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Prevalence and profile of depressive mixed state in patients with autism spectrum disorder

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ABSTRACT

Purpose: The present study aimed to clarify prevalence and profile of depressive mixed state (DMX) in depressed individuals with autism spectrum disorder (ASD).

Patients and methods: The Quick Inventory of Depressive Symptomatology Self-Report Japanese version (QIDS-SR-J) and global assessment of functioning (GAF) were administered to 182 consecutive patients (36 ASD and 146 non-ASD subjects) with a major depressive episode (MDE). DMX was categorically diagnosed according to the criteria for mixed depression (MD) by Benazzi and mixed features (MF) specifier by DSM-5. Severity of DMX was assessed by the self-administered 12-item questionnaire for DMX (DMX-12). Clinical backgrounds and incidence/severity of DMX were compared between the ASD and non-ASD groups.

Results: ASD patients showed higher prevalence of MD than non-ASD patients (36.1% versus 18.5%). Mood lability, distractibility, impulsivity, aggression, irritability, dysphoria and risk-taking behavior as mixed symptoms were more prevalent in ASD patients than those in non-ASD patients, together with higher scores of total DMX-12 and its disruptive emotion/behavior cluster. Multiple regression analysis revealed significant contribution of ASD to the disruptive emotion/behavior symptoms.

Conclusion: Careful monitoring and management of potential DMX are warranted in depressed ASD individuals.

1. Introduction

Depressive mixed state (DMX) during a major depressive episode (MDE) can often be overlooked as depressed patients rarely state their inner instability as their spontaneous expression(Kondo et al., 2016). In fact, the prevalence of DMX during MDE appears to be low (3.2-7.5%) (Perugi et al., 2015; Takeshima and Oka, 2015) when relatively strict criteria for mixed features (MF) specifier by DSM-5 (American Psychiatric Association, 2013) are applied to mixed psychopathology. On the other hand, Benazzi's definition of mixed depression (MD), including distractibility, irritability and agitation as nonspecific but frequent mixed symptoms (Benazzi, 2008a, 2007, 2002), seems to cover the broader concept of clinically relevant DMX. The prevalence of MD ranged from 12.8% to 32.3% even in patients with major depressive disorder (Benazzi, 2008b; Takeshima and Oka, 2015). Accordingly, the prevalence of DMX widely varies depending on categorical diagnoses used in different studies. Thus, we have recently developed a self-administered 12-item questionnaire for DMX (DMX-12) as a dimensional assessment tool for severity of DMX (Shinzato et al., 2019).

We also conducted a confirmative study for construct validity of the DMX-12 (Shinzato et al., 2020), demonstrating that selected components of the DMX-12 were closely associated with such established categorical criteria for depressive mixed state as "mixed depression" by Benazzi (Benazzi, 2007) and "mixed features" by DSM-5 (American Psychiatric Association, 2013).

Since DMX has previously been regarded as a mixture of both manic and depressive components in its psychopathology (Fornaro et al., 2012), various reports have suggested close association between bipolarity and DMX (Benazzi, 2008b; Inoue et al., 2015; Takeshima and Oka, 2015, 2013). We have also clarified that bipolarity can have a positive

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effect on severity of DMX, which can further affect symptoms of disruptive emotion/behavior (aggression, irritability, dysphoria, and risk-taking behavior) by using the DMX-12 (Shinzato et al., 2019). These findings clearly suggest that bipolar disorder is an important risk factor in the development of DMX. However, possible involvement of other psychiatric comorbidities including neurodevelopmental disorders in DMX during MDE have not been fully clarified yet.

Nowadays, autism spectrum disorder (ASD) is no longer perceived as a rare condition in clinical settings as the prevalence of ASD is estimated to have risen to approximately 1% in adults in the general population (Brugha et al., 2011). It has been also demonstrated that comorbid ASD is found in 11-16% of first-visit adult patients with MDE (Takara and Kondo, 2014a, 2014b). Thus, an important clinical question here is how the presence of ASD affects depressive psychopathology when ASD individuals suffer from clinical depression. It is a well-known fact that ASD patients often undergo irritability, hyperactivity and emotional dysregulation as listed in the Aberrant Behavior Checklist (Aman et al., 1985) and the Emotion dysregulation Inventory (Mazefsky et al., 2018). Recent studies have shown that higher risks of psychiatric comorbidity and suicidality are found even in subthreshold autistic traits (Dell'Osso et al., 2019a,b). In our previous study (Takara and Kondo, 2014b), agitation was the most significant contributor to suicidal attempts among depressed adults, and its incidence was extremely high (89%) among ASD suicide attempters. Since ASD and DMX have symptomatologic commonality like increased irritability, agitation, emotional dysregulation, and potential suicidality, it is possible that ASD individuals may reveal traits of mixed psychopathology during MDE.

Depressive disorder is relatively common among ASD individuals. Its prevalence widely ranges from 2.5% to 47.1% (Hossain et al., 2020), but is approximately four times higher than that in the general population (Hudson et al., 2019). Likewise, co-occurrence of bipolar disorders is estimated to range from 6% to 21.4% (Vannucchi et al., 2014) or from 3% to 6% (Lai et al., 2019) according to two systematic reviews, both of which appear to cite higher rates compared to what is expected in the general population. It has also been pointed out that young ASD subjects without an intellectual disability have a 5.8-8.5 times higher risk for bipolar disorders (Selten et al., 2015). Therefore, a close relationship may exist between ASD and bipolarity. This also implies that bipolar components may be more easily intruded into depressive psychopathology as DMX symptoms in depressed individuals with ASD.

However, there have been very few studies that look into intensively dealing with detailed psychopathology among depressed individuals with ASD or that have directly investigated the association between ASD and DMX during MDE. Thus, in the present study, we aimed to clarify the prevalence and profile of DMX in depressed individuals with ASD and the possible contribution ASD may have to mixed psychopathology.

2. Methods

2.1. Subjects

This study was conducted at the University of the Ryukyus Hospital from June 2014 to Dec 2019. A total of 301 new consecutive outpatients with suspected MDE presented to our outpatient clinic and were diagnosed by two experienced psychiatrists according to the DSM-5 diagnostic criteria (American Psychiatric Association, 2013). The 298 patients whose native language was Japanese were included in the study, two of the whom withdrew their consent during the study.

Eighty-six of the patients were determined not to have had a major depressive episode (schizophrenia: 7, delusional disorder: 1, generalized anxiety disorder: 9, obsessive-compulsive disorder: 2, panic disorder: 2, social anxiety disorder: 2, somatic symptom and related disorders: 2, bulimia nervosa: 1, dissociative disorder: 2, alcohol, methamphetamine, and benzodiazepine use disorder: 8, insomnia disorder: 1, major neurocognitive disorder: 1, and the rest were adjustment disorders or mood disorders that did not meet a current depressive episode e.g., in remission).

Two hundred and ten patients fulfilled the diagnostic criteria for a DSM-5 major depressive episode (American Psychiatric Association, 2013), 28 of whom (4 with some kind of use disorder, 3 with neurocognitive disorder, 8 with neurodevelopmental disorders other than ASD, and 13 with physical comorbidities that may affect the brain's organs: 5 with human immunodeficiency virus infection, 2 with epilepsy, 1 with amyotrophic lateral sclerosis, 1 with postoperative pituitary tumor, 1 with systemic lupus erythematosus, 1 with post liver transplant, 1 with multiple sclerosis, and 1 with pregnancy) were excluded from the analysis. As a result, 182 patients were included in the analysis.

Subjects finally consisted of 182 outpatients with MDE (69 males and 113 females; 44.0 ± 17.9 years between the ages of 13-85). The same experienced psychiatrists confirmed MDE according to the DSM-5 diagnostic criteria (American Psychiatric Association, 2013) and further classified MDE into unipolar depression ($n = 133$) and bipolar and related disorders ($n = 49$). Diagnosis of ASD was also made by the same trained psychiatrists according to the criteria of DSM-5 (American Psychiatric Association, 2013). Patients with substance-related/addictive disorders or neurocognitive disorders were not enrolled in the present study. Since this study aimed to highlight the effect of ASD on DMX during MDE, participants who had apparent comorbidities with other neurodevelopmental disorders, e.g., intellectual disability and attention deficit/hyperactivity disorder (ADHD) were excluded from the analyses.

Only the subjects who had the ability to verbally communicate with others voluntarily participated in the study and gave written informed consent. For patients under the age of 18, written informed consent was taken not only from patients themselves but also from their parents. Data was anonymously treated during the study. Only coded and grouped data were used for analyses. Explanation for the purpose of the study, measures for protection of personal information, and the right to withdraw from the study were provided to each participant. This study protocol was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Ethics Committee at the University of Ryukyus.

2.2. Assessment

The Quick Inventory of Depressive Symptomatology Self-Report (Rush et al., 2003) Japanese version (QIDS-SR-J) and global assessment of functioning (GAF) (Endicott et al., 1976) were administered to each participant.

DMX was categorically diagnosed according to criteria for MD by Benazzi (Benazzi, 2008a, 2008b, 2002) and MF by DSM-5 (American Psychiatric Association, 2013). Severity of DMX was assessed by DMX-12 (Appendix 1), which we recently developed (Shinzato et al., 2020, 2019). Internal consistency of its three subscales were guaranteed, i.e., spontaneous instability" (Cronbach's $\alpha = 0.868$), "vulnerable responsiveness" (Cronbach's $\alpha = 0.826$) and "disruptive emotion/behavior" (Cronbach's $\alpha = 0.769$) (Shinzato et al., 2019).

2.3. Statistical analyses

Association between ASD and MD or MF were statistically analyzed by either Chi square test or Fisher's exact test. The association between ASD and gender, education level, and bipolarity were similarly tested using Chi square. Group comparisons of clinical backgrounds (age, number of mood episodes, duration of illness, and duration of current episode), scores of QIDS-SR-J, GAF, and symptoms of the DMX-12 were performed by independent t-test.

Multiple regression analyses were conducted to evaluate contribution of abovementioned background factors, QIDS-SR-J, GAF, and presence/absence of ASD as independent variables to total DMX-12 and its subscale scores as dependent variables. Dummy variables were used

Table 1
Comparisons of clinical backgrounds between patients with and without autism spectrum disorder.

	Autism Spectrum Disorder		P
	Absent (n = 36)	Present (n = 146)	
Age (years)	35.6 ± 12.9	46.1 ± 18.3	0.001
Female gender (%)	58.3 %	63.0%	0.604
Number of mood episodes	3.1 ± 3.0	3.0 ± 3.0	0.901
Duration of mood disorder (year)	8.4 ± 7.9	6.2 ± 7.9	0.149
Duration of current depressive episode (month)	19.6 ± 30.3	12.7 ± 41.8	0.368
High Educational level	47.2%	35.6%	0.209
Bipolarity	38.9 %	24.0%	0.071

for gender (0: female, 1: male), education level (0: high school or lower, 1: university or upper), bipolarity (0: major depressive disorder, 1: bipolar disorder), and ASD (0: non-ASD, 1: ASD).

A two-tailed *P* value less than 0.05 was regarded as statistically significant. SPSS software 16.0 J for Windows (SPSS Japan Inc., Tokyo, Japan) was used to carry out the statistical analyses.

3. Results

Thirty-six patients (19.8%) were found to have ASD. Thus, the group comparisons were made between patients with ASD ($n = 36$) and those without ASD ($n = 146$). Regarding clinical backgrounds, no significant differences were found in gender distribution, number of mood episodes, duration of illness, duration of current episode, and education level between the ASD and non-ASD groups (Table 1). Although ASD patients had a higher proportion of bipolarity (38.9%) than non-ASD patients (24.0%), the difference did not reach a significant level ($P = 0.07$) (Table 1). Meanwhile, age range was found to be lower (younger) in the ASD group than that in the non-ASD group (35.6 ± 12.9 versus 46.1 ± 18.3 years, $P = 0.001$) (Table 1).

There were 40 cases (22.0%) with MD and 8 cases (4.4%) with MF among the overall patients (Table 2). ASD patients showed a higher prevalence of MD compared to non-ASD patients (36.1% versus 18.5%, $P = 0.022$) whereas differences in prevalence of MF remained marginal between the two groups (11.1% versus 2.7%, $P = 0.05$) (Table 2).

Among the DMX-12 symptoms, mood lability, distractibility, impulsivity, aggression, irritability, dysphoria, and risk-taking behavior were more prevalent in ASD patients than those in non-ASD patients (Table 3). Although the scores of QIDS-SR-J and GAF did not significantly differ between the ASD and non-ASD groups, the ASD group showed greater severity of total DMX-12 and its disruptive emotion/behavior cluster than the non-ASD group (Table 4).

Multiple regression analysis revealed negative correlations of age with total DMX-12 ($\beta = -0.249$, $P = 0.001$) and its three subscale scores of spontaneous instability ($\beta = -0.149$, $P = 0.049$), vulnerable responsiveness ($\beta = -0.278$, $P = 0.001$), and disruptive emotion/behavior ($\beta = -0.278$, $P = 0.001$) while the score of QIDS-SR-J was positively correlated with total DMX-12 ($\beta = 0.505$, $P = 0.001$) and its three subscale scores of spontaneous instability ($\beta = 0.504$, $P = 0.001$), vulnerable responsiveness ($\beta = 0.354$, $P = 0.001$), and disruptive emotion/behavior ($\beta = 0.370$, $P = 0.001$). ASD ($\beta = 0.161$, $P = 0.020$), bipolarity ($\beta = 0.170$, $P = 0.031$), and educational level ($\beta = -0.138$, $P = 0.040$) were also significantly linked to the disruptive emotion/behavior cluster of the DMX-12 (Table 5).

4. Discussion

Assessments of co-occurring psychiatric conditions is complicated and challenging in ASD because of overlapping symptoms, diagnostic overshadowing, and ambiguous presentation of symptoms in ASD individuals (Rosen et al., 2018). In fact, some ASD individuals are not good at expressing their inner emotions due to their poor capability of verbal and non-verbal communication (Lartseva et al., 2015). Such negative emotion can be easily masked by their constricted or flat affect and lowered help-seeking attitude, leading to underdiagnosis of depression including DMX by clinicians. Interestingly, it was suggested that life-time depression rates in ASD individuals could be significantly

Table 3
The DMX-12 symptom scores between patients with and without autism spectrum disorder DMX-12.

	Autism Spectrum Disorder		
	Present (n=36)	Absent (n=146)	*P*
Spontaneous instability			
Restlessness	1.64 ± 0.99	1.63 ± 1.04	0.964
Racing/crowded thought	2.08 ± 1.00	1.97 ± 1.00	0.553
Mood lability	1.92 ± 1.00	1.48 ± 1.03	0.022
Inner tension	2.06 ± 0.95	1.95 ± 0.96	0.536
Distractibility	2.31 ± 0.79	1.83 ± 1.05	0.003
Impulsivity	1.61 ± 0.99	1.12 ± 1.03	0.011
Vulnerable responsiveness			
Hypersensitivity	2.19 ± 1.01	2.01 ± 0.95	0.296
Overreactivity	2.11 ± 0.95	1.87 ± 1.02	0.199
Disruptive emotion/behavior			
Aggression	0.89 ± 1.06	0.49 ± 0.82	0.042
Irritability	1.58 ± 1.05	1.19 ± 1.01	0.040
Dysphoria	1.97 ± 0.94	1.54 ± 0.96	0.017
Risk-taking behavior	0.97 ± 0.97	0.52 ± 0.88	0.008

DMX-12: the 12-item questionnaire for quantitative assessment of depressive mixed state.

Table 4
Comparisons of depression severity, functional impairment and depressive mixed state between patients with and without autism spectrum disorder.

	Autism Spectrum Disorder		
	Present (n = 36)	Absent (n = 146)	*P*
QIDS-SR-J	17.2 ± 4.7	16.1 ± 5.3	0.236
GAF	46.5 ± 9.8	48.0 ± 11.4	0.467
Total DMX-12	21.3 ± 7.6	17.6 ± 8.0	0.012
Spontaneous instability	11.6 ± 4.0	10.0 ± 4.8	0.060
Vulnerable responsiveness	4.3 ± 1.8	3.9 ± 1.8	0.206
Disruptive emotion/behavior	5.4 ± 3.1	3.7 ± 2.8	0.002

QIDS-SR-J: Quick Inventory of Depressive Symptomatology Self-Report Japanese version, GAF: Global Assessment of Functioning, DMX-12: the 12-item questionnaire for quantitative assessment of depressive mixed state.

Table 2
Association between autism spectrum disorder and mixed depression/mixed features specifier.

		Mixed depression		Mixed features specifier		Total
		+	-	+	-	
Autism spectrum disorder	+	13	23	4	32	36 (19.8%)
	-	27	119	4	142	146 (80.2%)
	Total	40 (22.0%)	142 (78.0%)	8 (4.4%)	174 (95.6%)	182
		Odds: 2.491 (95%CI: 1.121-5.534)		Odds: 4.438 (95%CI: 1.053-18.692)		
		Chi square test: P=0.022		Fisher's exact test: P=0.050		

Table 5
Multiple regression analyses of possible determinants for total and subscale scores of the DMX-12.

Instability	DMX-12 (Total)		Spontaneous instability		Vulnerable Responsiveness		Disruptive Emotion/behavior	
	B	P	β	P	B	P	B	P
Age	-0.249	0.001	-0.149	0.049	-0.278	0.001	-0.278	0.001
Gender	0.006	0.927	0.035	0.619	-0.150	0.033	0.056	0.404
Educational level	-0.069	0.283	-0.027	0.691	-0.019	0.787	-0.138	0.040
Number of mood episodes	-0.057	0.507	-0.112	0.220	-0.008	0.929	0.027	0.757
Duration of Illness	-0.001	0.989	0.047	0.621	-0.035	0.711	-0.056	0.537
Duration of current episode	-0.012	0.850	-0.032	0.644	0.001	0.988	0.017	0.802
Bipolarity	0.148	0.052	0.107	0.184	0.111	0.171	0.170	0.031
ASD	0.103	0.123	0.073	0.305	0.013	0.851	0.161	0.020
QIDS-SR-J	0.505	0.001	0.504	0.001	0.354	0.001	0.370	0.001
GAF	0.012	0.859	0.089	0.209	-0.020	0.772	-0.098	0.154
	R=0.610, R2=0.372		R=0.537, R2=0.289		R=0.530, R2=0.281		R=0.577, R2=0.333	
	F=9.646, P=0.001		F=6.619, P=0.001		F=6.377, P=0.001		F=8.136, P=0.001	

β: standardized partial regression coefficient. Dummy variables were used for gender (0: female, 1: male), education level (0: high school or lower, 1: university or upper), bipolarity (0: major depressive disorder, 1: bipolar disorder) and ASD (0: non-ASD, 1: ASD).

elevated with older age (18 and over), higher intelligence (IQ>100), assessment with structured interviews, and information from self-report (Hudson et al., 2019). This suggests that self-rating questionnaires with a standardized format can be more helpful compared to unstructured medical interviewing by clinicians in the hopes of catching a sign of depression and the related mixed symptoms. This may also be the case with adult ASD patients who fall within normal intelligence scores since self-rating scales seem to be less stressful than face-to-face verbal inquiry from others especially when expressing their emotional problems. The DMX-12 focuses on inner mixed manifestations which can be conveniently self-evaluated by ASD individuals. Therefore, the DMX-12 would be requisite for effective and efficient screening of mixed psychopathology in depressed ASD individuals.

Apart from prototypical depression symptoms, ASD individuals may exhibit more atypical presentations of depression like increased irritability, anxiety, aggression, and self-injury as specific manifestations of depressive psychopathology (Greenlee et al., 2016; Pezzimenti et al., 2019). Such unstable and externalizing symptoms are also observed as nonspecific but frequent symptoms of DMX (Benazzi, 2008a, 2007, 2002) although symptomatologic commonality between ASD and DMX has never been directly confirmed to date. The present study firstly showed more prevalent mixed symptoms like mood lability, distractibility, impulsivity, aggression, irritability, dysphoria, and risk-taking behavior together with greater severity of DMX, especially its disruptive emotion/behavior component, in depressed ASD individuals. Furthermore, ASD patients exhibited greater proportions of categorically diagnosed DMX (MD as significant and MF as marginal) compared to non-ASD patients. These findings strongly suggest that a close relationship exists between ASD and DMX.

Meanwhile, the close association between ASD and bipolar disorder has been consistently suggested in several studies demonstrating greater comorbidity (Lai et al., 2019; Vannucchi et al., 2014) and higher risk (Selten et al., 2015) of bipolar disorders in ASD individuals. One longitudinal follow-up study (Borue et al., 2016) demonstrated that youth with both ASD and bipolar disorder exhibited an earlier onset of mood symptoms and more frequent mixed symptom presentation such as distractibility and racing thoughts compared with youth who only had bipolar disorder. Furthermore, a clinical trial of citalopram, a selective serotonin reuptake inhibitor, resulted in behavioral activation (hyperactivity, distractibility, impulsivity, disinhibition, and intrusive behavior) as unwanted effects in ASD children (5-17 years) without any mood problems (King et al., 2009). These findings imply that presence of autistic traits may provoke development of mixed psychopathology under potential or clinical bipolarity. In contrast, only a marginal relationship between ASD and bipolarity in the present study suggests that autistic traits are primarily involved in mixed psychopathology independent of bipolarity.

Possible interaction between ASD and DMX consequently reminds us of enhanced suicidal risk in depressed ASD adults. Surprisingly, a clinical cohort study with ASD individuals revealed that two-thirds of them self-reported suicidal ideation while one-third of them actually planned or attempted suicide in the 9-year study period (Cassidy et al., 2014). The same authors also demonstrated that suicidal ideation and suicide plans/attempts were more prevalent in ASD individuals comorbid with depression than those without depression (Cassidy et al., 2014). Meanwhile, a significant correlation was found between the number of life-time suicide attempts and DMX according to the Research-Based Diagnostic Criteria (Popovic et al., 2015). These findings clearly indicate that combined psychopathology with ASD and DMX can produce synergistic effects on acceleration of suicidal risk. In fact, our previous study (Takara and Kondo, 2014b) has pointed out that agitation during MDE is the most significant risk factor for suicidal attempts, which is also observed as a symptom of both ASD and DMX. The same study also revealed a sharp contrast in presence of agitation between suicide attempters (89%) and non-attempters (11%) among depressed ASD adults, suggesting that agitation is a potent promoter for suicidal action in depressed adults with ASD (Takara and Kondo, 2014b). Therefore, psychomotor agitation should be discussed and monitored for risk management of suicidality when treating depressed patients with ASD.

Evidence for effective medication against DMX is disappointingly lacking. From a clinical point of view, use of mood stabilizers with an antimanic property (e.g., valproic acid and lithium) and second-generation antipsychotics (e.g., olanzapine, quetiapine, lurasidone, and aripiprazole) are recommended while antidepressants should be avoided if possible (Takeshima, 2019). There is a paucity of evidence and lack of guidelines for recommended pharmacotherapy of DMX in ASD. Even in purely depressive episodes of ASD, validity for the use of antidepressants are still controversial (Vannucchi et al., 2014). Meanwhile, antipsychotics (e.g., risperidone and aripiprazole) (Sharma et al., 2018)and mood stabilizers like lithium (Vannucchi et al., 2014) have been reported to be effective for symptoms associated with irritability, agitation, and impulsivity in ASD patients irrespective of mood symptoms. Taking these findings together, it may be safer to avoid antidepressants and use mood stabilizers and/or atypical antipsychotics instead for DMX in ASD although these hypothetical recommendations needs to be confirmed by future controlled studies in these specific subjects.

This study has several limitations as follows. First, the results were obtained from a relatively small number of ASD subjects. Second, severity of DMX was substituted with assessment of its frequency on the basis of self-reported dimensional scales by the DMX-12. Third, reproducibility of the present results should be confirmed in other ethnic

populations by using the English version of the DMX-12. Fourth, the risk of suicidality was not directly evaluated in relation to ASD and DMX in this study. Nevertheless, it should be noted that there is a close relationship between ASD and DMX, and that this combination (ASD+DMX) may lead to drastically enhanced suicidal risk. Careful monitoring of disruptive emotion/behavior symptoms are warranted when treating ASD individuals during MDE.

5. Conclusions

ASD exhibits higher prevalence of MD and more frequent disruptive emotion/behavior symptoms during MDE. Careful monitoring and management of potential DMX are warranted in depressed individuals with ASD as they may be more prone to DMX during MDE.

CRediT authorship contribution statement

Yu Zamami: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing - original draft, Writing - review & editing. **Hotaka Shinzato**: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Visualization, Writing - original draft, Writing - review & editing. **Kazuhiro Kurihara**: Data curation, Investigation, Writing - review & editing. **Munenaga Koda**: Data curation, Investigation, Writing - review & editing. **Akifumi Nakamura**: Data curation, Investigation, Writing - review & editing. **Tsuyoshi Kondo**: Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

Hotaka Shinzato, Yu Zamami, Kazuhiro Kurihara and Munenaga Koda declare no conflicts of interest associated with this study. Akifumi Nakamura has received honoraria from Meiji Seika Pharma and Otsuka Pharmaceutical Co. and Tsuyoshi Kondo has received research fees from Otsuka Pharmaceutical Co., Shionogi & Co., Eisai Co. Ltd., Astellas Pharma. and Pfizer Japan Inc.

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Supplementary materials

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