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ORIGINAL RESEARCH

Predictors of Changes in Depressive Symptoms with Major Depressive Disorder - A Naturalistic 6-month Follow-up Study

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Purpose: There are limited reports, particularly in naturalistic settings, regarding predictors of clinical outcomes in patients with major depressive disorder (MDD). The objective of this observational, retrospective study is to describe 6-month clinical outcomes and identify their predictors among patients with MDD in Japan.

Patients and methods: A total of 546 patients diagnosed with MDD at their first visit were enrolled in this naturalistic follow-up study, of whom 217 completed follow-up assessments at six months. Depressive symptoms were measured using the Japanese Quick Inventory of Depressive Symptomatology (QIDS-J). Potential predictors, including demographic characteristics, personality traits (assessed using the Ten Item Personality Inventory-Japanese version [TIPI-J]), and psychotic symptoms (measured by the PRIME Screen-Revised [PS-R]), were analyzed.

Results: Among the 217 follow-up completers, 38% achieved response, and 20% reached remission. Persistent symptoms, particularly mid-nocturnal insomnia, remained prevalent at follow-up. Higher baseline depressive severity, presence of view of myself symptom, endorsement of suspiciousness/persecutory ideas, and lower educational attainment were consistently associated with greater depressive symptom severity at six months. Additionally, a robust association was observed between openness to experience and remission, while absence of view of myself symptom and endorsement of first-rank symptoms consistently predicted remission.

Conclusion: This study identified significant predictors of clinical outcomes in MDD patients over a 6-month period. These findings underscore the importance of considering baseline symptoms, personality traits, and psychosocial factors in predicting MDD outcomes, informing more tailored treatment strategies in real-world clinical practice.

Keywords: major depressive disorder, predictive factor, remission, response, naturalistic setting

Introduction

Depression is a serious mood disorder characterized by a heterogeneous symptomatology affecting emotional, physical, cognitive, and social functions.[1] Although it often emerges during early adulthood, its prevalence remains substantial throughout all stages of life.[2] In Japan, the lifetime prevalence of major depressive disorders (MDD) is estimated at 6%, with a 12-month prevalence of 3%, imposing a substantial public health burden.[3]

To date, efficacy studies with randomized controlled trials (RCTs) have published glowing results of MDD course treated with antidepressant.[4] However, in observational studies, antidepressants have not demonstrated the same effectiveness as in RCTs,[5] and MDD often persists over time.[6–8] In clinical practice, the course of MDD is often protracted, with complete recovery not always achieved. Evidence suggests that 12% of patients remain symptomatic for up to five years, highlighting the disorder's chronic nature.[6] A study conducted in primary care settings over a 39-month period found that only 43% of patients attained remission, while 17% developed chronic depression and 40% experienced a fluctuating symptom trajectory.[7] Furthermore, longitudinal data indicate that 37% of individuals diagnosed with MDD continue to experience persistent depressive symptoms even a decade later, underscoring the long-term burden of the

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illness.[8] Even in controlled research settings, up to 90% of patients who achieve remission exhibit residual symptoms, emphasizing the complexity of attaining full recovery.[9]

A key limitation of RCTs is their strict inclusion criteria, which often exclude individuals with high suicide risk, psychiatric comorbidities, or significant physical health conditions.[10,11] However, in real-world clinical settings, patients with MDD frequently present with these complexities, raising concerns about the generalizability of RCT findings. While naturalistic studies have been conducted to bridge this gap,[12] Japan lacks sufficient longitudinal research on the clinical course of MDD within such a framework.[13,14]

The present study aims to characterize the clinical course of patients with MDD over a six-month treatment period in Japan. Additionally, we seek to identify predictors of treatment outcomes in a naturalistic setting. By addressing these objectives, we hope to generate insights that will enhance clinical decision-making and contribute to improved patient care.

Methods

Design and Participants

This study utilized a naturalistic six-month follow-up design to investigate the clinical course of patients with MDD in a real-world treatment setting. Baseline assessments were conducted at the patients' initial visit, with a follow-up evaluation scheduled six months later. Participants included individuals diagnosed with MDD according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) between June 2019 and December 2023 at the Psychiatry Department of Dokkyo Medical University Hospital. A total of 615 patients met the initial diagnostic criteria. Among them, three individuals were excluded for being under the age of 16, and an additional 34 were excluded because they did not complete the baseline assessment, which included a self-report questionnaire. Of the 578 patients, 546 met the threshold for depressive symptoms (total score of 5 or lower) as determined by the Japanese Quick Inventory of Depressive Symptomatology (QIDS-J).[15,16] At the six-month follow-up, 217 participants completed the second evaluation (Figure 1). Patient data for individuals diagnosed with MDD were obtained from the Assessment for Identifying Subjective Symptoms in the Dokkyo Medical University Hospital Psychiatric Service Use (AID-P) database,[17–20] which consecutively registers information on all patients at the department. The timing of follow-up assessments was independent of treatment milestones, as the study was designed to capture naturalistic clinical outcomes. No specific pharmacological or psychotherapeutic interventions were mandated during the follow-up period. All treatments were determined by the attending physicians as part of routine clinical care, reflecting the naturalistic design of the study. Although 217 patients completed the 6-month follow-up, the remaining participants were lost due to clinical discontinuation of visits. Given the naturalistic design of this study and practical constraints, no direct contact was made with those who discontinued treatment, and thus detailed reasons for attrition could not be ascertained.

Depressive Symptoms

Depressive symptoms were assessed using the QIDS-J, a 16-item self-report questionnaire in which each item corresponds to a specific symptom. Each item is rated on a 4-point Likert scale (0 to 3), with symptom presence determined by a score of 2 or higher, as based on previous studies.[19–21] The QIDS-J evaluates symptoms across nine distinct domains that constitute the criteria for DSM-5 diagnosis of a MDD.[15,16] Among the nine domains, sleep (items 1–4), appetite/weight change (items 6–9), and psychomotor activity (items 15 and 16) are assessed using multiple items, with the highest score within each domain determining the final domain score. The remaining six domains-feeling sad, concentration/decision making, view of myself (guilty feelings), thoughts of death or suicide, general interest, and energy level-are evaluated using a single item each. The maximum possible total score, summing across the nine domains, is 27, with a score of 6 or higher indicating the presence of depression. Treatment response was characterized as a reduction of ≥50% in QIDS-J scores, while remission was defined as a total score of 5 or lower.

Treatment-emergent symptoms were defined as depressive symptoms that were absent at baseline (QIDS-J score < 2 on the corresponding item) and newly met the threshold (score ≥ 2) at the six-month follow-up.

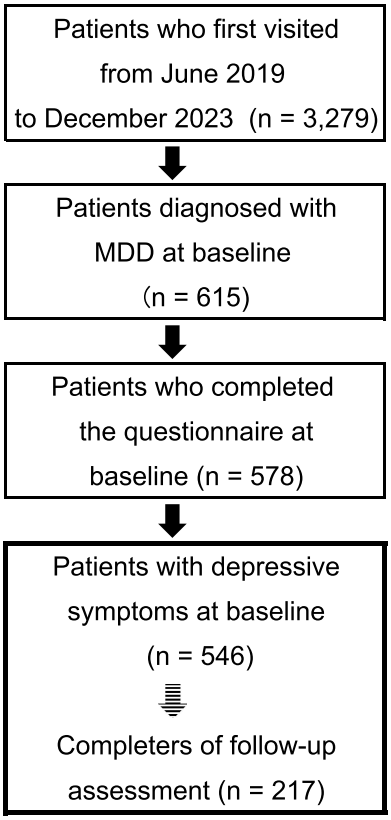

Figure 1 Flow chart of study sample selection.
Abbreviation: MDD, major depressive disorder.

Personality Traits

Personality traits were evaluated using the Ten-Item Personality Inventory (TIPI), a widely used tool assessing the Big Five personality dimensions: extraversion, agreeableness, conscientiousness, emotional stability, and openness to experience.[22] Each trait was assessed through two items rated on a 7-point Likert scale, with final trait scores calculated as the average of the two corresponding items, yielding a range from 1 to 7, where higher scores indicate stronger expression of that trait. In the Japanese version (TIPI-J), "emotional stability" was translated as "neuroticism" (shin-keisho keiko), with higher scores reflecting greater neuroticism (ie, lower emotional stability).[23] The reliability and validity of TIPI-J have been previously established.

Psychotic Symptoms

Psychotic symptoms experienced over the past year were self-reported using the Japanese version of the PRIME Screen-Revised (PS-R), a validated tool designed to assess attenuated positive symptoms.[24] The Japanese version consists of 11 items, as the 12th item from the original PS-R was excluded due to its lack of relevance to attenuated positive symptoms. Specifically, the 12th item ("I have been concerned that I might be 'going crazy') was intended to capture loss of insight rather than the presence of a specific psychotic experience. Unlike the other items, it was not directly derived from the Structured Interview for Prodromal Syndromes (SIPS) positive symptom criteria, and thus was removed to maintain consistency in evaluating attenuated positive symptoms. These 11 items evaluate six distinct categories of psychotic symptoms: perplexity and delusional mood (items 1 and 5), first-rank symptoms (items 3, 6, and 11), overvalued beliefs (items 2 and 4), suspiciousness/persecutory ideas (item 7), grandiose ideas (item 8), and perceptual abnormalities (items 9 and 10). Each item is rated on a 7-point Likert scale (0 = definitely disagree to 6 = definitely agree). Based on prior research, endorsement of a psychotic symptom was defined as a score of 5 (somewhat agree) or 6 (definitely agree). A symptom category was considered positive if at least one item within that category met this threshold.[25]

Statistical Analyses

Descriptive statistics were used to summarize the demographic and clinical characteristics of participants. Independent-sample t-tests were performed to compare continuous variables, while chi-square or McNemar tests were used for categorical variables. Data are reported as means ± standard deviations (SD) or percentages, as appropriate.

Given the substantial attrition over the study period, inverse probability weighting (IPW) was applied to mitigate potential selection bias. Propensity scores-representing the probability of completing the follow-up assessment-were estimated using logistic regression.[26,27] Baseline predictors included age, sex, education level, TIPI-J subscale scores, QIDS-J symptom presence, total QIDS-J score, and PS-R symptom endorsements. IPW adjustments were implemented to align clinical outcome distributions with the expected population characteristics.

To identify predictors of depressive symptoms at the six-month follow-up, a multivariable linear regression model incorporating IPW was employed. A forward selection method was used to include explanatory variables such as age, sex, education level, TIPI-J subscale scores, QIDS-J symptom presence, total QIDS-J score, and PS-R symptom endorsements. Additionally, a multivariate logistic regression model with IPW and forward likelihood ratio selection was applied to estimate adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for predicting remission at six months. In this model, variables were entered at $p < 0.05$ and removed at $p > 0.10$. The same baseline explanatory variables were included in both regression models. Statistical significance was set at $p < 0.05$. All analyses were conducted using SPSS for Windows, version 24 (IBM Corp., Armonk, NY, USA).

There were no adjustments for multiple comparisons to avoid making a priori assumptions about group differences. We did not want to strongly control the rate of false positive findings at the expense of false negatives.[28] The results should be considered exploratory findings.

Ethical Considerations

The Ethics Committee of Dokkyo Medical University School of Medicine reviewed and approved the study protocol (Approval No. R-85-4J). Informed consent was obtained using an opt-out method, allowing potential participants to decline participation by accessing the Department of Psychiatry's website at Dokkyo Medical University School of Medicine. This method was deemed ethically appropriate for a minimal-risk study involving standard clinical procedures. All procedures in this study adhered to the ethical principles outlined in the Declaration of Helsinki and complied with the Japanese Ethical Guidelines for Medical and Health Research Involving Human Subjects.

Results

Demographic and Clinical Characteristics

Comparisons between completers and non-completers revealed that those who discontinued participation exhibited significantly higher openness to experience and were more likely to present increased appetite. In contrast, completers more frequently reported symptoms related to energy levels symptom. No other significant demographic or clinical differences were observed between the two groups (Table 1).

Across the 16 items assessed in the QIDS-J, most depressive symptoms showed improvement over time, with the exception of mid-nocturnal insomnia, hypersomnia, and increased appetite, which persisted (Table 2). Notably, mid-nocturnal insomnia was frequently reported persistent symptom, followed by view of myself symptom and sleep-onset insomnia. Additionally, new symptoms emerged over the course of treatment, with increased weight being frequently reported, followed by increased appetite (Table 2). In the unweighted analysis presented in Table S1, similar trends were observed; however, significant improvement was not detected for mid-nocturnal insomnia and hypersomnia only. The proportions of symptoms that persisted from baseline and those newly emerged during follow-up were comparable between the weighted and unweighted analyses.

Predictors of Depressive Symptoms and Remission Among Follow-Up Completers

After adjusting for inverse probability weighting (IPW), several factors emerged as significant predictors of depressive symptom severity at follow-up. Higher educational attainment (associate degree or above), extraversion, and decreased

Table 1 Demographic and Clinical Characteristics of First-Visit Patients According to completion of Follow-Up Assessment

	Follow-Up Assessment		p value[a]	All Patients
	Completers	Non Completers		
	n = 217	n = 329		n = 546
Age	46.7 ±18.5	49.8 ±20.7	0.068	48.6 ±19.9
Male sex	40.1 (87/217)	32.2 (106/329)	0.060	35.3 (193/546)
Educational attainment				
Junior high school graduate	6.9 (15/217)	12.5 (41/329)	0.086	10.3 (56/546)
High school graduate	48.8 (106/217)	51.1 (168/329)		50.2 (274/546)
Associate Degree or higher	29.0 (63/217)	22.2 (73/329)		24.9 (136/546)
Missing data	15.2 (33/217)	14.3 (47/329)		14.7 (80/546)
TIPI-J scores				
Extraversion	3.6 ±1.5	3.8 ±1.5	0.295	3.7 ±1.5
Agreeableness	5.2 ±1.0	5.1 ±1.2	0.168	5.2 ±1.1
Conscientiousness	4.1 ±1.4	4.1 ±1.5	0.928	4.1 ±1.4
Neuroticism	5.0 ±1.2	5.1 ±1.3	0.672	5.1 ±1.2
Openness to experience	3.5 ±1.3	3.7 ±1.3	0.027	3.6 ±1.3
QIDS-J presence of each symptom item				
Sleep onset insomnia	62.2 (135/217)	64.4 (212/329)	0.597	63.6 (347/546)
Mid-Nocturnal insomnia	62.7 (136/217)	63.5 (209/329)	0.840	63.2 (345/546)
Early morning insomnia	51.2 (111/217)	58.1 (191/329)	0.112	55.3 (302/546)
Hypersomnia	15.2 (33/217)	17.0 (56/329)	0.574	16.3 (89/546)
Feeling sad	52.5 (114/217)	58.1 (191/329)	0.204	55.9 (305/546)
Decreased appetite	40.6 (88/217)	42.6 (140/329)	0.643	41.8 (228/546)
Increased appetite	9.7 (21/217)	16.4 (54/329)	0.025	13.7 (75/546)
Decreased weight	35.0 (76/217)	38.0 (125/329)	0.481	36.8 (201/546)
Increased weight	10.1 (22/217)	12.2 (40/329)	0.467	11.4 (62/546)
Concentration/decision making	51.6 (112/217)	50.5 (166/329)	0.791	50.9 (278/546)
View of myself	66.8 (145/217)	66.6 (219/329)	0.951	66.7 (364/546)
Thoughts of death or suicide	35.5 (77/217)	38.9 (128/329)	0.419	37.5 (205/546)
General Interest	65.9 (143/217)	63.5 (209/329)	0.571	64.5 (352/546)
Energy Level	72.4 (157/217)	62.6 (206/329)	0.018	66.5 (363/546)
Feeling slowed down	35.0 (76/217)	39.5 (130/329)	0.289	37.7 (206/546)
Feeling restless	22.6 (49/217)	19.1 (63/329)	0.331	20.5 (112/546)
QIDS-J total scores	16.2 ±4.4	16.2 ±4.8	0.885	16.2 ±4.6

(*Continued*)

Table 1 (Continued).

	Follow-Up Assessment		p value[a]	All Patients
	Completers	Non Completers		
	n = 217	n = 329		n = 546
PS-R endorsement of each category				
Perplexity and delusional mood	13.8 (30/217)	13.4 (44/329)	0.880	13.6 (74/546)
First-rank symptoms	14.3 (31/217)	17.6 (58/329)	0.301	16.3 (89/546)
Overvalued beliefs	5.1 (11/217)	4.3 (14/329)	0.656	4.6 (25/546)
Suspiciousness/persecutory ideas	8.3 (91/217)	6.1 (102/329)	0.319	7.0 (42/546)
Grandiose ideas	0.9 (2/217)	0.6 (2/329)	0.674	0.7 (4/546)
Perceptual abnormalities	6.5 (14/217)	8.6 (28/329)	0.377	7.7 (42/546)

Notes: [a]Continuous variables were analyzed with an unpaired *t*-test and categorical variables with a chi-square test.
Abbreviations: TIPI-J, Japanese version of the Ten Item Personality Inventory; QIDS-J, Quick Inventory of Depressive Symptomatology Japanese version; PS-R, PRIME Screen-Revised.

Table 2 Proportion of at Least Moderate Levels of Symptom with Weighting (n = 217)

	Baseline Assessment	6-Month Assessment	p value[a]	Proportion of Persistent Symptoms from Baseline	Proportion of Newly Emergent Symptoms At 6-Month Assessment
QIDS-J presence of each symptom item					
Sleep onset insomnia	64.5%(140/217)	31.3%(68/217)	<0.001	41.4%(58/140)	14.7%(10/68)
Mid-Nocturnal insomnia	62.7%(136/217)	56.2%(122/217)	0.180	60.3%(82/136)	32.8%(40/122)
Early morning insomnia	56.7%(123/217)	29.5%(64/217)	<0.001	39.0%(48/123)	25.0%(16/64)
Hypersomnia	15.3%(33/216)	9.7%(21/216)	0.058	30.3%(10/33)	52.4%(11/21)
Feeling sad	53.7%(116/216)	18.5%(40/216)	<0.001	25.9%(30/116)	25.0%(10/40)
Decreased appetite	43.3%(94/217)	12.9%(28/217)	<0.001	23.4%(22/94)	21.4%(6/28)
Increased appetite	13.4%(29/217)	17.5%(38/217)	0.272	24.1%(7/29)	81.6%(31/38)
Decreased weight	37.0%(80/216)	11.1%(24/216)	<0.001	10.0%(8/80)	66.7%(16/24)
Increased weight	12.0%(26/217)	19.8%(43/217)	0.040	15.4%(4/26)	90.7%(39/43)
Concentration/decision making	50.0%(108/216)	17.1%(37/216)	<0.001	24.1%(26/108)	29.7%(11/37)
View of myself	64.4%(139/216)	37.5%(81/216)	<0.001	48.9%(68/139)	16.0%(13/81)
Thoughts of death or suicide	37.0%(80/216)	16.2%(35/216)	<0.001	28.7%(23/80)	34.3%(12/35)
General Interest	64.5%(140/217)	28.1%(61/217)	<0.001	35.7%(50/140)	18.0%(11/61)
Energy Level	63.9%(138/216)	32.9%(71/216)	<0.001	37.0%(51/138)	28.2%(20/71)
Feeling slowed down	37.3%(81/217)	16.6%(36/217)	<0.001	25.9%(21/81)	41.7%(15/36)
Feeling restless	20.3%(44/217)	4.1%(9/217)	<0.001	11.4%(5/44)	44.4%(4/9)

(*Continued*)

Table 2 (Continued).

	Baseline Assessment	6-Month Assessment	p value[a]	Proportion of Persistent Symptoms from Baseline	Proportion of Newly Emergent Symptoms At 6-Month Assessment
Total scores	16.1 ±4.3	9.9 ±5.2	<0.001		
Responder ≥ 50%		37.8%(82/217)			
Remitter ≤ 5		19.5%(42/217)			

Notes: Associations between baseline clinical features and remission status at 6-month follow-up, analyzed using inverse probability weighting (IPW). Although the overall sample consisted of 217 participants, some variables have slightly different denominators (eg, n = 216 for certain QIDS items) due to missing values and the reweighting process inherent in IPW estimation. These small discrepancies reflect the weighted contribution of each case to the model rather than actual case-wise exclusion. a: Continuous variables were analyzed with an paired *t*-test and categorical variables with McNemar test.
Abbreviation: QIDS-J, Quick Inventory of Depressive Symptomatology Japanese version.

appetite at baseline were associated with lower depressive severity. Conversely, presence of view of myself symptom, a higher baseline QIDS-J total score, and endorsement of suspiciousness/persecutory ideas were significantly linked to greater symptom severity (Table 3). Notably, when IPW adjustments were omitted, the associations with extraversion and presence decreased appetite were no longer significant (Table S2).

Regarding remission predictors, openness to experience was positively associated with achieving remission, while baseline absence of hypersomnia, view of myself symptom, and endorsement of first-rank symptoms were significantly associated with remission (Table 4). However, without IPW adjustments, presence of hypersomnia was not a significant predictor of remission (Table S3).

Discussion

This study examined the clinical course of MDD patients receiving treatment in a naturalistic clinical setting in Japan. Among the 546 patients assessed at baseline, 217 completed follow-up evaluations, with 38% achieving treatment response and 20% attaining remission. Notably, more than half of the patients with mid-nocturnal insomnia at baseline continued to experience this symptom at six months. Several baseline factors, including higher educational attainment, elevated QIDS-J total scores, view of myself symptom, and suspiciousness/persecutory ideas, were associated with greater depressive severity at follow-up. Additionally, absence of view of myself and first-rank symptoms were

Table 3 Predictors of Depressive Symptoms Among Follow-up Completers with Weighting (n = 217)

	B	SE	Beta	t value	p value
Educational attainment					
Associate Degree or higher	−2.04	0.76	−0.17	−2.68	0.008
TIPI-J scores					
Extraversion	−0.57	0.21	−0.17	−2.70	0.007
QIDS-J presence of each symptom item					
Decreased appetite	−1.55	0.71	−0.15	−2.17	0.031
View of myself	1.61	0.76	0.15	2.12	0.035
QIDS-J total scores	0.32	0.09	0.27	3.67	0.000
PS-R endorsement of each category					
Suspiciousness/persecutory ideas	4.47	1.29	0.22	3.48	0.001

Abbreviations: TIPI-J, Japanese version of the Ten Item Personality Inventory; QIDS-J, Quick Inventory of Depressive Symptomatology Japanese version; PS-R, PRIME Screen-Revised.

Table 4 Predictors of Remission Among Follow-up Completers with Weighting (n = 217)

	Odds Ratio	95% confidence Interval			Wald Value	p value
TIPI-J scores						
Openness to experience	1.40	1.03	-	1.90	4.64	0.031
QIDS-J presence of each symptom item						
Hypersomnia	0.18	0.04	-	0.90	4.39	0.036
View of myself	0.46	0.23	-	0.95	4.44	0.035
PS-R endorsement of each category						
First-rank symptoms	0.20	0.05	-	0.85	4.77	0.029

Abbreviations: TIPI-J, Japanese version of the Ten Item Personality Inventory; QIDS-J, Quick Inventory of Depressive Symptomatology Japanese version; PS-R, PRIME Screen-Revised.

significant predictors of remission, while higher openness to experience emerged as a protective factor for achieving remission.

Achieving remission or full recovery is the ultimate goal of depression treatment. However, many patients continue to experience depressive symptoms despite intervention.[7] In this study, 62% of patients failed to achieve a 50% reduction in depressive symptoms, highlighting the chronic and often treatment-resistant nature of MDD. Mid-nocturnal insomnia was particularly persistent, affecting more than half of the individuals who reported it at baseline. This finding aligns with previous research identifying insomnia as one of the most common residual symptoms of depression.[29,30] Given its association with impaired social functioning and poorer overall treatment outcomes,[31] addressing residual insomnia should be a clinical priority. While both pharmacological (eg, gabapentin) and non-pharmacological interventions have been proposed, current evidence remains insufficient, underscoring the need for further research.[29]

Interestingly, 32.8% of patients who exhibited mid-nocturnal insomnia at follow-up developed this symptom after initiating treatment. This subset may require distinct consideration, as emergent insomnia could reflect an adverse effect of antidepressant medication rather than a continuation of preexisting symptoms.[32,33] Consequently, clinical management should involve a careful evaluation of medication side effects and potential treatment modifications. In particular, persistent mid-nocturnal insomnia may signal an incomplete therapeutic response and warrants interventions such as cognitive-behavioral therapy for insomnia or the adjustment of pharmacologic regimens. Additionally, new symptoms such as increased weight and appetite were frequently reported, which may indicate either antidepressant-induced metabolic effects or shifts in the underlying symptomatology of depression.[34] Given the overlap between somatic symptom emergence and pharmacologic side effects, individualized monitoring is crucial to distinguish transient drug reactions from meaningful symptom evolution. Differentiating between medication-related adverse effects and meaningful clinical symptom evolution is essential for optimizing treatment strategies.

Hypersomnia present at baseline emerged as a predictor of non-remission in the follow-up study, emphasizing its potential role as an early clinical indicator of a more persistent depressive course. Notably, hypersomnia also developed after treatment initiation in a considerable number of patients, suggesting that both preexisting and treatment-emergent hypersomnia may converge into residual symptoms that hinder full remission. This pattern raises the possibility of undiagnosed bipolar disorder, as hypersomnia is more prevalent in bipolar depression.[35] Additionally, comorbid conditions such as obstructive sleep apnea may contribute to the persistence of hypersomnia, underscoring the need for comprehensive sleep evaluations in patients with poor treatment response.

Patients with higher levels of education experienced less severe depressive symptoms at follow-up, aligning with prior studies indicating that greater educational attainment may contribute to increased self-awareness of their symptoms or greater cognitive flexibility.[36,37] This underscores the significant influence of educational background on depression management, highlighting its potential role in shaping treatment responses. Given these findings, it might be necessary to investigate whether interventions specifically designed to accommodate lower levels of educational attainment could optimize therapeutic effectiveness.

Among the depressive symptoms assessed, absence of view of myself (guilty feelings) symptom emerged as a key predictor of both lesser symptom severity and remission. Maladaptive guilt has been strongly associated with prolonged depressive episodes and suicidality,[38,39] emphasizing the need for targeted interventions to address this symptom. Similarly, suspiciousness and persecutory ideas were linked to more severe depressive symptoms, potentially due to heightened stress sensitivity and cognitive distortions that impair social functioning.[40] Absence of first-rank symptoms, which are closely linked to psychotic depression, emerged as a strong predictor of remission. This aligns with existing literature suggesting that psychotic features in MDD are associated with greater illness severity and poorer treatment response.[41] These findings underscore the importance of personalized treatment approaches, particularly for patients exhibiting psychotic symptoms.

In contrast to the factors associated with persistent depression, openness to experience was a significant predictor of remission. This suggests that cognitive flexibility and receptivity to novel experiences may promote resilience and adaptive coping strategies. Prior research has demonstrated that openness is linked to greater psychological flexibility and improved coping mechanisms.[42] These findings highlight the potential therapeutic benefits of interventions aimed at enhancing cognitive flexibility, such as cognitive therapy (CBT), in fostering remission in MDD patients. Furthermore, openness may contribute to remission not only through cognitive mechanisms but also via improved treatment adherence. For instance, individuals with lower openness scores have been found to be significantly more likely to show nonadherence to prescribed medication regimens, suggesting that openness influences behavioral engagement with treatment protocols.[43] This reinforces the relevance of openness as a multidimensional factor affecting both psychological and behavioral pathways toward recovery.

Limitation

Several limitations should be acknowledged. First, this study was conducted in a single university hospital in Japan, which may limit the generalizability of the findings. Patients seeking care at specialized institutions often present with more severe illness, which may not reflect broader clinical populations. Second, more than half of the participants were lost to follow-up. Although IPW adjustments were applied to mitigate potential bias, we were unable to obtain detailed reasons for dropout because patients who discontinued visits were not contacted for ethical and practical reasons. Therefore, unmeasured factors such as treatment satisfaction, adherence, symptom improvement, or socioeconomic issues might have contributed to loss to follow-up, raising the possibility of selection bias. Similar to the first point regarding site-specific limitations, caution is warranted when considering the applicability of these findings to broader clinical settings. Patients who remained in the study may differ systematically from those lost to follow-up in ways not fully captured by observed covariates. To enhance external validity, future research should employ multicenter designs with higher retention rates and more diverse patient populations. Third, important clinical variables, including illness duration, duration of untreated depression, adverse childhood experiences, socioeconomic status, and comorbid physical conditions, were not assessed, introducing potential residual confounding. These unmeasured variables are known to influence both the severity and treatment response of major depressive disorder, and their omission may have limited the accuracy of the predictive models. For instance, prior trauma and socioeconomic adversity are associated with greater chronicity and poorer outcomes in MDD, while comorbid conditions such as anxiety disorders or medical illnesses may interact with depressive symptoms and complicate recovery trajectories. Future studies should incorporate these variables to more comprehensively evaluate their contribution to MDD outcomes and strengthen the validity of predictive findings. Forth, the follow-up duration of six months may be insufficient to fully capture the chronic and fluctuating nature of MDD. Prior longitudinal research has indicated that MDD often follows a protracted course, with many patients remaining symptomatic over several years. Future studies should aim for extended follow-up periods and adopt multicenter designs to enhance the generalizability and robustness of predictive models. Finally, the naturalistic study design precluded analysis of specific treatment regimens, limiting our ability to evaluate the impact of pharmacological interventions on symptom trajectories.

Conclusion

This six-month naturalistic study of MDD patients in Japan highlights the complexity of depressive symptom course in routine clinical practice. Despite limitations such as high attrition and the absence of detailed treatment regimen data, this study provides valuable insights into MDD's real-world course in Japan. While some patients demonstrated symptom improvement, a substantial proportion remained symptomatic, particularly with persistent mid-nocturnal insomnia. Given its association with poor functional outcomes and treatment resistance, targeted interventions for sleep disturbances-such as behavioral therapies or adjunctive pharmacological strategies-should be considered as part of comprehensive depression management. Psychological factors such as guilty feelings and psychotic symptoms were key predictors in sustaining depressive symptoms, whereas openness to experience emerged as a potential protective factor for remission. Additionally, higher educational attainment was associated with less depressive severity, underscoring the need for research on targeted interventions based on educational background. Future research should include larger, multicenter cohorts to refine predictive models and optimize personalized treatment strategies for MDD.

Abbreviations

MDD, major depressive disorder; QIDS-J, the Japanese Quick Inventory of Depressive Symptomatology; TIPI-J, Ten Item Personality Inventory-Japanese version; PS-R, the PRIME Screen-Revised; RCT, randomized controlled trial; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; SD, standard deviation; IPW, inverse probability weighting; OR, odds ratios; CI, confidence interval.

Data Sharing Statement

The institutional review board of Dokkyo Medical University School of Medicine has restricted data sharing because the data contain potentially identifying or sensitive patient information. Please contact the institutional review board of Dokkyo Medical University School of Medicine with data requests. Upon request, the board will decide whether to share the data.

Ethics Approval Statement

The ethics committee of Dokkyo Medical University School of Medicine approved the protocol of this study.

Patient Consent Statement

Informed consent was obtained in the form of an opt-out option on the website of the Department of Psychiatry, Dokkyo Medical University School of Medicine.

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Author Contributions

All authors made a significant contribution to the work reported, whether in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflicts of interest in this work.

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