

# Relationship between Matrix Metalloproteinase-9 and Lifetime History of Suicidal Behavior in Remitted Patients with Bipolar I Disorder: A Cross-Sectional Pilot Study

To the editor,

Bipolar disorder (BD) is a chronic recurring mood disorder with a lifetime prevalence of 1.06%.<sup>[1]</sup> BD is associated with comorbid substance use, medical illnesses, suicidal behaviors, and biorhythm irregularities, leading to increased morbidity and mortality.<sup>[2,3]</sup>

Suicidality is one of the preventable causes of mortality in BD. The prevalence rates of suicide attempts (25–50%) and suicidal deaths (8–19%) are higher among BD-I patients than the general population.<sup>[4]</sup> There are various biopsychosocial risk factors for suicidality in BD.<sup>[5]</sup>

Neurotrophins such as brain-derived neurotrophic factor (BDNF) and matrix metalloproteinase-9 (MMP-9) are actively researched as biomarkers in BD. BDNF is biologically activated by MMP-9, leading to effective neuronal growth and synaptic plasticity.<sup>[6]</sup> Studies reveal that suicidality and BD are independently associated with raised MMP-9 levels.<sup>[7,8]</sup>

The present study aimed to evaluate the relationship between MMP-9 levels and lifetime history of suicide attempt in remitted BD-I patients.

## MATERIALS AND METHODS

The study was cross-sectional in design, and the participants were recruited by purposive sampling in a tertiary-cum-teaching hospital in southern India. Patients with BD-I ( $n = 150$ ) were enrolled into the parent study, which analyzed the course and outcome of BD-I among Indian patients.<sup>[9]</sup> A subset of patients ( $n = 60$ ) from the parent study was studied for neurotrophic markers (MMP-9) and cognitive functions in another unpublished research. Those patients with data on illness course, suicidality, and neurotrophic markers were included in the present pilot study.

Patients aged 18–65 years, with BD-I diagnosis as per Structured Clinical Interview for DSM-IV-TR Axis-I Disorders (SCID-I),<sup>[10]</sup> with illness duration of minimum 3 years, and currently in clinical remission as defined by Hamilton Depression Rating Scale (HDRS) score  $< 8$  and Young Mania Rating Scale (YMRS) score  $< 7$  were included.<sup>[11,12]</sup> Patients with active substance use in the past 12 weeks or having medical/neurological illnesses were excluded.

Sociodemographic data were collected using a semi-structured proforma. The illness course was systematically charted in the National Institute of Mental Health – Life Chart Methodology (Retrospective) chart.<sup>[13]</sup> The severity of lifetime suicide behavior was assessed using the Columbia Suicide Severity Rating Scale (C-SSRS).<sup>[14]</sup> Serum MMP-9 levels were assessed using the enzyme-linked immunoassay method. Informed consent was obtained from all the participants, and the Institute Ethics Committee approved the study protocol.<sup>[9]</sup>

Non-parametric tests were chosen for this sample due to the non-uniform distribution of MMP-9 values. After appropriate descriptive analyses, Mann–Whitney *U* test was used for comparison for dichotomous variables and Kendall's  $\tau b$  was used for non-parametric correlation with the continuous data. No sensitivity analysis was performed. Statistical analyses were conducted using SPSS 19 (IBM Corp, Armonk, NY), and  $P < 0.05$  was considered significant.

## RESULTS

Remitted BD-I patients ( $n = 25$ ) were recruited. The mean age was 34.0 years (range 22–56 years), with 60% being females. The participants were mainly home-makers, and were educated above 10<sup>th</sup> grade. A major proportion (92%) belonged to the lower socioeconomic status. The mean duration of BD was 12.1 years (range 3–24 years), with a mean of 5 episodes (range 2–13). Eleven participants (44%) had unipolar mania. The lifetime history of a suicide attempt was noted in 20% ( $n = 5$ ) of the participants.

In the present study, only 6 out of 25 subjects (24%) had MMP-9 levels within the standard normal range (11.4–59.4 ng/ml), with the remainder having less than normal levels. The mean MMP-9 level in the entire sample was  $9.09 \pm 11.58$  ng/ml. The levels of MMP-9 were higher in patients with a lifetime history of a suicide attempt when compared to those without ( $20.25 \pm 169.49$  ng/ml vs.  $6.29 \pm 8.24$  ng/ml,

Mann–Whitney  $U = 14.000$ ,  $P = 0.014$ ). MMP-9 levels negatively correlated with the age of the participants (Kendall's  $\tau b = -0.264$ ,  $P = 0.068$ ) and the duration of BD (Kendall's  $\tau b = -0.279$ ,  $P = 0.057$ ), with a trend toward significance [Table 1].

## DISCUSSION

The prevalence rate of suicide attempts in the study population was comparable to those observed in a previously reported study.<sup>[15]</sup> A preponderance of T-allele versus C-allele of 1562C/T of the MMP-9 gene was found in BD patients compared to control subjects, leading to pro-inflammatory changes.<sup>[16,17]</sup> Considering the neuroinflammatory hypothesis of BD, increased MMP-9 levels could be considered a marker of an inflammatory state.

In the current study, elevated MMP-9 levels were associated with a lifetime history of suicide attempt in BD, suggesting the role of a state marker for suicidality.<sup>[9]</sup> However, the evidence remains inconclusive on the nature of the association of MMP-9 with the illness phase (acute/remission). While some studies reported elevated MMP-9 during the remission phase,<sup>[17]</sup> some other studies have revealed increased MMP-9 during both acute and remission phases of depression.<sup>[18,19]</sup> Variation of MMP-9 levels with age, as noted in previous studies, could not be replicated in the present study, probably due to the low sample size.<sup>[18]</sup>

Despite being one of the first Indian studies exploring the role of MMP-9 in suicidality, the study has the following limitations:

- The present study is a pilot study with a small sample size, and a minuscule proportion with the variable of interest (i.e., suicidal attempts in the past) would have influenced the negative association between MMP-9 and clinical characteristics
- Lack of a control group precludes an interpretation of MMP-9 levels as a marker of suicidality in BD-I
- The retrospective study design had inherent recall bias.

Nevertheless, the present study emphasizes the need to assess newer markers such as MMP-9 in suicidality observed in BD. Future studies with a large sample size and a control group will help elucidate the role of biomarkers in suicidality associated with BD.

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**Table 1: Relationship of MMP-9 with clinical variables**

Variable	Relationship with MMP-9 levels <sup>†</sup> Test statistic ( <i>P</i> )
Age <sup>‡</sup>	-0.264 (0.068)
Gender <sup>§</sup>	75.0 (1.000)
Duration of BD-I <sup>‡</sup>	-0.279 (0.057)
Number of episodes <sup>‡</sup>	0.042 (0.776)
Only manic polarity <sup>‡</sup>	74.0 (0.893)
Past history of suicide attempt <sup>§</sup>	14.0 (0.012)*

<sup>†</sup>Relationship assessed using Kendall  $\tau b$  (for continuous data<sup>‡</sup>) or Mann–Whitney *U* (dichotomous data<sup>§</sup>), \* $P < 0.05$ . BD-Bipolar Disorder-type I, MMP-Matrix Metalloproteinase

**Conflicts of interest**

There are no conflicts of interest.

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