




# The Clinical Characteristics and Manifestation of Anxious Depression Among Patients With Major Depressive Disorders-Results From a Taiwan Multicenter Study

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**Objective** Anxious depression is a prevalent characteristic observed in Asian psychiatric patients diagnosed with major depressive disorder (MDD). This study aims to investigate the prevalence and clinical presentation of anxious depression in Taiwanese individuals diagnosed with MDD.

**Methods** We recruited psychiatric outpatients aged over 18 who had been diagnosed with MDD through clinical interviews. This recruitment took place at five hospitals located in northern Taiwan. We gathered baseline clinical and demographic information from the participants. Anxious depression was identified using a threshold of an anxiety/somatization factor score  $\geq 7$  on the 21-item Hamilton Rating Scale for Depression (HAM-D).

**Results** In our study of 399 patients (84.21% female), 64.16% met the criteria for anxious depression. They tended to be older, married, less educated, with more children, and an older age of onset. Anxious depression patients had higher HAM-D and Clinical Global Impression-Severity scale score, more panic disorder (without agoraphobia), and exhibited symptoms like agitation, irritability, concentration difficulties, psychological and somatic anxiety, somatic complaints, hypochondriasis, weight loss, and increased insight. Surprisingly, their suicide rates did not significantly differ from non-anxious depression patients. This highlights the importance of recognizing and addressing these unique characteristics.

**Conclusion** Our study findings unveiled that the prevalence of anxious depression among Taiwanese outpatients diagnosed with MDD was lower compared to inpatients but substantially higher than the reported rates in European countries and the United States. Furthermore, patients with anxious depression exhibited a greater occurrence of somatic symptoms.

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**Keywords** Anxiety; Major depressive disorder; Nervousness; Unipolar depression.

## INTRODUCTION

The association between depressive disorders and anxiety spectrum disorders has been extensively studied.<sup>1</sup> It has been

found that over half of the patients experience comorbidity of both anxiety and depressive episodes, which is often linked to poorer outcomes.<sup>2</sup> Notably, the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), introduced

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a specifier for “major depressive episode with anxious distress” to recognize this condition. The International Classification of Diseases, 11th Revision (ICD-11 PHC), also introduced a new category for anxious depression, encompassing individuals with concurrent anxiety and depressive symptoms. Thus, distinguishing between anxious depression and non-anxious depression is of paramount importance for primary caregivers.

A global mental health survey conducted by the World Health Organization across 24 countries indicated that anxious depression, in comparison to non-anxious depression, is associated with more severe functional impairment and increased suicidal ideation.<sup>3</sup> Patients meeting the DSM-5 criteria for anxious distress specifier exhibited more severe depressive symptoms and higher scores for bipolarity.<sup>4</sup> Another cross-country survey demonstrated that individuals with anxious depression (as defined by ICD-11) had levels of disability and suicidal ideation comparable to those with longer-lasting anxiety disorders.<sup>5</sup> Regardless of the specific definition used, anxious depression is consistently linked to unfavorable outcomes, increased side effects, and a higher rate of non-response to treatment.<sup>6-8</sup> Patients with anxious depression tend to be older, experience more severe depression, and display more melancholic features compared to those with non-anxious depression.<sup>9,10</sup> Anxious depression is also associated with a heightened risk of suicide, greater pain complaints, increased functional impairment, and reduced quality of life.<sup>9</sup>

In Germany, a study found that the prevalence of anxious depression was 49% among inpatients diagnosed with a depressive episode,<sup>10</sup> which is similar to the outpatient prevalence of 53.2% reported in the STAR\*D study conducted in the United States.<sup>8</sup> However, in Asian countries, the prevalence of anxious depression appears to be even higher. For instance, in China, the prevalence of anxious depression reached 64.5% among outpatients with treatment-resistant depression (TRD).<sup>11</sup> A previous study in Taiwan estimated that the prevalence of anxious depression among 174 inpatients with major depressive disorder (MDD) was as high as 81%.<sup>9</sup> Given these variations, a more comprehensive exploration with a larger sample size is necessary to delineate the profile of anxious depression in the Asian population, particularly among psychiatric outpatients. Consequently, this study aims to investigate the prevalence of anxious depression among MDD outpatients in Taiwan, to characterize the features of anxious depression, and to discern the distinctions between anxious and non-anxious depression using data obtained from Taiwan Government Research Grants, which are expected to offer adequate representativeness.

## METHODS

### Participants

From May 2006 to December 2009, we recruited patients from the outpatient psychiatric clinics of five hospitals in or around Taipei, Taiwan, namely Chang Gung Memorial Hospital, Mackay Memorial Hospital, Far Eastern Memorial Hospital, TMU-Wan Fang Hospital, and the Songde branch of the Taipei City Hospital. These patients were identified as of Han Chinese ethnicity based on the documented background of their parents. Inclusion criteria consisted of individuals who were 1) over the age of 18, 2) currently experiencing a depressive episode, as confirmed during an interview, and 3) scoring more than 14 points on the 21-item Hamilton Rating Scale for Depression (HAM-D). All participants underwent interviews conducted by trained research nurses using the structured clinical interview for DSM-IV-TR Axis-I Disorders, and the diagnosis of MDD was established based on the criteria outlined in the DSM-IV.<sup>12</sup> Those individuals who had comorbid conditions such as schizophrenia, bipolar disorder, schizoaffective disorder, substance dependence, dementia, or any significant medical condition were excluded from the study. Additionally, participants who had previously been treated with escitalopram or paroxetine were also excluded.

Before enrollment in the study, all participants were thoroughly informed and provided written informed consent. The study was approved by institutional review boards of the National Health Research Institutes in Taiwan (NSC 95-2314-B-400-001). Furthermore, it was registered with ClinicalTrials.gov (NCT00384020) and additional information can be found at the following link: <https://classic.clinicaltrials.gov/ct2/show/NCT00384020>. It was also registered with the Chang Gung Memorial Hospital Research Program (CMRPG COR-PG3L0021).

### Demographic data

The demographic data was recruited from the participants, including age, sex, body mass index, marital status, education, children, employment status, depression onset age, previous episodes, length of illness, and smoking. Additionally, we recorded comorbid psychiatric disorders among the participants.

### Anxiety and depression scales

The HAM-D<sup>13</sup> was utilized as a depression assessment tool, assessed by experienced healthcare providers, and widely employed in clinical trials. This scale categorized its items into several domains, including core depressive symptoms, sleep patterns, daily activities, and various facets of anxiety (both psychic and somatic), as well as delusions. For this study, anxious depression was defined as having an anxious depression

factor score of  $\geq 7$  on the HAM-D. The method for categorizing depression based on this score has been mentioned in several literature sources and was explicitly outlined in the original analysis plan,<sup>14-17</sup> including the STAR\*D study.<sup>8</sup> The specific items contributing to the anxiety/somatization (anxious depression) factor scores in the HAM-D included items 10 (anxiety-psychic), 11 (anxiety-somatic), 12 (somatic symptoms-gastrointestinal), 13 (somatic symptoms-general), 15 (hypochondriasis), and 17 (insight). Scores on this scale ranged from 0 to 18.

Similarly, the 14-item Hamilton Rating Scale for Anxiety (HAM-A14) was frequently employed by clinical healthcare providers to assess anxiety levels. It was scored on a scale ranging from 0 to 4 and was further divided into two components, distinguishing between psychic and somatic anxiety.<sup>18</sup> The research nurses are responsible for conducting the assessments using both the HAM-D and HAM-A14, who underwent standardized training procedures.<sup>19</sup>

In addition to the clinician-administered assessments, the Beck Depression Inventory-II (BDI-II) was employed as a self-report depression scale.<sup>20</sup> This scale consists of 21 items, each rated on a scale from 0 to 3. The BDI-II was translated into Mandarin Chinese and validated by the Chinese Behavioral Science Corporation.<sup>21</sup>

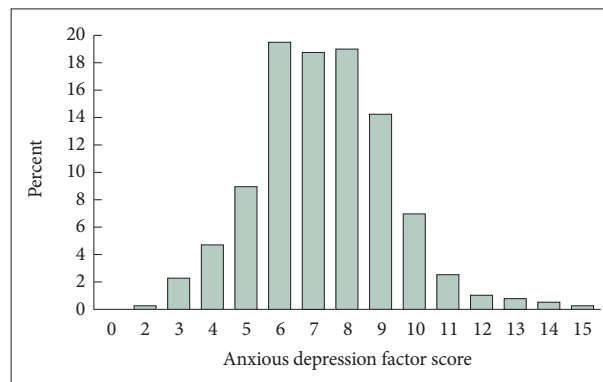
## Statistics

We conducted a comparative analysis between the anxious and non-anxious depression groups, considering baseline demographic data, severity levels, and the profile of depression scales. For continuous variables, we calculated the mean and standard deviation, while categorical variables were represented using the total count and percentage. Additionally, we computed the distribution of anxiety/somatization (anxious depression) factor scores within the HAM-D.

To assess the associations between the anxious and non-anxious depression groups and the baseline demographics, severity levels, and depression scale scores, we employed bivariate logistic regression models. The odds ratios were then calculated using these logistic regression models. To further refine our analysis and account for potential confounding factors, we utilized a multivariate logistic regression model. This model allowed us to adjust for each variable, excluding those directly related to defining anxious depression. These variables included psychological anxiety, somatic anxiety, gastrointestinal somatic symptoms, general somatic symptoms, hypochondria, and insight.

## RESULTS

In our study, a total of 399 participants with MDD were en-



**Figure 1.** Distribution of HAM-D anxiety/somatization (anxious depression) factor scores (N=399). The anxiety/somatization factor includes six items from the 21-item HAM-D including anxiety (psychic), anxiety (somatic), somatic symptoms (gastrointestinal), somatic symptoms (general), hypochondriasis, and insight. HAM-D, 21-item Hamilton Rating Scale for Depression.

rolled, and the majority of them were female (84.21%). Among these participants, 256 (64.16%) were classified into the anxious depression group. The distribution of HAM-D anxiety scores was continuous, ranging from 2 to 15, with a median score of 7 (Figure 1).

Compared to the non-anxious depression group, the anxious depression group exhibited several significant differences. Specifically, the anxious depression group was, on average, older ( $42.0 \pm 13.34$  vs.  $38.5 \pm 13.40$ ,  $p=0.0037$ ), had a higher percentage of married individuals (68.87% vs. 31.13%,  $p=0.0016$ ), a lower educational level (mean years of schooling  $11.5 \pm 3.79$  vs.  $12.2 \pm 3.64$ ,  $p=0.0314$ ), a higher proportion of individuals with children (71.04% vs. 28.96%,  $p<0.0001$ ), and an older age of first episode onset ( $39.0 \pm 14.00$  vs.  $35.9 \pm 13.26$ ,  $p=0.0067$ ) (Table 1).

In terms of clinical presentation, the anxious depression group had a significantly higher HAM-D score ( $23.6 \pm 4.40$  vs.  $19.5 \pm 3.18$ ,  $p=0.0006$ ) and Clinical Global Impression-Severity scale (CGI-S) score ( $4.9 \pm 0.53$  vs.  $4.6 \pm 0.65$ ,  $p<0.0001$ ). Additionally, this group exhibited a higher prevalence of panic disorder without agoraphobia (82.86% vs. 17.14%,  $p=0.0222$ ).

Analyzing individual items from the Beck Depression Inventory (BDI), the anxious depression group displayed a higher occurrence of agitation (95.20% vs. 86.52%,  $p=0.0086$ ), irritability (89.20% vs. 78.72%,  $p=0.0127$ ), and concentration difficulty (95.60% vs. 88.65%,  $p=0.0259$ ) in comparison to the non-anxious depression group (Table 2). However, there was no significant difference between the two groups regarding suicidal thoughts or wishes (77.60% vs. 77.30%,  $p=0.5171$ ).

Analyzing individual items from the HAM-D, the anxious depression group displayed a higher prevalence of psychological anxiety (98.05% vs. 88.81%,  $p=0.0005$ ) and somatic anxiety (99.61% vs. 94.41%,  $p=0.0057$ ) in comparison to the

**Table 1.** Baseline characteristics and their association with anxious depression (absence/presence)

Characteristics	Total (N=399)	Non-anxious depression (N=143 [35.84%])	Anxious depression (N=256 [64.16%])	Unadjusted OR <sup>†</sup>	P	Adjusted OR <sup>‡</sup>	P
Age (yr)	40.7±13.45	38.5±13.40	42.0±13.34	1.020	0.0147** <sup>  </sup>	1.024	0.0037*** <sup>  </sup>
Sex					0.1224		0.1527
Male	63 (15.79)	28 (44.44)	35 (55.56)	1 (ref)			
Female	336 (84.21)	115 (34.23)	221 (65.77)	1.537		1.496	
BMI categorization (N=371, kg/m <sup>2</sup> )					0.2602		0.3144
Underweight (<18.5)	58 (15.63)	25 (43.10)	33 (56.90)	0.599	0.0963	0.629	0.1351
Healthy range (18.5≤BMI<23)	189 (50.94)	59 (31.22)	130 (68.78)	1 (ref)		1 (ref)	
Overweight (23≤BMI<25)	56 (15.09)	17 (30.36)	39 (69.64)	1.041	0.9028	1.120	0.7335
Obese (BMI≥25)	68 (18.33)	27 (39.71)	41 (60.29)	0.689	0.2045	0.723	0.2721
Marital status					0.0338** <sup>  </sup>		0.0197** <sup>  </sup>
Married	212 (53.13)	66 (31.13)	146 (68.87)	1 (ref)		1 (ref)	
Widowed	25 (6.27)	7 (28.00)	18 (72.00)	1.162	0.7485	1.393	0.4867
Divorced	29 (7.27)	10 (34.48)	19 (65.52)	0.859	0.7159	0.817	0.6330
Separated	8 (2.01)	0 (0.00)	8 (100.00)	>999.999	0.9845	>999.999	0.9845
Never married	125 (31.33)	60 (48.00)	65 (52.00)	0.490	0.0021*** <sup>  </sup>	0.476	0.0016*** <sup>  </sup>
Education (years of schooling) (N=398)	11.7±3.75	12.2±3.64	11.5±3.79	0.947	0.0555	0.940	0.0314** <sup>  </sup>
Have any children					0.0001*** <sup>  </sup>		<0.0001*** <sup>  </sup>
No	140 (35.09)	68 (48.57)	72 (51.43)	1 (ref)		1 (ref)	
Yes	259 (64.91)	75 (28.96)	184 (71.04)	2.317		2.499	
Employment status					0.8624		0.9352
Unemployed	193 (48.37)	70 (36.27)	123 (63.73)	1 (ref)		1 (ref)	
Employed	206 (51.63)	73 (35.44)	133 (64.56)	1.037		0.983	
Age at first episode (N=394)	37.9±13.80	35.9±13.26	39.0±14.00	1.017	0.0308** <sup>  </sup>	1.022	0.0067*** <sup>  </sup>
Previous episodes					0.1069 <sup>  </sup>		0.1310 <sup>  </sup>
0	243 (60.90)	86 (35.39)	157 (64.61)	1 (ref)		1 (ref)	
1–10	128 (32.08)	41 (32.03)	87 (67.97)	1.162	0.5169 <sup>  </sup>	1.126	0.6120 <sup>  </sup>
>10	8 (2.01)	5 (62.50)	3 (37.50)	0.329	0.1342	0.323	0.1294
Unknown	20 (5.01)	11 (55.00)	9 (45.00)	0.448	0.0871	0.460	0.1001
Live with others (N=398)					0.3980		0.3860
No	46 (11.56)	19 (41.30)	27 (58.70)	1 (ref)		1 (ref)	
Yes	352 (88.44)	123 (34.94)	229 (65.06)	1.310		1.322	
Family history (N=395)					0.3941		0.4144
No	299 (75.70)	104 (34.78)	195 (65.22)	1 (ref)		1 (ref)	
Yes	96 (24.30)	38 (39.58)	58 (60.42)	0.814		0.820	
Length of illness (in years) (N=394)	2.9±5.82	2.8±5.08	2.9±6.21	1.004	0.8108	1.000	0.9856
Smoking (N=373)					0.8687		0.7552
No	320 (85.79)	111 (34.69)	209 (65.31)	1 (ref)		1 (ref)	
Yes	53 (14.21)	19 (35.85)	34 (64.15)	0.950		0.907	
HAM-D total score	22.1±4.47	19.5±3.18	23.6±4.40	1.338	<0.0001*** <sup>  </sup>	>999.999	0.0006*** <sup>  </sup>
BDI total score (N=391)	31.8±10.89	30.1±9.88	32.7±11.32	1.023	0.0206** <sup>  </sup>	1.013	0.2611

**Table 1.** Baseline characteristics and their association with anxious depression (absence/presence) (continued)

Characteristics	Total (N=399)	Non-anxious depression (N=143 [35.84%])	Anxious depression (N=256 [64.16%])	Unadjusted OR <sup>†</sup>	P	Adjusted OR <sup>‡</sup>	P
CGI-S score	4.8±0.60	4.6±0.65	4.9±0.53	2.823	<0.0001*** <sup>  </sup>	3.184	<0.0001*** <sup>  </sup>
CGI-S					<0.0001*** <sup>  </sup>		<0.0001*** <sup>  </sup>
Normal, not at all ill	0 (0.00)	0 (0.00)	0 (0.00)	-	-	-	-
Borderline mentally ill	0 (0.00)	0 (0.00)	0 (0.00)	-	-	-	-
Mildly ill	13 (3.26)	9 (6.23)	4 (30.77)	1 (ref)		1 (ref)	
Moderately ill	76 (19.05)	45 (59.21)	31 (40.79)	1.550	0.4966	1.714	0.4101
Markedly ill	284 (71.18)	85 (29.93)	199 (70.07)	5.268	0.0069*** <sup>  </sup>	6.655	0.0044*** <sup>  </sup>
Severely ill	25 (6.27)	4 (16.00)	21 (84.00)	11.812	0.0023*** <sup>  </sup>	16.933	0.0017*** <sup>  </sup>
Extremely ill	1 (0.25)	0 (0.00)	1 (100.00)	>999.999	0.9855	>999.999	0.9850
CGI-I score (N=8) <sup>§</sup>	4.0±0.93	-	4.0±0.93	-	-	-	-
CGI-I							
Very much improved	0 (0.00)	0 (0.00)	0 (0.00)	-	-	-	-
Much improved	0 (0.00)	0 (0.00)	0 (0.00)	-	-	-	-
Minimally improved	2 (0.50)	0 (0.00)	2 (100.00)	-	-	-	-
No change	5 (1.25)	0 (0.00)	5 (100.00)	-	-	-	-
Minimally worse	0 (0.00)	0 (0.00)	0 (0.00)	-	-	-	-
Much worse	1 (0.25)	0 (0.00)	1 (100.00)	-	-	-	-
Very much worse	0 (0.00)	0 (0.00)	0 (0.00)	-	-	-	-
Not available	391 (97.99)	143 (36.57)	248 (63.43)	-	-	-	-
Co-morbidities							
Mood episodes							
Current major depressive episode					0.9870		0.9871
No	1 (0.25)	0 (0.00)	1 (100.00)	1 (ref)		1 (ref)	
Yes	398 (99.75)	143 (35.93)	255 (64.07)	<0.001		<0.001	
Past major depressive episode					0.8624		0.7704
No	245 (61.40)	87 (35.51)	158 (64.49)	1 (ref)		1 (ref)	
Yes	154 (38.60)	56 (36.36)	98 (63.64)	0.964		0.939	
Current manic episode (no)	399 (100.00)	143 (35.84)	256 (64.16)	-	-	-	-
Current hypomanic episode (no)	399 (100.00)	143 (35.84)	256 (64.16)	-	-	-	-
Past manic episode (no)	399 (100.00)	143 (35.84)	256 (64.16)	-	-	-	-
Past hypomanic episode (no)	399 (100.00)	143 (35.84)	256 (64.16)	-	-	-	-
Dysthymic disorder					0.8924		0.7686
No	372 (93.23)	133 (35.75)	239 (64.25)	1 (ref)		1 (ref)	
Yes	27 (6.77)	10 (37.04)	17 (62.96)	0.946		0.884	
Substance causing mood symptoms (no)	399 (100.00)	143 (35.84)	256 (64.16)	-	-	-	-
GMC causing mood symptoms (no)	399 (100.00)	143 (35.84)	256 (64.16)	-	-	-	-
Psychotic symptoms (no)	399 (100.00)	143 (35.84)	256 (64.16)	-	-	-	-
Mood differential (no)	399 (100.00)	143 (35.84)	256 (64.16)	-	-	-	-

**Table 1.** Baseline characteristics and their association with anxious depression (absence/presence) (continued)

Characteristics	Total (N=399)	Non-anxious depression (N=143 [35.84%])	Anxious depression (N=256 [64.16%])	Unadjusted OR <sup>†</sup>	P	Adjusted OR <sup>‡</sup>	P
<b>Substance use disorders</b>							
Alcohol abuse (no)	399 (100.00)	143 (35.84)	256 (64.16)	-	-	-	-
Alcohol dependence (no)	399 (100.00)	143 (35.84)	256 (64.16)	-	-	-	-
Substance abuse (no)	399 (100.00)	143 (35.84)	256 (64.16)	-	-	-	-
Substance dependence (no)	399 (100.00)	143 (35.84)	256 (64.16)	-	-	-	-
<b>Anxiety disorders</b>							
Panic disorder with agoraphobia					0.9138		0.8972
No	376 (94.24)	135 (35.90)	241 (64.10)	1 (ref)		1 (ref)	
Yes	23 (5.76)	8 (34.78)	15 (65.22)	1.050		0.943	
Panic disorder without agoraphobia					0.0203** <sup>  </sup>		0.0222** <sup>  </sup>
No	364 (91.23)	137 (37.64)	227 (62.36)	1 (ref)		1 (ref)	
Yes	35 (8.77)	6 (17.14)	29 (82.86)	2.917		2.884	
Agoraphobia without a history of panic disorder					0.9872		0.9872
No	397 (99.50)	141 (35.52)	256 (64.48)	1 (ref)		1 (ref)	
Yes	2 (0.50)	2 (100.00)	0 (0.00)	<0.001		<0.001	
Social phobia					0.1209		0.1151
No	389 (97.49)	137 (35.22)	252 (64.78)	1 (ref)		1 (ref)	
Yes	10 (2.51)	6 (60.00)	4 (40.00)	0.363		0.354	
Specific phobia					0.5786		0.5044
No	385 (96.49)	137 (35.58)	248 (64.42)	1 (ref)		1 (ref)	
Yes	14 (3.51)	6 (42.86)	8 (57.14)	0.737		0.689	
Obsessive-compulsive disorder					0.8974		0.8834
No	393 (98.50)	141 (35.88)	252 (64.12)	1 (ref)		1 (ref)	
Yes	6 (1.50)	2 (33.33)	4 (66.67)	1.119		1.138	
Posttraumatic stress disorder					0.8454		0.6843
No	394 (98.75)	141 (35.79)	253 (64.21)	1 (ref)		1 (ref)	
Yes	5 (1.25)	2 (40.00)	3 (60.00)	0.836		0.686	
Generalized anxiety disorder					0.0618		0.0851
No	201 (50.38)	81 (40.30)	120 (59.70)	1 (ref)		1 (ref)	
Yes	198 (49.62)	62 (31.31)	136 (68.69)	1.481		1.441	
Substance causing anxiety symptoms (no)					-	-	-
GMC causing anxiety symptoms					0.9879		0.9880
No	397 (99.50)	143 (36.02)	254 (63.98)	1 (ref)		1 (ref)	
Yes	2 (0.50)	0 (0.00)	2 (100.00)	>999.999		>999.999	
Anxiety disorder NOS					0.2491		0.4844
No	359 (89.97)	132 (36.77)	227 (63.23)	1 (ref)		1 (ref)	
Yes	40 (10.03)	11 (27.50)	29 (72.50)	1.533		1.303	
Suicide – HAM-D					1.130	0.2610	0.976
Suicide –BDI (N=391)					1.062	0.5853	0.955
	1.2±0.96	1.1±0.95	1.2±0.97			0.976	0.6970

Categorical data: number (%); continuous variables: mean±standard deviation. \*p<0.05 (2-tailed); \*\*p<0.01 (2-tailed); \*\*\*p<0.001 (2-tailed); <sup>†</sup>bivariate logistic regression model; <sup>‡</sup>logistic regression model, after adjusting for the HAM-D score, not including the items used to identify anxious depression; <sup>§</sup>not available due to the first time interviewed (N=391); <sup>||</sup>statistically significant. OR, odds ratio; BMI, body mass index; HAM-D, 21-item Hamilton Rating Scale for Depression; BDI, Beck Depression Inventory; CGI-S, Clinical Global Impression–Severity scale; CGI-I, Clinical Global Impression–Improvement; GMC, general medical condition; NOS, not otherwise specified

**Table 2.** Baseline BDI: anxious/non-anxious depression

BDI items	Total (N=391)		Non-anxious depression (N=141 [36.06%])		Anxious depression (N=250 [63.94%])		Unadjusted OR†	Unadjusted P	Adjusted OR‡	Adjusted P
	Absent	Present	Absent	Present	Absent	Present				
Sadness	58 (14.83)	333 (85.17)	23 (16.31)	118 (83.69)	35 (14.00)	215 (86.00)	1.197	0.5372	1.031	0.9200
Pessimism	47 (12.02)	344 (87.98)	19 (13.48)	122 (86.52)	28 (11.20)	222 (88.80)	1.235	0.5071	1.021	0.9508
Past failure	128 (32.74)	263 (67.26)	43 (30.50)	98 (69.50)	85 (34.00)	165 (66.00)	0.852	0.4786	0.705	0.1423
Loss of pleasure	23 (5.88)	368 (94.12)	9 (6.38)	132 (93.62)	14 (5.60)	236 (94.40)	1.149	0.7522	0.971	0.9482
Guilty feelings	121 (30.95)	270 (69.05)	51 (36.17)	90 (63.83)	70 (28.00)	180 (72.00)	1.457	0.0941	1.320	0.2273
Punishment feelings	131 (33.50)	260 (66.50)	51 (36.17)	90 (63.83)	80 (32.00)	170 (68.00)	1.204	0.4018	1.078	0.7416
Self-dislike	55 (14.07)	336 (85.93)	18 (12.77)	123 (87.23)	37 (14.80)	213 (85.20)	0.842	0.5789	0.645	0.1781
Self-criticalness	99 (25.32)	292 (74.68)	37 (26.24)	104 (73.76)	62 (24.80)	188 (75.20)	1.079	0.7530	0.942	0.8106
Suicidal thoughts or wishes	88 (22.51)	303 (77.49)	32 (22.70)	109 (77.30)	56 (22.40)	194 (77.60)	1.017	0.9465	0.843	0.5171
Crying	63 (16.11)	328 (83.89)	28 (19.86)	113 (80.14)	35 (14.00)	215 (86.00)	1.522	0.1320	1.234	0.4750
Agitation	31 (7.93)	360 (92.07)	19 (13.48)	122 (86.52)	12 (4.80)	238 (95.20)	3.087	0.0034***	2.787	0.0086***
Loss of interest	16 (4.09)	375 (95.91)	5 (3.55)	136 (96.45)	11 (4.40)	239 (95.60)	0.799	0.6829	0.785	0.6626
Indecisiveness	60 (15.35)	331 (84.65)	26 (18.44)	115 (81.56)	34 (13.60)	216 (86.40)	1.436	0.2038	1.228	0.4839
Worthlessness	105 (26.85)	286 (73.15)	40 (28.37)	101 (71.63)	65 (26.00)	185 (74.00)	1.127	0.6119	0.932	0.7785
Loss of energy	10 (2.56)	381 (97.44)	6 (4.26)	135 (95.74)	4 (1.60)	246 (98.40)	2.732	0.1245	2.588	0.1518
Changes in sleeping pattern	28 (7.16)	363 (92.84)	11 (7.80)	130 (92.20)	17 (6.80)	233 (93.20)	1.160	0.7125	0.912	0.8250
Irritability	57 (14.58)	334 (85.42)	30 (21.28)	111 (78.72)	27 (10.80)	223 (89.20)	2.232	0.0056***	2.075	0.0127**
Changes in appetite	78 (19.95)	313 (80.05)	33 (23.40)	108 (76.60)	45 (18.00)	205 (82.00)	1.392	0.2002	1.220	0.4523
Concentration difficulty	27 (6.91)	364 (93.09)	16 (11.35)	125 (88.65)	11 (4.40)	239 (95.60)	2.780	0.0120**	2.497	0.0259**
Tiredness or fatigue	16 (4.09)	375 (95.91)	9 (6.38)	132 (93.62)	7 (2.80)	243 (97.20)	2.366	0.0947	2.046	0.1708
Loss of interest in sex	101 (25.83)	290 (74.17)	43 (30.50)	98 (69.50)	58 (23.20)	192 (76.80)	1.453	0.1144	1.290	0.2948

Values are presented as number (%) unless otherwise indicated. \*p<0.05 (2-tailed); \*\*p<0.01 (2-tailed); †bivariate logistic regression model; ‡logistic regression model, after adjusting for the HAM-D score, not including the items used to identify anxious depression; †statistically significant. BDI, Beck Depression Inventory; OR, odds ratio; HAM-D, 21-item Hamilton Rating Scale for Depression

**Table 3.** Baseline HAM-D: anxious/non-anxious depression

HAM-D items	Total (N=399)		Non-anxious depression (N=143 [35.84%])		Anxious depression (N=256 [64.16%])		Unadjusted OR <sup>†</sup>	Unadjusted p	Adjusted OR <sup>‡</sup>	Adjusted p
	Absent	Present	Absent	Present	Absent	Present				
Depressed mood (sadness, hopeless, helpless, worthless)	0 (0.00)	399 (100.00)	0 (0.00)	143 (100.00)	0 (0.00)	256 (100.00)	-	-	-	-
Feelings of guilt	88 (22.06)	311 (77.94)	32 (22.38)	111 (77.62)	56 (21.88)	200 (78.13)	1.030	0.9074	0.950	0.8413
Suicide	45 (11.28)	354 (88.72)	22 (15.38)	121 (84.62)	23 (8.98)	233 (91.02)	1.842	0.0552	1.641	0.1259
Insomnia early	112 (28.07)	287 (71.93)	44 (30.77)	99 (69.23)	68 (26.56)	188 (73.44)	1.229	0.3702	1.210	0.4106
Insomnia middle	67 (16.79)	332 (83.21)	24 (16.78)	119 (83.22)	43 (16.80)	213 (83.20)	0.999	0.9972	0.902	0.7178
Insomnia late	99 (24.81)	300 (75.19)	36 (25.17)	107 (74.83)	63 (24.61)	193 (75.39)	1.031	0.9000	0.936	0.7867
Work and activities	7 (1.75)	392 (98.25)	2 (1.40)	141 (98.60)	5 (1.95)	251 (98.05)	0.712	0.6872	0.652	0.6142
Retardation (slowness of thought and speech; impaired ability to concentrate; decreased motor activity)	339 (84.96)	60 (15.04)	118 (82.52)	25 (17.48)	221 (86.33)	35 (13.67)	0.748	0.3082	0.716	0.2488
Agitation	313 (78.45)	86 (21.55)	114 (79.72)	29 (20.28)	199 (77.73)	57 (22.27)	1.126	0.6438	1.028	0.9152
Anxiety (psychological) <sup>§</sup>	21 (5.26)	378 (94.74)	16 (11.19)	127 (88.81)	5 (1.95)	251 (98.05)	6.324	0.0004 <sup>***</sup>	6.336	0.0005 <sup>***</sup>
Anxiety somatic	9 (2.26)	390 (97.74)	8 (5.59)	135 (94.41)	1 (0.39)	255 (99.61)	15.101	0.0109 <sup>**</sup>	19.487	0.0057 <sup>***</sup>
Somatic symptoms (gastrointestinal) <sup>§</sup>	134 (33.58)	265 (66.42)	67 (46.85)	76 (53.15)	67 (26.17)	189 (73.83)	2.487	<0.0001 <sup>***</sup>	2.258	0.0003 <sup>***</sup>
Somatic symptoms general	26 (6.52)	373 (93.48)	20 (13.99)	123 (86.01)	6 (2.34)	250 (97.66)	6.775	<0.0001 <sup>***</sup>	6.189	0.0002 <sup>***</sup>
Genital symptoms (symptoms such as loss of libido, and menstrual disturbances)	199 (49.87)	200 (50.13)	75 (52.45)	68 (47.55)	124 (48.44)	132 (51.56)	1.174	0.4425	1.117	0.5998
Hypochondriasis <sup>§</sup>	254 (63.66)	145 (36.34)	128 (89.51)	15 (10.49)	126 (49.22)	130 (50.78)	8.804	<0.0001 <sup>***</sup>	10.205	<0.0001 <sup>***</sup>
Loss of weight	198 (49.62)	201 (50.38)	86 (60.14)	57 (39.86)	112 (43.75)	144 (56.25)	1.940	0.0018 <sup>**</sup>	1.898	0.0026 <sup>**</sup>
Insights	318 (79.70)	81 (20.30)	132 (92.31)	11 (7.69)	186 (72.66)	70 (27.34)	4.515	<0.0001 <sup>***</sup>	4.663	<0.0001 <sup>***</sup>
Diurnal variation	279 (69.92)	120 (30.08)	102 (71.33)	41 (28.67)	177 (69.14)	79 (30.86)	1.110	0.6477	1.075	0.7535
Depersonalization and derealization (such as feelings of unreality; and nihilistic ideas)	366 (91.73)	33 (8.27)	133 (93.01)	10 (6.99)	233 (91.02)	23 (8.98)	1.313	0.4897	1.240	0.5888
Paranoid symptoms	365 (91.48)	34 (8.52)	135 (94.41)	8 (5.59)	230 (89.84)	26 (10.16)	1.908	0.1228	1.896	0.1287
Obsessional and compulsive symptoms	368 (92.23)	31 (7.77)	130 (90.91)	13 (9.09)	238 (92.97)	18 (7.03)	0.756	0.4623	0.815	0.5951

Values are presented as number (%) unless otherwise indicated. \*p<0.05 (2-tailed); \*\*p<0.01 (2-tailed); \*\*\*p<0.001 (2-tailed); †bivariate logistic regression model; ‡logistic regression model, after adjusting for the HAM-D score, not including the item itself, and not including the items used to identify anxious depression; §the anxious depression factors from HAM-D; ‖statistically significant. HAM-D, 21-item Hamilton Rating Scale for Depression; OR, odds ratio



**Table 4.** Baseline HAM-A14: anxious/non-anxious depression

HAM-A14 items	Total (N=399)		Non-anxious depression (N=143 [35.84%])		Anxious depression (N=256 [64.16%])		Unadjusted OR <sup>†</sup>	Unadjusted P	Adjusted OR <sup>‡</sup>	Adjusted P
	Absent	Present	Absent	Present	Absent	Present				
Anxious mood	18 (4.51)	381 (95.49)	14 (9.79)	129 (90.21)	4 (1.56)	252 (98.44)	6.837	0.0009***§	6.558	0.0012***§
Tension	7 (1.75)	392 (98.25)	4 (2.80)	139 (97.20)	3 (1.17)	253 (98.83)	2.426	0.2503	2.503	0.2393
Fears	290 (72.68)	109 (27.32)	101 (70.63)	42 (29.37)	189 (73.83)	67 (26.17)	0.852	0.4919	0.800	0.3440
Insomnia	18 (4.51)	381 (95.49)	10 (6.99)	133 (93.01)	8 (3.13)	248 (96.88)	2.330	0.0819	1.919	0.1868
Intellectual	8 (2.01)	391 (97.99)	4 (2.80)	139 (97.20)	4 (1.56)	252 (98.44)	1.813	0.4053	1.306	0.7136
Depressed mood	0 (0.00)	399 (100.00)	0 (0.00)	143 (100.00)	0 (0.00)	256 (100.00)	-	-	-	-
Somatic (muscular)	33 (8.27)	366 (91.73)	16 (11.19)	127 (88.81)	17 (6.64)	239 (93.36)	1.771	0.1175	1.734	0.1351
Somatic (sensory)	72 (18.05)	327 (81.95)	33 (23.08)	110 (76.92)	39 (15.23)	217 (84.77)	1.669	0.0522	1.561	0.0949
Cardiovascular symptoms	106 (26.57)	293 (73.43)	45 (31.47)	98 (68.53)	61 (23.83)	195 (76.17)	1.468	0.0984	1.430	0.1268
Respiratory symptoms	61 (15.29)	338 (84.71)	29 (20.28)	114 (79.72)	32 (12.50)	224 (87.50)	1.781	0.0400*§	1.780	0.0420*§
Gastrointestinal symptoms	85 (21.30)	314 (78.70)	40 (27.97)	103 (72.03)	45 (17.58)	211 (82.42)	1.821	0.0158*§	1.720	0.0307*§
Genitourinary symptoms	164 (41.10)	235 (58.90)	63 (44.06)	80 (55.94)	101 (39.45)	155 (60.55)	1.209	0.3704	1.144	0.5294
Autonomic symptoms	60 (15.04)	339 (84.96)	31 (21.68)	112 (78.32)	29 (11.33)	227 (88.67)	2.166	0.0063***§	2.145	0.0075***§
Behavior at interview	276 (69.17)	123 (30.83)	108 (75.52)	35 (24.48)	168 (65.63)	88 (34.38)	1.616	0.0409*§	1.402	0.1669

Values are presented as number (%) unless otherwise indicated. \*p<0.05 (2-tailed); \*\*p<0.01 (2-tailed); \*\*\*p<0.001 (2-tailed); †bivariate logistic regression model; ‡logistic regression model, after adjusting for the HAM-D score, not including the items used to identify anxious depression; §statistically significant. HAM-A14, 14-item Hamilton Rating Scale for Anxiety; HAM-D, 21-item Hamilton Rating Scale for Depression; OR, odds ratio

non-anxious depression group (Table 3). Moreover, the anxious depression group exhibited more somatic symptoms, including gastrointestinal symptoms (73.83% vs. 53.15%,  $p=0.0003$ ) and general somatic symptoms (97.66% vs. 86.01%,  $p=0.0002$ ). Hypochondriasis (50.78% vs. 10.49%,  $p<0.0001$ ) and weight loss (56.25% vs. 39.86%,  $p=0.0026$ ) were also more common among individuals with anxious depression. Furthermore, patients with anxious depression tended to have greater insight into their condition (27.34% vs. 7.69%,  $p<0.0001$ ).

In the HAM-A14 scale, the anxious depression group exhibited a higher prevalence of anxious mood (98.44% vs. 90.21%,  $p=0.0012$ ), respiratory symptoms (87.50% vs. 79.72%,  $p=0.0420$ ), gastrointestinal symptoms (82.42% vs. 72.03%,  $p=0.0307$ ), and autonomic symptoms (88.67% vs. 78.32%,  $p=0.0075$ ) compared to the non-anxious depression group (Table 4). During the interviews, the anxious depression group displayed significantly more observable anxiety-related behaviors than the non-anxious depression group (34.38% vs. 24.48%,  $p=0.0409$ ), although this significance disappeared after adjusting for the HAM-D total score ( $p=0.1669$ ).

## DISCUSSION

Our study revealed a prevalence rate of 64.16% for anxious depression among outpatients, which is in line with a prior study conducted in China among individuals with MDD (64.5%)<sup>11</sup> and those with TRD (69.9%).<sup>22</sup> However, our findings demonstrated a much higher prevalence rate compared to previous studies conducted among German inpatients (49%)<sup>10</sup> and U.S. outpatients (53.2%)<sup>8</sup> with depression. Furthermore, our results indicated a lower prevalence rate of anxious depression than a previous Taiwanese study among psychiatric inpatients with MDD (81%).<sup>9</sup> These disparities may be attributed to several factors, including cultural variations and differences in healthcare-seeking behavior. In prior reports, patients with anxious depression often exhibit greater severity of depressive symptoms and an increased risk of suicide,<sup>3,9</sup> which may lead to hospitalization rather than regular outpatient follow-up. These findings suggest that the prevalence rate of anxious depression can vary significantly across different cultures and may be higher among inpatients compared to outpatient or community populations.

Regarding the demographic characteristics of individuals with anxious depression, we observed that patients with anxious depression were significantly more likely to be older, married, have lower educational levels, have more children, and experience an older age of first episode onset. These associations persisted even after adjusting for the total HAM-D score. Aligning with previous research, patients with anxious depression are more likely to be female, non-single, unem-

ployed, less educated, and experience more severe depression.<sup>23</sup> As for marital status, during the child-bearing years, women face the highest risk of depression, and untreated maternal depression and anxiety can negatively affect both the mother and child, including the parent-child bond.<sup>24</sup> This negative impact may stem from attachment insecurity and the interconnectedness of depression and negative outcomes in parent-child relationships.<sup>25</sup>

Moreover, the study revealed a correlation between anxious depression and being married, which warrants further investigation. Marriage, known for its potential to reduce depression and anxiety, plays a protective role in mental health.<sup>26</sup> However, separated individuals tend to report higher levels of depression and anxiety,<sup>27</sup> possibly influenced by cultural factors such as the repression of Asian women or traditional early marriages and gender roles.

Lastly, regarding the onset of depression in older age, studies indicate an increase in depression incidence and prevalence,<sup>28</sup> particularly among elderly women, with neuroticism identified as a risk factor.<sup>29</sup> Thus, anxiety and aging may contribute to late-life depression risk factors.

While patients with anxious depression in the STAR\*D study in the U.S. were more likely to have comorbid Axis I disturbances,<sup>8</sup> our study found that patients with anxious depression primarily exhibited higher comorbidity of panic disorder without agoraphobia, rather than another Axis I condition. This finding aligns with a previous German study.<sup>10</sup> These differences in results may be attributed in part to variations in sample sizes and differences in clinical and cultural contexts. The STAR\*D study included a total of 2,876 outpatients,<sup>8</sup> the German study recruited 429 inpatients,<sup>10</sup> and our study enrolled 399 outpatients, which is more akin to the German study in terms of sample size. Further research is therefore warranted to explore these differences in diverse population groups.

Besides, by comparing the 6-item anxiety/somatization factors of the HAM-D and HAM-A14, we discovered that the severity of anxiety is not only related to mood, but also manifests in respiratory, gastrointestinal, and autonomic symptoms. In other words, when observing whether depressive patients have anxious distress, we can focus more on the aforementioned somatic symptoms.

In addition to the defining features of anxious depression, our study also revealed that patients with anxious depression exhibited higher levels of agitation, irritability, and concentration difficulty, as measured by items in the BDI. One possible explanation for this finding is the subjective and private nature of the experience of depression.<sup>9,30</sup> BDI focuses more on an individual's own feelings of depression rather than clinical observations. Another explanation is that individuals with low extraversion and high neuroticism tended to report more

depressive symptoms on the BDI than on the HAM-D.<sup>31</sup> However, a strong correlation still exists between BDI-II and HAM-D, with an average Spearman correlation coefficient of approximately 0.76. Moderate correlations were also found in change scores, with Spearman correlation coefficients of 0.61 between HAM-D and BDI-II.<sup>32</sup>

Another potential contributing factor could be the personality trait of neuroticism, which has been strongly associated with symptoms of depression and anxiety.<sup>33</sup> Previous research by Ma et al.<sup>34</sup> suggested that individuals with high neuroticism tendencies may tend to overreport depressive symptoms. When combined with the higher frequency of somatic complaints observed in the anxious depression group, these factors may contribute to a poorer quality of life and functional impairment, as noted in previous studies.<sup>9</sup>

While previous research has indicated a higher risk of suicide in patients with anxious depression,<sup>3</sup> our study did not find a significantly elevated suicide risk among this group. However, suicidal thoughts were reported in approximately 77% of cases assessed by the BDI for anxiety depression, and approximately 91% assessed by the HAMD, indicating a relatively high percentage. This suggests that suicidality may be influenced by multiple factors besides anxiety. A survey conducted on Taiwanese psychiatric inpatients by Lin et al.<sup>9</sup> reported that 27% of their study population was admitted for self-harm or suicide attempts, and 33% were admitted for suicidal ideation, considering that suicide risk is a major concern in psychiatric admissions. According to the American Psychiatric Association Steering Committee on Practice Guideline, risk factors for suicidality with evidence include hopelessness, impulsiveness, anhedonia, panic attacks, or anxiety, particularly in patients with MDD.<sup>35</sup> The increased suicidality associated with anxiety depression still warrants attention.

Currently, there are only a limited number of studies that have attempted to describe the clinical presentation of patients with anxious depression. The prevalence and presentation of anxious depression in Asian countries differ from those in Western countries, highlighting the importance of understanding the characteristics of anxious depression across different cultures. Our study focused on Taiwanese depressive outpatients, which is distinct from previous studies that concentrated on inpatients or outpatients with TRD. Patients with anxious depression often present with more somatic complaints and may mask their psychiatric symptoms, making it crucial for clinicians to gain a better understanding of their clinical manifestations and identify them early for appropriate treatment.

However, it is essential to acknowledge several limitations in our study. Firstly, our study population was limited to psychiatric outpatients in hospitals, and the results may not be generalizable to inpatient groups or patients from communi-

ty or psychiatric clinics. Secondly, we lacked data regarding the participation rate among patients with and without anxious depression, potentially impacting the prevalence estimate. Thirdly, our definition of anxious depression relied on psychometric measures rather than diagnostic interviews conducted by psychiatrists. Additionally, anxiety is often dimensionally presented in clinical settings, but our study categorized individuals into anxious and non-anxious depression groups, potentially overlooking variability within these groups. Further research is needed to explore these factors in more depth.

In conclusion, the prevalence rate of anxious depression among Taiwanese psychiatric outpatients was found to be 64.16%, which closely aligned with the Chinese study but was lower than what was observed in the Taiwanese inpatient group. This study contributes to clinicians' understanding of the clinical presentation of Asian outpatients with anxious depression, particularly emphasizing the presence of somatic complaints.

### Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

### Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

### Author Contributions

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