design, variables from the overall symptomatologic dimension of MDD are supposed to be collected. At the same time, the differentiated symptoms of MDD are considered able to efficiently achieve a comprehensive assessment for predicting the prognosis. Therefore, commonly used clinical rating scales are good candidates for this research. The selected scales should not only have good discriminative validity and test-retest reliability, but also be convenient for clinical use. Thus, these corresponding results will be able to benefit internal and external uses, such as the fine distinctions made through these scales.

2. Materials and methods

2.1. Settings and participants

Data of participants were consecutively collected from four psychiatric hospitals and four psychiatric departments of general hospitals, across seven cities from four provinces and a municipality directly under the central government of mainland China between 2012 and 2014. Patients with depressive episodes were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition Text Revision (DSM-IV-TR) criteria. The psychiatric hospitals included Shanghai Mental Health Center (SMHC), Shanghai Changning Mental Health Center, Shanghai Hongkou Mental Health Center, Nanjing Brain Hospital, Wuhan Mental

Health Center, the Second Affiliated Hospital of Zhejiang University School of Medicine, Huzhou Third People's Hospital and the First Affiliated Hospital of Kunming Medical University. The study was approved by the Institutional Ethical Committee for clinical research of SMHC (2012BAI01B04) and all subcenters. The study was approved by the institutional review boards at each site, and written informed consents were obtained from all participants prior to research entry according to the Declaration of Helsinki. This study has been registered as a clinical trial at the International Clinical Trials Registry Platform (No. NCT01764867), and ethical approval (2012–42) has been obtained from SMHC.

2.2. Inclusion and exclusion criteria

The inclusion criteria were : (1) aged 18–75 years, (2) meeting DSM-IV criteria for a current episode of depression, (3) Hamilton Depression Rating Scale-17 items (HAMD-17) score ≥14 points, (4) sufficient to understand informed consent and research content; (5) sufficient audio-visual level to complete the study, (6) necessary and suitable for receiving antidepressant treatment.

Overall exclusion criteria included : (1) physical illness (history of cerebral trauma, central nervous system disease, neuroendocrine disease, hepatic injury, renal injury, or heart disease), (2) severe suicide attempt (Item 3, "Suicide" score of HAMD-17 ≥ 3 points), (3) pregnant or lactating women, or those who have a plan for pregnancy, (4) substance abuse except nicotine, (5) drug interaction among current medications for physical disease and the antidepressant, (6) those who have received modified electroconvulsive therapy in the past six months, (7) history of treatment failure to any of the two protocol drugs (mirtazapine or escitalopram), (8) excessive use of tranquilizing drugs (≥15 mg/day diazepam equivalents).

2.3. Study design

The study was based on the Program of Algorithm Guided Treatment for Depression (PAGT*D), which is a 12-week randomized, open label, parallel-group trail. The treatment of MDD was divided into two groups: AGT and TAU. The AGT group employed escitalopram and mirtazapine as protocol drugs, while TAU group was defined as an antidepressant monotherapy. A total of 987 patients were randomized into AGT (n = 663, escitalopram/mirtazapine = 340/323) or TAU (n = 324) group. Psychiatrists were allowed to adjust the dose of the antidepressant within the therapeutic range. If no response was reached from the initial intervention for at least six weeks, the treatment would be switched from mirtazapine to escitalopram and vice versa, and then a combination therapy of the two drugs in the next treatment step for at least six weeks if necessary. Meanwhile, no more arrangements would be intervened in the therapeutic alliance of the TAU group, starting from monotherapy. Participants were randomly allocated into one of the three treatment strategies after screening. The measurement was administered at baseline, weeks 2, 4, 6, 8, and 12. The HAMD-17 [20] (9 items rated using a 5-point scale, from 0 = not at all to 4 = extreme and 8 items rated using a 3-point scale, from 0 = not at all to 2 = major, with a score of >7 indicating depressive symptoms), the Hamilton Anxiety Rating Scale-14 items (HAMA-14) [21] (14 items rated using a 5-point scale, from 0 = not at all to 4 = extreme, with a score of >7 indicating anxiety symptoms), the 6-Item Life of

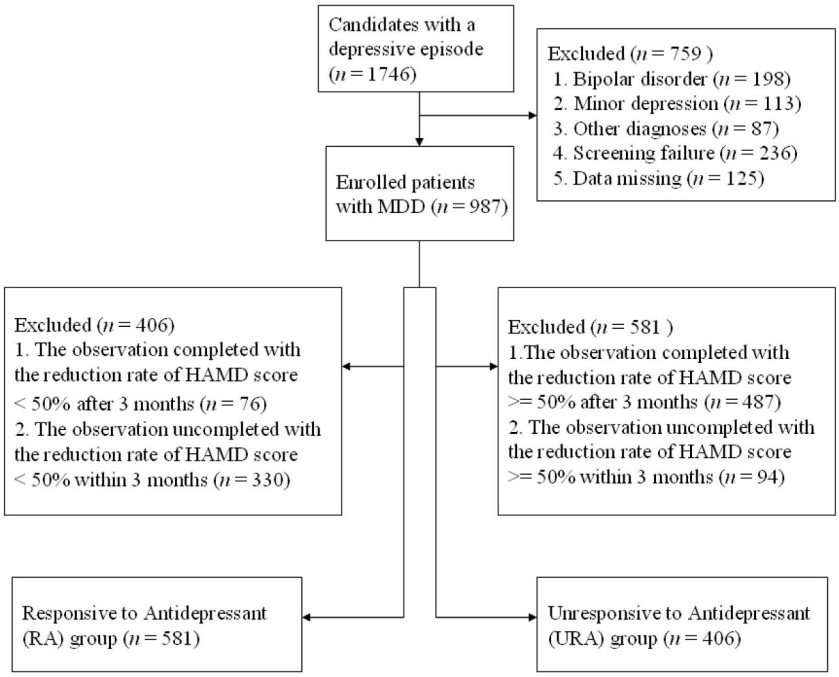

Fig. 1. Flowchart of the screening process and data classification.

Quality Questionnaires (QOL-6) [22](6 domains including physical health, psychological health, economic circumstances, work, family relationships, and relationships with non-family associates, rated using a 5-point scale, from 1 = very poor to 5 = excellent), the Depression and Somatic Symptoms Scale (DSSS) [23] (22 items rated using a 4-point scale, from 0 = not at all to 3 = major, with a higher score suggesting greater severity level of depression and somatic symptoms), the Visual Analogue Scales (VAS) [24] (rated using a 10-point scale, from 1 = no pain to 10 = severe pain, for estimating the severity of somatic pain) and the Self-report Version of the Quick Inventory of Depressive Symptoms (QIDS-SR16) [25] (16 items rated using a 4-point scale, from 0 = not at all to 3 = major, three depression clinical clusters—core emotional, atypical and sleep symptoms estimated by the sum of the corresponding items, with a higher score implying greater severity level of corresponding symptoms) were used to evaluate the therapeutic outcome retrospectively.

2.4. Participant description

Candidates who have had at least one depressive episode from a total of 1746 patients were selected. Exclusion criteria of the candidates included the following five reasons: (1) bipolar disorder (BD), (2) minor depression, (3) other diagnoses, (4) screening failure, or (5) data missing. Patients were divided into two groups by whether having reached a response by 50 % improvement of the HAMD-17 score from baseline to endpoint after three months' antidepressant treatment [26], as MDD responsive to antidepressant (RA) or unresponsive to antidepressant (URA). With or without 50 % reduction rate of the HAMD-17 score was the second-level observation of each individual. The HAMD-17 response ($\geq$50 % score reduction) was widely evaluated in meta-analysis [27,28] and clinical guidelines [1]. Enrolled patients were supposed to keep on drug adherence until they meet an adequate reason for medication discontinuation. After excluding the unnecessary cases, a total of 581 MDD-respond patients and 406 MDD-non-respond patients were selected. (see Fig. 1 for a flowchart of sample selection).

2.5. Statistical methods

IBM SPSS version 17.0 for Windows (Chicago Inc., USA) was applied for statistical analysis. Treatment response was the outcome, and the two treatments (AGT vs. TAU) were the main research factors under the consideration of the adjustment for untreated duration, comorbidity, and severity of depressive symptoms. Multivariate Cox regression analysis (enter section) was employed to compare the therapeutic effect. Kaplan-Meier survival analysis was utilized to compare different treatments. Continuous variables were represented as mean $\pm$ SD for normality and homogeneity. The between-group variance with skewed distribution was compared by the Mann-Whitney *U* test. Categorical variables were represented as n (%) and examined by the Chi-square test. Statistical significance was defined as p value < 0.05. An odds ratio (OR) was yielded if p value < 0.05. We used the last observation carried forward method, which is a statistical approach for longitudinal repeated measures data where data of observations might be missing in the 12-weeks follow-up.

The formula method of Box-Tidwell was used to test the linear correlation between the $\log_e$ (In)-transformed continuous variables and the corresponding variables. A total of 180 (90* 2) items were involved in the linear test model, first, including sociodemographic factors (3), clinical traits (6), psychiatric rating scales (6), and their subscales (75) [HAMD-17 (17), QOL-6 (6), HAMA-14 (14), DSSS (22), QIDS (16)]. We tried to assessed selected depressive symptoms with psychometrically acceptable properties, making them suitable for use in busy practices [29–31]. All of the 180 items yielding linear relationships after Bonferroni correction were applied, with the level of 0.0003 (0.05/180). Furthermore, outliers were deleted if their Studentized Residual was more than two standard deviations away from the mean.

Before building the regression model, factors with multicollinearity under 0.1 of tolerance and above 10 of variance inflation were excluded, including the item of the total course of depression and all of the six psychiatric rating scales. We then compiled a total of 96 variables, with 83 continuous variables including sociodemographic factors (3), clinical traits (5), and subscales (75), and 13 dichotomous categorical variables extracted from clinical traits and symptomatic assessments except the item of hospitalization, which were dichotomized into absent (score = 0) vs. present (scores = 1) for the estimation of frequency. For the identification of the objective clinical traits of the MDD-non-respond patients, a backward Wald method in the Binary Logistic regression was performed, with a p value criterion of 0.05 and 0.10 for entry and removal, respectively. Events per variable (EPV) of the effective sample size (n = 987) to the predictor variables (n = 96) were beyond the criteria ($\geq$10) [32,33].

Finally, it yielded 20 risk factors deployed in the binary logistic regression, including three dichotomous categorical variables and 17 In-transformed continuous variables. A receiver operating characteristic (ROC) curve was examined to discriminate the accuracy of the model by the area under the curve (AUC) of the ROC curve [34]. The actual positive state was 2 = URA group. The ability of the prediction models was calibrated via Hosmer-Lemeshow goodness of fit test [35,36].

3. Results

3.1. Comparison of sociodemographic factors, clinical traits and psychiatric rating scales between responders and non-responders of MDD patients

In the analysis of sociodemographic factors, age and age at onset of the RA group were 2.54 years and 2.39 years older than that of the URA group, respectively(p-value$<$0.05), while higher number of depressive episodes and number of untreated episodes in the RA group were observed compared to the URA group(p-value$<$0.05). No statistically significant difference was found in the other items

between the two groups(p-value>0.05). See Table 1.

In Table 2, the six psychiatric rating scales were selected, and no difference was found in any of the scales (HAMD-17, HAMA-14, QOL-6, DSSS, QIDS-SR16, and VAS) (p-value>0.05).

Comparison of dichotomous categorical variables between responders and non-responders of MDD Patients.

The completion of the observation period (83.8 % vs. 18.7 %), married status (70.1 % vs. 62.5 %), with anxious distress (58.4 % vs. 51.5 %), moderate to severe depressive symptoms (81.4 % vs. 72.7 %) and hospitalization (23.3 % vs. 14.7 %) in the RA group was significantly higher than those in the URA group, while co-morbidity (19.8 % vs. 27.0 %) in the RA group was significantly lower (p-value<0.05). No statistical difference was found in any of the other categorical variables. See Table 3.

3.2. Outcome analysis of treatments utilizing Kaplan-Meier survival analysis

In this dataset, 42.8 % of AGT and 37.7 % of TAU in the duration of 12 weeks were censored, a level at which bias is negligible, even when the survival distribution is highly skewed. The result of multivariate Cox regression analysis showed no difference ($p = 0.459$), and the two treatments had the same risk of affecting the efficacy, with a hazard ratio (HR) = 0.931 (95%CI: 0.772–1.124). No statistical difference was found in the total number of weeks in treatment response comparing AGT (10.9 weeks) vs. TAU (11.3 weeks). Time to symptomatic remission was longer in TAU using standard survival analyses, which showed no statistically significant (p-value = 0.11) using log-rank testing. See Fig. 2.

3.3. Binary logistic regression analysis of factors for predicting responders or non-responders of MDD patients

In this research, we tried to associate clinical traits with 96 symptomatic predictors, as shown above, through the backward method Wald of the binary logistic regression. After eliminating the missing items, a total of 694 cases were available (416 cases in the RA group and 278 in the URA group). The regression model was constructed by X_1 = untreated duration, X_2 = co-morbidity (0 = no, 1 = yes), X_3 = treatment regimen (0 = TAU, 1 = AGT), X_4 = severity of depressive symptoms (mild = 0, moderate to severe = 1), X_5 = HAMD-17-3, X_6 = HAMD-17-4, X_7 = HAMD-17-14, X_8 = HAMD-17-15, X_9 = HAMA-8, X_{10} = HAMA-13, X_{11} = HAMA-14, X_{12} = QOL-6-2, X_{13} = DSSS-1, X_{14} = DSSS-9, X_{15} = DSSS-15, X_{16} = DSSS-16, X_{17} = QIDS-SR16-2, X_{18} = QIDS-SR16-3, X_{19} = QIDS-SR16-6, X_{20} = QIDS-SR16-10. See Table 4. Details of these subscales are shown in Supplementary Material 1. Other variables did not enter the model. The regression equation was finally observed as follows:

$$\text{Logit (P)} = 0.310\text{-}0.005X_1+0.630X_2+0.378X_3\text{-}0.552X_4+0.337X_5+0.295X_6+0.182X_7\text{-}\ 0.169X_8\text{-}0.263X_9\text{-}0.192X_{10}\text{-}0.171X_{11}\text{-}0.343X_{12}+0.238X_{13}\text{-}0.194X_{14}+0.242X_{15}+0.196X_{16}\text{-}0.190X_{17}+0.178X_{18}\text{-}0.409X_{19}\text{-}0.213X_{20}.$$

The regression model statistics was observed (Nagelkerke $R^2 = 0.183$, $\chi^2 = 100.689$, $p < 0.001$).

The ROC curve in Fig. 3 showed a fair accuracy of this model, yielding an AUC of 0.701 (95 % CI, 0.665–0.738). The decision-rule cut-off that optimizes the sensitivity/specificity tradeoff was 0.325. There was no statistical difference between the expected and the observed values for the model via the Hosmer-Lemeshow Goodness-of-Fit Test, in which the calibration was satisfactory ($p > 0.05$). See Table 5.

4. Discussion

This research was carried out based on the PAGT*D, which was primarily tried in China. Some risk factors were found by comparing the groups of responders vs. non-responders in the first step. The average age and age at onset of non-responders were 2.5 years and 2.4 years younger than those of the responders, respectively. This study supported the view that antidepressant treatment might be particularly effective in older patients with MDD [37,38], while Maarsingh OR et al. [39] found early onset of MDD could identify patients at risk of an unfavorable outcome. Earlier onset is associated with greater illness burden across a wide range of indicators [40].

Besides, the number of depressive episodes and untreated episodes before diagnosis provided the same message as age and onset age. Physicians have suggested that patients who have experienced more recurrences are at a greater risk of recurrence, and they can continue to benefit from medication during the first year after recovery [41]. It was investigated that about three-quarters of patients

Table 1
Sociodemographic factors of MDD patients in RA and URA groups.

Variable ($\bar{x} \pm SD$)	Total (n = 987)	Responders (n = 581)	Non-responders (n = 406)	z	p
Sociodemographic factors					
Age (y)	38.86 ± 14.07	40.01 ± 14.08	37.47 ± 13.94	2.975	0.003
Age at onset (y)	35.48 ± 13.74	36.46 ± 13.77	34.07 ± 13.59	2.826	0.005
Education Level (y)	12.20 ± 3.89	12.01 ± 4.03	12.48 ± 3.67	−1.780	0.075
Clinical traits					
Number of hospitalizations	0.30 ± 0.72	0.33 ± 0.68	0.27 ± 0.78	0.677	0.498
Number of depressive episodes	1.99 ± 3.71	2.03 ± 4.29	1.94 ± 2.70	1.998	0.046
Number of untreated episodes before diagnosis	1.17 ± 1.33	1.19 ± 1.56	1.15 ± 0.92	2.623	0.009
Untreated duration (y)	1.87 ± 3.66	2.08 ± 4.20	1.57 ± 2.67	0.629	0.529
Current course of the depressive episodes (y)	0.93 ± 1.83	0.95 ± 1.91	0.89 ± 1.72	1.945	0.052
Total course of depression (y)	3.63 ± 5.85	3.69 ± 5.79	3.55 ± 5.94	0.186	0.852

Table 2
Comparison of psychiatric rating scales between responders and non-responders.

Variable ($\bar{x} \pm SD$)	Responders (n = 581)	Non-responders (n = 406)	z	p
HAMD-17	21.27 ± 4.51	20.85 ± 4.61	1.613	0.107
HAMA-14	18.42 ± 6.48	17.79 ± 5.70	0.825	0.409
QOL-6	15.36 ± 2.73	15.28 ± 2.64	0.344	0.731
DSSS	26.21 ± 9.34	27.11 ± 9.42	−1.811	0.070
QIDS-SR16	19.54 ± 6.06	19.28 ± 5.60	1.058	0.290
VAS	3.68 ± 3.07	3.52 ± 3.13	0.992	0.321

HAMD-17: Hamilton Depression Scale-17 items; HAMA-14: Hamilton Anxiety Rating Scale-14 items; QOL-6: 6-item Life of Quality Questionnaires; DSSS: Depression and Somatic Symptoms Scale; VAS: Visual Analogue Scales; QIDS-SR16: Self-report Version of the Quick Inventory of Depressive Symptoms.

Table 3
Comparison of categorical variables between responders and non-responders.

Variable (n, %)	Responders	Non-responders	χ2	p	OR (95% CL)
Observation period			413.4	<0.001	22.5 (16.1, 31.4)
Discontinuation	94 (16.2%)	330 (81.3%)			
Adherence	487 (83.8%)	76 (18.7%)			
Sex	192 (33.6%)	141 (35.2%)	0.267	0.606	
Male	380 (66.4%)	260 (64.8%)			
Female					
Marital status			5.703	0.017	0.710 (0.535,0.941)
Unmarried	168 (29.9%)	131 (37.5%)			
Married	394 (70.1%)	218 (62.5%)			
Family history of mood disorders			0.172	0.679	
No	511 (89.5%)	318 (90.3%)			
Yes	60 (10.5%)	34 (9.7%)			
Comorbidity			6.131	0.013	1.494 (1.086, 2.054)
No	388 (80.2%)	276 (73.0%)			
Yes	96 (19.8%)	102 (27.0%)			
Depressive episode			0.002	0.963	
First	369 (64.6%)	228 (64.8%)			
Recurrent	202 (35.4%)	124 (35.2%)			
Treatment regimen			2.413	0.120	/
TAU	202 (34.8%)	122 (30.0%)			
AGT	379 (65.2%)	284 (70.0%)			
With anxious distress			4.204	0.040	0.754 (0.575, 0.988)
No	202 (41.6%)	184 (48.5%)			
Yes	284 (58.4%)	195 (51.5%)			
Severity			10.601	0.001	0.607 (0.449, 0.821)
Mild	108 (18.6%)	111 (27.3%)			
Moderate to severe	473 (81.4%)	295 (72.7%)			
Atypical symptom			0.068	0.794	
No	513 (95.4%)	314 (95.7%)			
Yes	25 (4.6%)	14 (4.3%)			
Somatopathy			0.001	0.973	/
No	475 (81.8%)	293 (81.8%)			
Yes	106 (18.2%)	65 (18.2%)			
Seasonal depression			0.760	0.383	/
No	526 (93.6%)	322 (92.3%)			
Yes	35 (6.2%)	27 (7.7%)			
Morning depression			1.273	0.259	/
No	414 (77.4%)	242 (74.0%)			
Yes	121 (22.6%)	85 (26.0%)			
Hospitalization			10.185	0.001	0.563 (0.395,0.804)
No	431 (76.7%)	298 (85.2%)			
Yes	131 (23.3%)	51 (14.7%)			

TAU: treatment as usual; AGT: algorithm guided treatment; OR: odd radio; CL: confidence interval.

discontinued antidepressants during maintenance therapy after 24 weeks [42], while the majority of non-responders discontinued antidepressants during maintenance therapy in clinical practice [12].

There are some factors that can be predicted. For example, patients in married status run less risk of non-response to treatment (OR: 0.710 [95 % CI: 0.535 to 0.941]). More reduced levels of social functioning (unmarried, divorced, or widowed [43,44]) play an adverse role in treatment responding. Emotional loneliness is associated with depressive symptoms [45]. This result also indicates that family support from marriage is vital for a favorable outcome of the disease.

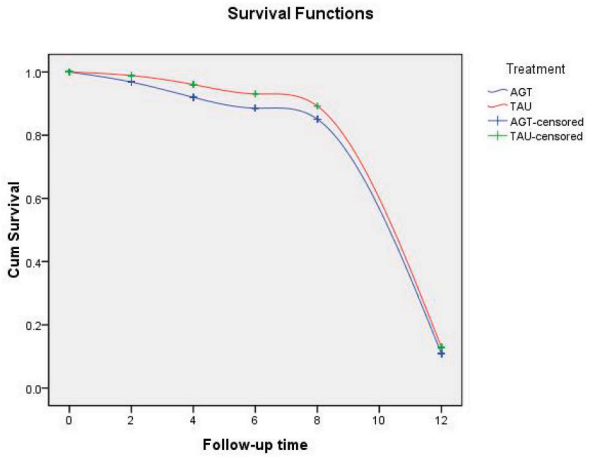

Fig. 2. Kaplan–Meier survival curve focusing on the occurrence and timing of treatment response.

Table 4
Binary logistic regression analysis (backward wald) of factors for predicting responders or non-responders of MDD patients.

Model	β	S.E.	Wald	p	EXP(β)	95 % C.L. for EXP(B)	
						Lower	Upper
Constant	0.310	0.499	0.385	0.535	1.363		
Untreated duration	−0.005	0.002	4.958	0.026	0.995	0.991	0.999
Co-morbidity	0.630	0.205	9.472	0.002	1.878	1.257	2.805
Treatment regimen	0.378	0.181	4.334	0.037	1.459	1.022	2.082
Severity of depressive symptoms	−0.552	0.226	5.954	0.015	0.576	0.370	0.897
HAMD-17-3	0.337	0.110	9.472	0.002	1.401	1.130	1.736
HAMD-17-4	0.295	0.112	6.902	0.009	1.343	1.078	1.674
HAMD-17-14	0.182	0.103	3.108	0.078	1.199	0.980	1.467
HAMD-17-15	−0.169	0.100	2.859	0.091	0.844	0.694	1.027
HAMA-14-8	−0.263	0.098	7.173	0.007	0.768	0.634	0.932
HAMA-14-13	−0.192	0.105	3.362	0.067	0.825	0.672	1.013
HAMA-14-14	−0.171	0.096	3.192	0.074	0.843	0.699	1.017
QOL-6-2	−0.343	0.152	5.083	0.024	0.710	0.527	0.956
DSSS-1	0.238	0.103	5.289	0.021	1.269	1.036	1.554
DSSS-9	−0.194	0.110	3.126	0.077	0.824	0.664	1.021
DSSS-15	0.242	0.109	4.892	0.027	1.273	1.028	1.578
DSSS-16	0.196	0.110	3.156	0.076	1.216	0.980	1.509
QIDS-SR16-2	−0.190	0.091	4.423	0.035	0.827	0.692	0.987
QIDS-SR16-3	0.178	0.083	4.639	0.031	1.195	1.106	1.405
QIDS-SR16-6	−0.409	0.113	13.243	<0.001	0.664	0.533	0.828
QIDS-SR16-10	−0.213	0.111	3.669	0.055	0.808	0.649	1.005

HAMD-17: the Hamilton Depression Scale-17 items; HAMA-14: the Hamilton Anxiety Rating Scale-14 items; QOL-6: the 6-Item Life of Quality Questionnaires; DSSS: the Depression and Somatic Symptoms Scale; QIDS-SR16: the Self-report Version of the Quick Inventory of Depressive Symptoms.

Other interesting findings include that patients with anxious distress (OR: 0.754 [95 % CI: 0.575 to 0.988]) and moderate to severe depressive symptoms (OR: 0.607 [95 % CI: 0.449 to 0.821]) are associated with less URA risks in the MDD-respond group than those in the MDD-non-respond group. There are several reasons we may infer. First, the outcomes of MDD patients were evaluated by the 50 % reduction rate of HAMD total score from baseline, thus patients with a higher baseline score may have a more substantial reduction percent after treatment response [46]. The primary efficacy variable is the change of HAMD from baseline. More score reduction would be reached within patients having higher baseline scores who achieved remission corresponding to HAMD scores $\leq$7. Second, the average scores of HAMD and HAMA in the RA group were higher than those of the URA group (Table 2). Although there is no statistical difference between the two groups, the higher average scores might partially explain these results. Third, due to the severer symptoms of treatment responders, the probability of receiving hospitalization for them is higher (23.3 % vs. 14.7 %).

Discontinuing anti-depressive therapy within three months can be a strong risk factor for URA (OR: 22.5 [95 % CI: 16.1 to 31.4]) and comorbidity is also associated with a higher URA risk (OR: 1.494 [95 % CI: 1.086 to 2.054]). Patients would not give a definite answer at the beginning of the treatment about whether they would adhere to the treatment or not. Therefore, medication adherence and comorbidity should be considered as a factor affecting treatment outcome rather than a potential predictor in the regression model [12]. We recommend that treatment strategies should be based on our results for mitigating symptoms.

Finally, twenty parameters were finally deployed for the predictive algorithms in the regression model, including three clinical

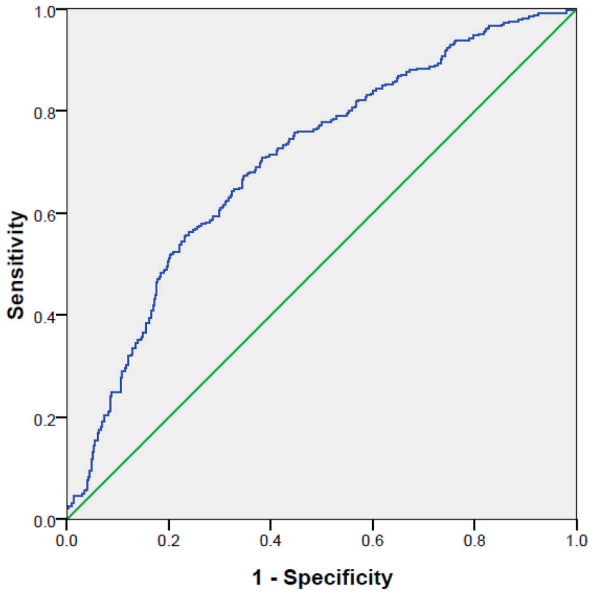

Fig. 3. ROC curve of the logistic regression model for prediction of URA

Table 5
Discrimination and calibration of the recognition algorithms for predicting MDD with or without response.

	Youden index	AUC (95%CI)	Sensitivity	Specificity	Balanced Accuracy	Calibration[a]	
						$\chi 2$	p
Backward Wald	0.325	0.701 (0.665, 0.738)	0.708	0.617	0.663	10.102	0.258

[a] Hosmer-Lemeshow Goodness-of-Fit Test; AUC, the area under the curve.

traits, one treatment regimen, and 16 subscales. The AUC was identified as a fair accuracy for predicting non-responding to the treatment of MDD. The three parameters (untreated duration, comorbidity, and severity of depressive symptoms), which we have discussed above, and the "Treatment regimen" entered the model. This model showed AGT could be a prognostic risk factor, while TAU might be a prognostic protective factor. Namely, TAU based on the experience of doctors is likely to be more efficient than AGT, suggesting that the immediate adjustment of treatment by the doctor's instruction within three months can be more effective than a fixed AGT [47]. Another reason for the limited effect of AGT could be that the later treatment steps in the AGT were rarely utilized because participants who did not receive any benefit have dropped out early [48]. Even if the pharmacological strategies have been proven to be clinically effective, they cannot be used directly without considering individual differences, which may be systematically associated with the responses to antidepressants in MDD beyond placebo effects or statistical factors [49]. Time to symptomatic remission by standard survival analyses was longer in TAU, although without statistically significance.

In addition, we employed six scales, which are widely used in clinical practice, and tried to find the relationship between clinical characteristics and the efficacy of medications. In the remaining 16 subscales after modeling, the interpretation of the "Suicide" factor is limited because we have excluded patients with high risk of suicide attempts (Item 3, "Suicide" score of HAMD-17 $\geq$ 3 points). Then, "Early insomnia" and "Waking up too early" are URA predictors. We observed that patients often regard insomnia symptoms as an assessment of whether they are remitted during the clinic service process. Treating insomnia in patients with depression has a positive effect on mood [50]. Other symptoms of these risk factors tend to be summarized as anxiety characteristics, from which patients are more difficult to recover. Anxiety was associated with an ineffective treatment response in MDD regardless of the treatment type [51, 52] in which insomnia plays an important role. Therefore, it is essential for the prognosis of the disease to formulate an early insomnia-specific intervention to improve depressive and anxious mood [50]. Furthermore, "Headache" was involved. Increasing intensity of headache is associated with comorbidities related to depression, anxiety, and insomnia [53]. Co-morbid and co-occurring conditions in sleep disturbance might increase the risk of intensity and frequency of headache. Many antidepressant agents have anti-anxiety effects, however, we found that "Anxious or nervous" is still a risk factor for URA. Therefore, sleep disturbance and anxiety are prior to treatment targets for MDD with comorbidity. These predictive risk factors should be recognized frequently during clinical interviews.

Among the protective factors, the symptoms tend to have typical depressive characteristics with the absence of comorbid illness [38]. Patients with these protective factors (eight clinical symptoms) are more likely to be cured. It's an important finding that the variable of the "Hypochondriasis" is able to increase the positive treatment response. Although hypochondriasis has low recovery rates (30%–50 %) [54], the related symptoms at baseline can be actually beneficial to treatment responding where treatment compliance

may take effect. It may be the reason for becoming a protective factor although itself is a symptom. Regarding sleep disturbance, on the contrary to "Early insomnia" and "Waking up too early", "Sleep during the night (sleep quality)" is acceptable for patients and does not affect the outcome of treatment for MDD. Everitt H et al. [55]. found a moderate improvement in subjective sleep quality over placebo. A better prediction of prognosis may result from perceived sleep quality. Reduction of anticipatory stress is associated with improved subjective sleep quality on a day-to-day basis, regardless of the severity of insomnia [56]. Other protective factors are closely related to the effectiveness of the antidepressant agents on the above symptoms.

5. Conclusions

At present, many psychiatric rating scales are used clinically. However, comprehensive evaluation for each patient based on scales is far from cost-effectiveness, which cannot be used comprehensively in clinical practice. Baseline characteristics allow prediction of non-response, which could be sufficiently certain for physicians to identify patients with prolonged exposure to ineffective treatment, thereby personalizing depression management as well as saving time, cost, and medical resources [18]. Therefore, the 16 subscales we extracted from the six commonly used scales would greatly save valuable time for clinicians. We found that the baseline scores of these encoded items: Suicide, Early insomnia, Genital symptoms, Mental state in the last month (reverse scoring of severity), Headache, Shortness of breath or difficulty breathing, Anxious or nervous, and Waking up too early contributed to non-responding to treatment, while Hypochondriasis, Somatic (sensory), Autonomic symptoms, Behavior at interview, Dizziness, Sleep during the night, Decreased appetite and Concentration/decision-making are protective factors of treatment responding. A fairly accurate model was constructed for the prognosis by assessing the 3-months treatment. Under the consideration of the unfavorable prognostic factors, combination drug therapy, physical therapy, or psychological therapy could be considered able to improve the outcome of MDD patients by increasing the clarification and elucidation of different symptom clusters to them. Measurement-based care is defined as the clinical practice where physicians collect patient data through validated outcome scales and use the results to guide their decision-making processes [57] may increase chances of achieving remission of MDD. Benefits on treatment response to AGT were not found in our study, indicating a one-size-fits-all approach may not work.

6. Limitations

There were several main limitations of the cohort study. First, the relatively high drop-out rates were observed, especially in the AGT group (42.8 % of AGT and 37.7 % of TAU at week 12). The strict-guided strategy may be responsible for the high drop-outs in the AGT that required patients to stick to at least six weeks of the initial intervention [58]. Although a statistical method was conducted for missing value inputation, loss to follow-up bias cannot be ruled out. Second, misdiagnosis rate of depressive episode (unipolar or bipolar) still existed even after we excluded the patients with BD (n = 198). The misdiagnosis and BD-conversion will increase with observation time [59]. Third, the AUC of 0.701 which is defined as a balanced statistics, presents the authenticity of the detection method. The discrimination accuracy of the model was examined by using the AUC of the ROC curve and was categorized as fair (0.70–0.80), almost poor (0.60–0.70), indicating the limited use in clinical practice. Further researches are required to validate our results and explore the predictors or moderators with a long follow-up period, adjusted parameters, and quality control of drop-outs.

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Data availability statement

Data will be made available on request.

CRediT authorship contribution statement

Yuncheng Zhu: Writing – review & editing, Writing – original draft, Investigation. **Yuncheng Zhu:** Performed the experiments and wrote the paper. **Fang Wang:** Analyzed and interpreted the data , and wrote the paper. **Fan Wang:** Performed the experiments. **Hongmei Liu:** Performed the experiments. **Xiaoyun Guo:** Performed the experiments. **Zuowei Wang:** Performed the experiments. **Ruoqiao He:** contributed reagents, materials, analysis tools or data. **Xiaohui Wu:** Performed the experiments. **Lan Cao:** Performed the experiments. **Zhiguo Wu:** Performed the experiments. **Daihui Peng:** conceived and designed the experiments. **Yiru Fang:** Conceived and designed the experiments.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e20951.

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