



Memory Impairment and Plasma BDNF Correlates of the *BDNF Val66Met* Polymorphism in Patients With Bipolar II Disorder

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Studies suggest that a functional polymorphism of brain-derived neurotrophic factor (BDNF), polymorphism *BDNF Val⁶⁶Met* affects cognitive functions, however, the effect is unclear in bipolar II (BD-II) disorder. We used the Wechsler Memory Scale-third edition (WMS-III), the presence of the *BDNF Val⁶⁶Met* polymorphism, and plasma concentrations of BDNF to investigate the association between memory impairment and BDNF in BD-II disorder. We assessed the memory functions of 228 BD-II patients and 135 healthy controls (HCs). BD-II patients had significantly lower scores on five of the eight WMS-III subscales. In addition to education, the BDNF polymorphism were associated with the following subscales of WMS-III, auditory delayed memory, auditory delayed recognition memory and general memory scores in BD-II patients, but not in HC. Moreover, BD-II patients with the *Val*-homozygote scored significantly higher on the visual immediate memory subscale than did those with the *Met/Met* and *Val/Met* polymorphisms. The significantly positive effect of the *Val*-homozygote did not have a significantly positive effect on memory in the HC group, however. We found no significant association between BDNF polymorphisms and plasma concentrations of BDNF. The plasma BDNF was more likely to be associated with clinical characteristics than it was with memory indices in the BD-II group. The impaired memory function in BD-II patients might be dependent upon the association between the *BDNF Val⁶⁶Met* polymorphism and peripheral BDNF levels.

Keywords: bipolar II disorder, BDNF genotype, plasma concentrations of BDNF, memory, auditory delayed memory

INTRODUCTION

Patients with bipolar disorder (BD) have a variety of cognitive deficits (Bearden et al., 2001; Murphy and Sahakian, 2001; Quraishi and Frangou, 2002) that might affect drug adherence, therapeutic outcomes, and prognosis (Simonsen et al., 2008). Most prior studies focused on patients with bipolar I disorder (BD-I) (Dickerson F. et al., 2004; Dickerson F.B. et al., 2004; Jamrozinski et al., 2009). Bipolar II disorder (BD-II) patients have a more chronic course with depressive episodes and shorter periods in remission than do BD-I patients (Judd et al., 2003). Rihmer and Kiss (2002) found that BD-II patients had the highest risk of suicide, interpersonal conflict, and family breakdown among people with major mood disorders. In addition, there is no consensus on whether BD-I and BD-II are different subtypes of BD. Evidence from biological, clinical, and pharmacological studies indicates that they are (Vieta et al., 1997; Vieta and Suppes, 2008; Wang et al., 2012). Moreover, BD-I and BD-II patients are reported to have two distinct genotypes (Charney et al., 2017). Compared with healthy controls, BD patients had significantly poorer executive function and memory that was more impaired than did healthy controls during remission (Martinez-Aran et al., 2004). This high correlation between poor memory and learning might explain the daily dysfunction in BD patients during remission.

Evidence has shown a negative effect of mood episode duration and severity on memory performance and executive function (Cavanagh et al., 2002; Martinez-Aran et al., 2004; Bearden et al., 2006). The more mood episodes the patients had, the poorer their higher order cognitive performance would be (Ciammola et al., 2007; Levy et al., 2009). Gualtieri and Johnson (2006) reported that verbal memory impairment seemed to present across mood phases, stable marker which implied that it was a stable marker for BD.

Brain-derived neurotrophic factor (BDNF), a member of the neurotrophins family, is important for neuron survival and proliferation (Berk et al., 2011). More specifically, BDNF is highly correlated with learning- and memory-related hippocampal neurons (Poo, 2001; Lu et al., 2008). Guzowski et al. (2000) reported that inhibiting BDNF signaling by gene knockdown or antisense RNA would impair spatial learning and memory. Altar et al. (1997) reported an association between BDNF and dopamine survival and functioning in the midbrain. Preclinical evidence suggests BDNF is involved in the hippocampal functions of learning and memory (Hariri et al., 2003). An SNP (rs6265) producing a valine (*Val*)-to-methionine (*Met*) substitution in the pro-BDNF protein at codon 66 (*Val*⁶⁶*Met*) correlates with hippocampal-mediated memory performance in humans (Egan et al., 2003; Hariri et al., 2003). In addition, Toh et al. (2018) recently reported that *Val*-homozygotes had better performance in the tasks related to memory in healthy participants and clinical population.

Kim et al. (2010) reported a significant postmortem decrease of serum BDNF level in BD-II patients, which indicates an association with brain atrophy and progressive cognitive changes in BD-II. Pan et al. (1998) concluded that there is a positive correlation between serum and central BDNF levels. Serum

BDNF levels gradually decline in the later stages of BD episodes (Kapczinski et al., 2008a; Kauer-Sant'Anna et al., 2009). Studies have also reported lower serum BDNF levels during manic and depressive episodes, and higher levels during remission (Kapczinski et al., 2008b; Lin, 2009).

BDNF might be a biomarker of normal cognitive function in healthy adults (Yu et al., 2008). In addition, BD patients with *Val* homozygotes are more likely to perform better cognition (Mandolini et al., 2018). Moreover, serum BDNF levels fall significantly in progressive cognitive decline, e.g., mild cognitive impairment (Yu et al., 2008), Alzheimer's disease (Gunstad et al., 2008), Huntington's disease (Ciammola et al., 2007), and schizophrenia (Zhang et al., 2012). Furthermore, peripheral BDNF levels have therapeutic effects on acute mania episodes, but not on depressive episodes (Fernandes et al., 2015). However, Chen et al. (2014) concluded that "plasma BDNF profiles in different mental disorders are not affected by *BDNF Val*⁶⁶*Met* gene variants, but by the process and progression of the illness itself" and they suggested a positive correlation between BDNF levels in the peripheral and central areas. Thus, the plasma concentration of BDNF can be examined as a possible biomarker for the clinical course of BD.

We hypothesized that the BD-II group would have relatively lower scores than would the HC group in some memory performance domains. In addition, such memory impairment is correlated with various BDNF polymorphisms. Moreover, the plasma concentration of BDNF might be a biomarker for predicting memory performance in BD-II patients.

MATERIALS AND METHODS

Participants

The research protocol was approved by the Institutional Review Board (IRB) for the Protection of Human Subjects at National Cheng Kung University Hospital. All the participants were given full information about the study and provided a signed written informed consent form. The patient groups were recruited from outpatient and inpatient settings at National Cheng Kung University Hospital. Each patient was initially evaluated by an attending psychiatrist and then interviewed by well-trained research team members using the structured interview of the Chinese Version of the Modified Schedule of Affective Disorder and Schizophrenia-Life Time (SADS-L) (Endicott and Spitzer, 1978), which has good interrater reliability (Huang et al., 2004) and is based on the diagnosis of BD in the *Diagnostic and Statistical Manual of Mental Disorders, fourth edition-TR* (DSM-IV-TR). Patients diagnosed with any illness other than BD-II were excluded. The Young Mania Rating Scale (YMRS) (Young et al., 1978) and the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960, 1967) were used to evaluate the severity of their mood symptoms. Healthy controls were volunteers recruited from the community via advertisements. The Chinese version of the SADS-L was used to screen and exclude all with a history of psychiatric illness. All HCs were free of present or past major mental illness (affective disorder, schizophrenia, anxiety disorder, personality disorder, and substance use disorders), and none had

a family history of psychiatric disorder among their first-degree relatives. Moreover, only Han Chinese participants were recruited to reduce the effect of ethnic heterogeneity in the genetic analysis.

Measuring Plasma Concentrations of BDNF

Twenty milliliters of blood was drawn using venipuncture from each participant. Plasma was isolated from the whole blood after it had been centrifuged at 3000 *g* for 15 min at 4°C, and then it was immediately stored at –80°C. The BDNF levels were quantified using an antibody pair assay system (Flexia; BioSource Intl., Camarillo, CA, United States). Sample processing and data analysis were done according to the manufacturer's instructions. The genotypes of the *BDNF Val⁶⁶Met* polymorphisms were determined using polymerase chain reactions plus restriction fragment length polymorphism (PCR-RFLP) analysis (Neves-Pereira et al., 2002). The laboratory technician who did the genotyping and read out the genotype data was blinded to the patients' diagnoses. The genotype error rate was less than 5%.

Wechsler Memory Scale-Third Edition

The Wechsler Memory Scale-third edition (WMS-III) (Wechsler and Stone, 1997) is the most commonly used test for memory functions. Composite scores were calculated for the eight standardized primary indices: Auditory Immediate Memory Index (WMS-AIM), Visual Immediate Memory (WMS-VIM), Immediate Memory (WMS-IM), Auditory Delayed Memory (WMS-ADM), Visual Delayed Memory (WMS-VDM), Auditory Delayed Recognition Memory (WMS-ADRM), General Memory (WMS-GM), and Working Memory (WMS-WM).

Statistics

Pearson χ^2 analysis was used to examine the gender differences, BDNF genotype distribution between groups, and other categorical variables. The distribution of alleles and genotypes were calculated and compared between groups using χ^2 tests. Hardy-Weinberg equilibrium was computed for the expected genotype distribution using the standard goodness-of-fit test. Multivariate analysis of covariance (MANCOVA) was used to compare WMS-III subscales between two groups; age, educational level, and gender were covariates. Multivariate linear regression analyses were done to explore the interaction between BDNF variants and plasma concentrations of BDNF on memory subscales. Although the Bonferroni correction is the popularly used correction for multiple comparisons, it is too conservative and leads to type II error. Thus, we used the false discovery rate method suggested by Benjamini and Hochberg (1995) to correct for multiple correlations.

RESULTS

Demographic Data and Clinical Characteristics

We enrolled 363 participants (228 BD-II and 135 HC). BD-II group was significantly older ($F = 7.59$, $p = 0.006$), had

significantly more females ($F = 4.66$, $p = 0.03$), and had significantly less formal education ($F = 45.07$, $p < 0.005$) than did the HC group (Table 1). Plasma concentrations of BDNF were significantly higher in the HC group than in the BD-II group ($F = 3.94$, $p = 0.04$).

To explore which clinical characteristics and demographic variables are associated with plasma concentrations of BDNF, demographic data, age and gender, clinical characteristics, HDRS score, YMRS score, age at onset of BD-II, and duration of illness were independent variables in the multivariate linear regression analyses, and plasma concentrations of BDNF were dependent variables. Stepwise linear regression showed a significant association between plasma concentrations of BDNF level and duration of illness and HDRS scores ($F = 4.55$, $p = 0.01$). Stepwise linear regression also showed that the plasma concentrations of BDNF were significantly negatively associated with the duration of illness ($\beta = -0.17$, $t = -2.51$, $p = 0.017$) and positively associated with HDRS scores ($\beta = 0.14$, $t = 2.00$, $p = 0.047$).

Memory was assessed using a multivariate analysis of covariance (MANCOVA) with WMSI-III subscales as dependent variables, group (HC and BD-II) as independent variables, and age, educational level, and gender as covariates. There was no significant interaction between the variables of group, age, gender, and educational level ($ps > 0.05$). A subsequent multivariate analysis of variance (MANOVA) that compared the subscales of the WMS-III between groups showed a significant difference between the groups ($F = 7.50$, $p < 0.0005$). In addition, the BD-II patients had significantly lower scores on five subtests of eight indices: WMS-IM, WMS-ADM, WMS-ADRM, WMS-GM, and WMS-WM after the recommended *p*-value correction of multiple comparisons by Benjamini and Hochberg (1995) (Table 1).

Genotype Effects on Memory Subscales Between Patients and Healthy Controls

The distribution of *BDNF Val⁶⁶Met* genotypes for all participants in the study was as follows: 79 *Val/Val*; 185 *Val/Met*; and 99 *Met/Met*. Allele frequencies were 47.2% for *Val* and 52.8% for *Met*. Genotypes were in Hardy-Weinberg equilibrium using the standard goodness-of-fit test: $\chi^2 = 2.34$, $p > 0.05$. Genotypes in the BD-II and the HC groups were in Hardy-Weinberg equilibrium, according to the standard goodness-of-fit test: $\chi^2 = 2.12$, $p > 0.05$ and $\chi^2 = 0.845$, $p > 0.05$, respectively.

BDNF Val⁶⁶Met frequencies were significantly different between the two groups ($\chi^2 = 7.81$, $p = 0.02$). The frequency of *Val/Val* genotype carriers (17.1%) was significantly lower than the frequency of *Met/Met* genotype carriers (28.9%) in the BD-II group, but not in the HC (29.6% *Val*-homozygote carriers vs. 24.4% *Met*-homozygote carriers) (Table 1).

To explore the effect and association between *BDNF Val⁶⁶Met* genotypes and plasma concentration of BDNF on WMS-III subscales between two groups, stepwise multivariate linear regression analyses were done. In the following analyses, the demographic variables, age, educational level and gender, and BDNF variant and plasma concentration BDNF were counted

TABLE 1 | Demographic characteristics and *BDNF* allele and genotype distributions in healthy controls and patients with BP-II.

Variables	Bipolar II disorder (n = 228)	Healthy controls (n = 135)	F/ χ^2 (p-value)
Gender (Male/Female)	105/123	78/57	4.66 (0.03)
Age (Mean \pm SD)	35.17 \pm 13.26	31.69 \pm 7.94	7.59 (0.006)
Educational level (years)	13.27 \pm 3.28	15.31 \pm 1.65	44.52 (<0.005)
Age at onset of disorder	14.75 \pm 4.43	–	
Duration of illness (years)	19.63 \pm 12.57	–	
Hamilton depression rating scale score	15.82 \pm 4.11	–	
Young mania rating scale score	12.81 \pm 3.45	–	
Plasma concentrations of BDNF (ng/ml)	13.86 \pm 13.04	16.53 \pm 9.15	3.94 (0.048)
BDNF genotype (n, %)			7.81 (0.02)
<i>Met/Met</i>	66 (28.9%)	33 (24.4%)	
<i>Val/Met</i>	123 (53.9%)	62 (45.9%)	
<i>Val/Val</i>	39 (17.1%)	40 (29.6%)	
BDNF allele frequency (n, %)			4.93 (0.03)
<i>Met</i>	255 (55.9%)	128 (47.4%)	
<i>Val</i>	201 (45.1%)	142 (52.6%)	
WECHSLER MEMORY SCALE-THIRD EDITION (WMS-III)			
Auditory immediate (AIM)	100.73 \pm 43.20	106.84 \pm 13.44	2.31 (0.13)
Visual immediate (VIM)	95.95 \pm 17.46	100.26 \pm 14.50	4.95 (0.03)
Immediate memory (IM)	96.57 \pm 17.26	104.35 \pm 12.22	18.62 (<0.0005)
Auditory delayed (ADM)	97.83 \pm 18.47	106.98 \pm 13.00	25.17 (<0.0005)
Visual delayed (VDM)	95.53 \pm 18.31	98.96 \pm 13.95	3.53 (0.06)
Auditory recognition delayed (ARDM)	97.10 \pm 17.15	107.15 \pm 13.01	34.00 (<0.0005)
General memory (GM)	96.37 \pm 17.91	104.36 \pm 13.08	20.07 (<0.0005)
Working memory (WM)	95.07 \pm 14.69	104.53 \pm 15.06	34.30 (<0.0005)

TABLE 2 | Linear regression analyses with stepwise for each subscale of WMS-III in the BP-II group.

	Educational level (β , t , p)	Gender (β , t , p)	BDNF variant (β , t , p)	F (p-value)
WMS-AIM	$\beta = 0.17$, $t = 2.48$ (0.01)	–	–	5.90 (0.02)
WMS-VIM	$\beta = 0.18$, $t = 2.69$ (0.008)	$\beta = 0.31$, $t = 4.69$ (<0.0005)	–	12.49 (<0.0005)
WMS-IM	$\beta = 0.22$, $t = 3.39$ (0.001)	$\beta = 0.25$, $t = 3.83$ (<0.0005)	–	10.79 (<0.0005)
WMS-ADM	$\beta = 0.22$, $t = 3.28$ (0.001)	$\beta = 0.20$, $t = 3.00$ (0.003)	$\beta = 0.17$, $t = 2.52$ (0.01)	6.79 (<0.0005)
WMS-VDM	–	$\beta = 0.26$, $t = 4.03$ (<0.0005)	–	16.23 (<0.0005)
WMS-ARDM	$\beta = 0.24$, $t = 3.48$ (0.001)	$\beta = 0.18$, $t = 2.70$ (0.007)	$\beta = 0.14$, $t = 2.18$ (0.03)	6.29 (<0.0005)
WMS-GM	$\beta = 0.21$, $t = 3.16$ (0.002)	$\beta = 0.26$, $t = 3.98$ (<0.0005)	$\beta = 0.13$, $t = 2.03$ (0.04)	7.84 (<0.0005)
WMS-WM	$\beta = 0.31$, $t = 4.71$ (<0.0005)	–	–	22.22 (<0.0005)

WMS-AIM, auditory immediate memory index; WMS-VIM, visual immediate memory index; WMS-IM, immediate memory index; WMS-ADM, auditory delayed memory index; WMS-ARDM, auditory delayed recall memory index; WMS-GM, general memory index; WMS-WM, working memory index.

as independent variables on each subscale of the WMS-III. There was a significant effect of BDNF variants and educational level on WMS-ADM ($F = 5.19$, $p = 0.006$), but not on other memory subscales (Table 2). For other subscales of the WMS-III, educational level and gender seemed to have a significant effect on all variables for both groups. However, the effect of BDNF polymorphisms was found only in the BD-II group, and for some memory indices.

Subsequently, taking the number of *Val* alleles into account, linear regression analyses in BD-II patients with the *Val* homozygote variant showed a significantly negative association with the WMS-ADM ($\beta = -4.24$, $t = -2.36$, $p = 0.02$). Moreover, a comparison of each memory subscale of the WMS-III stratified by different BDNF variants in both groups

showed no significant effect of BDNF polymorphisms in the HC group. However, BD-II patients with the *Val* homozygote had significantly higher visual immediate memory scores after correction for multiple comparisons (Table 3). Furthermore, a comparison of the plasma concentrations of BDNF between the two groups stratified by BDNF variants showed that among *Met* homozygote, the BD-II patients with the *Met* homozygote had significantly lower plasma concentrations of BDNF than did the HCs. There was no significant interaction between BDNF polymorphisms and plasma BDNF levels ($F = 2.32$, $p = 0.1$) in either group, which indicated that the BDNF Val⁶⁶Met polymorphism and the plasma concentration of BDNF might be independent of each other in both groups.

TABLE 3 | Comparisons of scores on the WMS-III subtests by genotype groupings in the BP and HC groups.

	Bipolar II disorder			Healthy Controls			F (p)
	Met/Met	Val/Met	Val/Val	Met/Met	Val/Met	Val/Val	
WECHSLER MEMORY SCALE-THIRD EDITION (WMS-III)							
Auditory immediate (AIM)	97.86 ± 15.16	101.68 ± 57.20	102.59 ± 15.25	108.10 ± 13.05	106.08 ± 12.18	106.98 ± 15.70	0.24 (0.786)
Visual immediate (VIM)	97.24 ± 16.25	93.02 ± 18.72	103.00 ± 12.71	99.79 ± 19.92	101.11 ± 12.08	99.33 ± 12.90	0.20 (0.815)
Immediate memory (IM)	97.33 ± 15.90	94.36 ± 18.41	103.28 ± 14.00	106.30 ± 14.02	104.10 ± 10.95	103.13 ± 12.61	0.63 (0.533)
Auditory delayed (ADM)	96.39 ± 18.00	96.17 ± 18.67	105.44 ± 17.08	106.73 ± 13.08	105.98 ± 11.98	108.73 ± 14.52	0.55 (0.581)
Visual delayed (VDM)	97.24 ± 18.59	92.58 ± 18.87	101.79 ± 13.97	97.12 ± 15.10	100.52 ± 13.88	98.05 ± 13.12	0.76 (0.472)
Auditory recognition delayed (ARDM)	95.68 ± 16.05	96.28 ± 18.35	102.05 ± 14.36	108.18 ± 14.51	106.05 ± 12.32	108.00 ± 12.95	0.41 (0.666)
General memory (GM)	96.32 ± 17.16	94.10 ± 18.95	103.49 ± 13.94	103.15 ± 15.16	104.32 ± 12.25	105.40 ± 12.73	0.27 (0.768)
Working memory (WM)	96.12 ± 13.12	94.33 ± 15.87	95.59 ± 13.59	99.45 ± 20.29	107.44 ± 11.97	104.20 ± 13.49	3.13 (0.047)
Plasma concentration of BDNF (ng/ml)	11.26 ± 5.17	14.11 ± 7.33	12.98 ± 7.93	17.42 ± 8.81	15.27 ± 9.03	17.73 ± 9.56	1.09 (0.034)

There was a linear positive correlation between the number of Val alleles and the ARDM in BP-II ($p < 0.05$); *significant level after p -value correction according to FDR.

DISCUSSION

Our findings were that BD-II patients had less formal education than did the HCs, which indicates that BD interrupted the patients' education (Breslau et al., 2008). The BDNF genotype did not affect the age of onset of BD, which was consistent with Hong et al. (2003). BD-II patients with the Val/Val variant had significantly better memory scores on the Auditory Delayed Memory index, Auditory Delayed Recognition Memory index, and General Memory index among patients with BDNF genotypes. This finding supported a claim (Egan et al., 2003) that the Val⁶⁶Met polymorphism is associated with hippocampal BDNF production and hippocampal structural and functional changes.

Compared with other factors, the HDRS score was more likely to predict the plasma concentrations of BDNF in BD-II patients, which was consistent with Brunoni et al. (2008), who reported an association between BDNF levels and BD-II patients with chronic depression. The neuroplastic changes in BD-II might be caused by depression instead of hypomania. Larger samples are required to confirm this association between peripheral levels (both plasma and serum) of BDNF and mood episodes of BD-II. Other studies have reported that serum BDNF levels rise during manic and depressive episodes, but because our study was not longitudinal, we were unable to confirm this claim.

We found no significant association between BDNF variants and plasma concentrations of BDNF in our study, which was consistent with Tramontina et al. (2007), who reported in euthymic Caucasians. They concluded that the BDNF polymorphism might play a role during acute episodes, as suggested by Cunha et al. (2006). Previous study reported significantly different frequencies for BDNF Val⁶⁶Met genotypes and alleles between Asian (Korea) and Caucasian (Croatia) (Pivac et al., 2009). They found that significantly higher frequency of Met allele (46.3%) in Asian country compared to 53.7% in the Caucasian. In Shen et al. (2018)'s review, that approximate 50% of Asians carried Val/Met genotype, but in the Caucasians, more than half carried Val/Val genotype. The results in our study was consistent with previous finding. The BDNF Met allele may have a specific role in memory dysfunction among BD-II patients. Unlike the HCs, patients with BD-II the Met-homozygote scored consistently lower than did their Val-homozygous counterparts on the WMS-ADM subscale and had lower plasma levels of BDNF. We did not find a superior performance of Val-homozygote carriers to the other two genotype groups on the WMS-ADM in the HC, which was previously reported (Chang and Yeh, 2012; Yeh et al., 2012) in undergraduate students. Another possibility is that the undergraduate students were not screened for their history of mental illness. The mechanisms through which the BDNF Val⁶⁶Met variant affects memory warrants further investigation. The negative association between BDNF level and duration of BD-II indicates that long-term BD-II reduces BDNF levels more than does short-term BD-II (Barbosa et al., 2013). Our findings were consistent with Pacheco et al. (2012), who reported an association between BDNF genotype and memory in older adults which implied that BD-II

is a neurodegenerative disorder. However, this hypothesis needs further investigation.

Our study has several limitations that prevent the results from being generalized. First, the sample size is small. Secondly, this cross-sectional study does not allow examination of the interaction between BDNF plasma concentrations and memory: a longitudinal study is necessary. Third, all the participants were Han Chinese; thus, generalizing our findings to other ethnic groups is probably not possible. Using a transmission disequilibrium test (TDT) might confirm our results. Finally, future studies are needed to clarify how BDNF concentrations might affect memory in BD-II patients.

CONCLUSION

The association between the *BDNF Met* allele and poor memory, especially auditory delayed memory in BD-II patients, suggests a specific role of the *BDNF Val⁶⁶Met* variant in some aspects of memory dysfunction. In addition, peripheral BDNF levels might be a biomarker of auditory memory performance in BD-II patients. The association between decreased plasma

concentrations of BDNF and the degree of cognitive impairment in BD-II patients appears to be independent of the presence of the *BDNF Val⁶⁶Met* polymorphism.

AUTHOR CONTRIBUTIONS

Y-HC wrote the first draft of this manuscript and designed this study with R-BL. T-YW, S-YL, S-LC, and C-CH managed the lab work and statistical analyses. T-YW, C-CH, PSC, YKY, J-SH, and R-BL managed the patients' recruitment and literature review. This study was reviewed by all authors.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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