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Comparative analysis of serum hs-CRP and IL-1β levels in major depressive disorder patients and healthy controls in a tertiary care setting in Sikkim

Aiusha Mawlong, Rinchen Doma Bhutia, Samrat Singh Bhandari & Mingma Lhamu Sherpa*
Department of Biochemistry and Psychiatry, Sikkim Manipal Institute of Medical Sciences,
Sikkim Manipal University, Gangtok-737 102, Sikkim, India

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Systemic inflammation is increasingly linked to Major Depressive Disorder (MDD), and its expression may vary across populations .This study evaluates serum high sensitive C-reactive protein (hs-CRP) and Interleukin-1β (IL-1β) levels in MDD patients (n-40) and healthy controls (n=40) to understand the biological basis of depression within the unique ethnic and environmental context of Sikkim. Females were the majority in both MDD (67.5%) and control (70%) groups. Most participants had a normal BMI (MDD: 62.5%, Control: 67.5%), with few cases of obesity or underweight. Nepali ethnicity was predominant in both MDD: 80% and,Control: 77.5% followed by Bhutias and others however statistically insignificant. hs-CRP differed significantly between MDD (3335.7 pg/L) and controls (3164.7 pg/L) $P< 0.05$, though it did not vary by depression severity. hs-CRP showed fair diagnostic ability (AUC = 0.746, 95% CI: 0.638–0.854, $P< 0.01$; sensitivity 65%, specificity 77.5%), whereas IL-1β demonstrated poor performance. hs–CRP shows potential as an adjunct inflammatory marker in assessing depression. Future studies should explore composite biomarker approach combined with clinical tools to enhance diagnostic and treatment strategies.

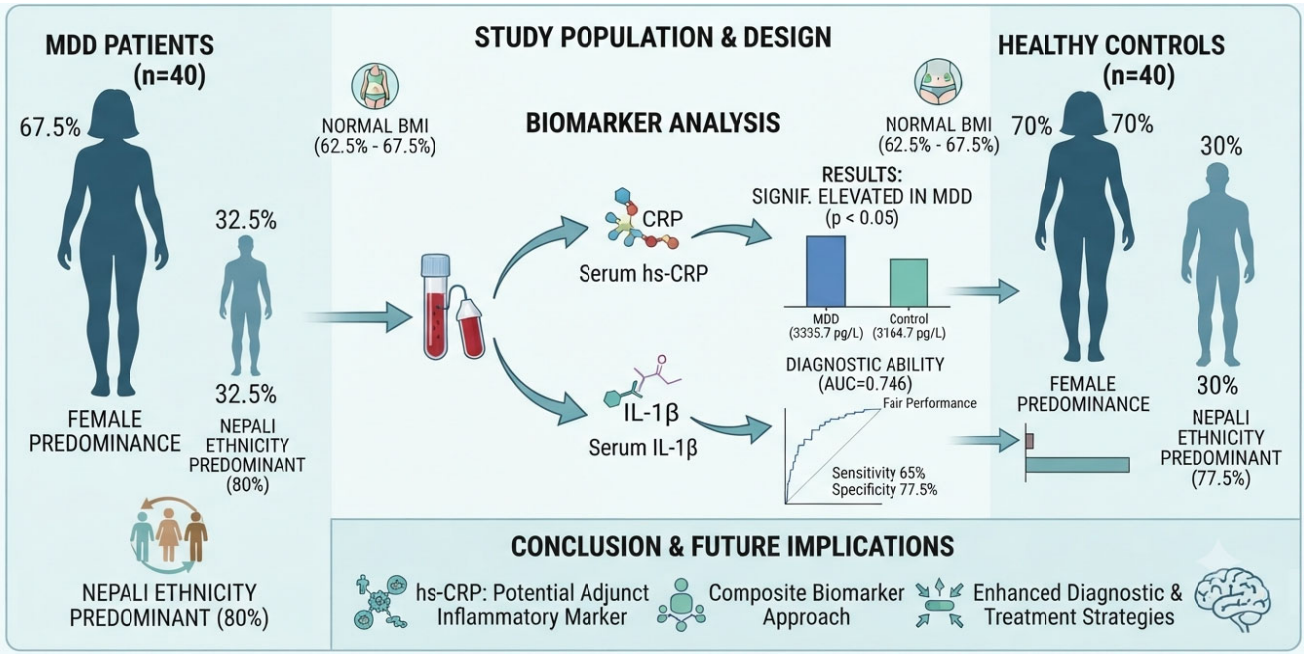
Keywords: Biomarkers, Brain-derived neurotrophic factor (BDNF), hs-CRP, IL-1β, Hypothalamic-pituitary-adrenal (HPA), Major depressive disorder (MDD), Neuroinflammation

Major depressive disorder (MDD) is a complex and heterogeneous mood disorder. It contributes to the global disease burden, affecting millions worldwide, and has been among the leading causes of disability for nearly three decades[1]. Up to 60% of patients with MDD exhibit some level of treatment resistance that prolongs and exacerbates depressive episodes [2.]. The lifetime prevalence of MDD is estimated at 15–18%, and the disorder can occur at any age, with initial episodes most commonly arising from adolescence to middle adulthood[3]. Inflammatory mediators have a notable impact on several neurobiological processes implicated in the etiopathogenesis of MDD[4,5]. It is well established that inflammation can influence neurotransmission by decreasing serotonin, increasing glutamate toxicity, reducing neurogenesis through the suppression of brain-derived neurotrophic factor (BDNF), and activating the hypothalamic-pituitary-adrenal (HPA) axis[6].

C-reactive protein (CRP), a pentameric protein with both pro- and anti-inflammatory properties[7], and cytokines like interleukin-1β (IL-1β), a key regulator of the innate immune response[8], have been closely linked to depressive symptoms and neuroinflammatory mechanisms. Although the blood–brain barrier restricts direct entry of large peripheral molecules, these mediators can influence central nervous system function indirectly through peripheral immune–neural signaling pathways. IL-1β has also been shown to modulate serotonin metabolism via elevated 5-hydroxyindoleacetic acid (5-HIAA) levels, further supporting its role in depressive pathophysiology[10] such as CRP and cytokines, they may still have indirect effects on the CNS.

While CRP and IL-1β have been repeatedly implicated in depression[11,12], existing findings remain inconsistent, likely due to differences in population characteristics, sample sizes, and comorbidities across studies. Importantly, data from the Northeastern Himalayan region of India are lacking, despite its distinct genetic, dietary, and environmental factors that may influence inflammatory and psychiatric profiles. Unlike most previous Indian studies that have examined inflammatory markers individually, this study simultaneously evaluates hs-CRP and IL-1β levels in clinically diagnosed MDD patients and healthy controls, exploring their relationship with

*Correspondence:
E-mail: mingmals@yahoo.com



Graphical abstract

depression severity. By focusing on a hospital-based population from Sikkim, the study aims to provide region-specific insight into the inflammatory underpinnings of depression and assess the potential clinical utility of these biomarkers in differentiating depressive states. Sikkim, which also reports one of the highest suicide rates in the country, represents a unique population for studying the biological correlates of depression. Hence, this study aims to compare the levels of inflammatory biomarkers—hs-CRP and IL-1β—between patients with MDD and healthy individuals to identify any significant differences that may reflect underlying biological changes associated with depression. It further explores whether these biomarker levels vary according to the severity of depression, providing insight into their potential role in disease progression. Additionally, the study evaluates the ability of hs-CRP and IL-1β to distinguish individuals with depression from those without, supporting their potential as diagnostic indicators.

Materials and Methods

This was a hospital-based cross-sectional study conducted in the Departments of Biochemistry and Psychiatry, Sikkim Manipal Institute of Medical Sciences (SMIMS), Gangtok, Sikkim. Selection of the sample and its collection were carried out in the Outpatient Department of Psychiatry after obtaining due patient consent and approval from the Institutional Review Committee and Institutional Ethics Committee, SMIMS (Reg No: SMIMS/IEC/2023-35). The minimum required sample size was calculated to detect a significant difference in the mean serum IL-1β levels between patients with MDD and healthy controls, using the formula for comparing two independent means[13]; n= [2 (Zα + Zβ) 2 σ2/ δ2]. Assuming, 5% level of significance (α = 0.05; Zα/2 = 1.96) and a power of 80% (β = 0.20; Zβ = 0.84), with an expected mean difference (δ) of 4.2 pg/L and a standard deviation (σ) of 5.98 derived from a previous study on serum IL-1β levels in MDD patients[14], the minimum sample size was found to be 32 participants per group. To improve statistical power and account for potential data exclusions, 40 subjects were enrolled in each group (total = 80). Cases were identified as newly diagnosed patients with MDD, exhibiting a HAM-D score of 17 or higher, whereas controls were healthy participants with a HAM-D score below 5. Participants with any reported infection, h/o COVID-19 of less than 12 months, any surgery done within the past 1-month, metabolic disorders like diabetes mellitus, arteriosclerosis, hypertension, inflammatory or immune disorder, present history of smoking or substance use, pregnancy, reported malignancy, and unwilling participants were excluded. A 2 mL blood sample was then collected from eligible participants in a plain vial; serum was separated by centrifugation at 3000rpm for 10 mins and stored at -80°C until analysis. hs-CRP and IL-1β concentrations in the patient sample were estimated in a single batch using

a quantitative sandwich ELISA kit from Elabscience. Serum samples were added to pre- coated antibody micro wells for target antigens; hs-CRP and IL-1β, respectively. Upon addition of the sample, the antigen present in the sample binds to the antibody. A biotin-labeled detection antibody was then added, followed by Avidin-HRP, to form an antibody-antigen complex. The wells were washed for any unbound material, and substrate was added. A blue color developed upon the presence of the test antigen. The reaction was then stopped with a stop solution. The intensity of the yellow color developed was then measured in a Biorad Multiplate reader at 450 ± 2 nm.

Analytical performance of the ELISA assays was established using manufacturer-provided validation data. The intra- and inter-assay coefficients of variation were <10% for both IL-1β (Cat no. E-EL-H0149) and hs-CRP(Cat No. E-EL-H5134). The limits of detection were 4.69 pg/mL and 9.38 pg/mL, with assay ranges of 7.81–500 pg/mL and 15.63–1000 pg/mL for IL-1β and hs-CRP, respectively. To ensure procedural validity, selected standards of known concentration (for *e.g*. Standard no.4 and 8) were treated as an Internal control sample. Quantification was performed using a 4-parameter logistic (4-PL) standard curve with R^2 values ≥0.99 (0.994 for hs-CRP and ~0.999 for IL-1β), indicating good fit.

Hamilton Depression Rating Scale: HAM-D (available at public domain) Depression severity was assessed using the 17-item Hamilton Depression Rating Scale (HAM-D), a clinician-administered instrument. Based on HAM-D scores, participants were categorized as follows: 0–7 (normal), 8–13 (mild depression), 14–18 (moderate depression), 19–22 (severe depression), and ≥23 (very severe depression).

Statistical analysis

All statistical analyses were performed using SPSS version 27 -IBM SPSS Statistics. Data were checked for normal distribution, and appropriate statistical tests were applied. Categorical data were presented as frequencies and percentages. Group comparisons were conducted by the Mann–Whitney U test and the Kruskal–Wallis test for continuous variables, and the Chi-square test was done for categorical variables. To estimate the discriminative ability of serum hs-CRP and IL-1β levels in diagnosing MDD, a Receiver Operating Characteristic (ROC) curve analysis was performed. A *p*-value below 0.05 was considered to indicate statistical significance.

Results

A total of 80 participants — 40 patients diagnosed with MDD and 40 healthy controls — matched for age and gender were included in the study. Participants had a mean age of 34 years. Females constituted the majority in both groups (MDD: 67.5%; Control: 70%). Most participants had a normal BMI (MDD: 62.5%; Control: 67.5%), although a few were overweight or obese, particularly in the MDD group.

With respect to ethnicity, the Nepali group was predominant (MDD: 80%; Control: 77.5%), followed by Bhutia and other ethnic backgrounds. Overall, the two groups were comparable in terms of age, gender, BMI, and ethnicity, but no statistically significant differences were observed (P> 0.05 for all; Table 1).

A Mann-Whitney U test was performed to determine whether a difference existed in hs-CRP and IL-1β levels between MDD patients and healthy controls. Median value for hs-CRP was statistically

Table 1 — The sociodemographic and baseline clinical characteristics of the study participants

S. No		Major Depressive Disorder (MDD) (n=40)	Control (n=40)	*p* value
1.	Age (mean ± SD)	34.5 ±12.9	34.8 ± 12.7	0.832
2.	Gender (n%)			0.809
	Male	13 (32.5)	12 (30)	
	Female	27(67.5)	28 (70)	
3.	BMI (n%)			0.581
	Normal	25 (62.5)	27 (67.5)	
	Overweight	10 (25)	12 (30)	
	Obese	3 (7.5)	0	
	Underweight	2 (5)	1 (2.5)	
4.	Ethnicity (n%)			0.92
	Nepali	32 (80)	31 (77.5)	
	Bhutia	3 (7.5)	4 (10)	
	Others	5 (12.5)	5 (12.5)	

higher in participants with MDD (3335.7 pg/L) than healthy controls (3164.7 pg/L), U=406, Standardized Test Statistic (z) = -3.804, *P*= 0.0001. However, median values for IL-1β were not statistically significant between MDD (14.5 pg/L) and healthy controls (14.7 pg/L), as shown in (Table 2).

A Kruskal-Wallis H test was performed to find out if there were any differences in hs-CRP between patients with: moderate depression (n=16); severe depression (n=17) and very severe depression (n=7); and no depression (n=40). The values represent mean ranks unless specified otherwise. Distributions of hs-CRP were not similar for all groups, as evaluated by visual inspection of a boxplot. The mean ranks of hs-CRP differed significantly between groups [χ^2 (3) = 14.9, *P*= 0.002], as shown in (Table 3). Similarly, a Kruskal-Wallis H test was used to assess IL-1β levels among the same four groups. Although IL-1β levels appeared higher in the depression group compared to the controls, the difference was not statistically significant. χ^2 (3) = 1.55, *P*= .670, suggesting that IL-1β levels did not differ meaningfully across groups (Table 3).

Thereafter, a *post hoc* analysis for pairwise comparison of hs-CRP was performed using Dunn's procedure with a Bonferroni correction for multiple comparisons to identify specific group differences in hs-CRP. As demonstrated in (Fig. 1), the mean rank of hs- CRP increased progressively with the severity of depression from 30.65 pg/L in the no depression group to 55.93 pg/L in the very severe depression group. However, no statistically significant differences were noted among the depression subgroups themselves (moderate *vs.* severe, severe *vs.* very severe, and moderate *vs.* very severe; *P*> 0.05), suggesting that hs-CRP levels do not significantly differ between varying severities of depression.

Table 4 and Figure 2 describe Receiver Operating Characteristic (ROC) analysis performed to evaluate the diagnostic performance of serum hs-CRP and IL-1β in distinguishing MDD cases from healthy controls. The Area Under the Curve (AUC) for hs-CRP was 0.746 (95% CI: 0.638–0.854) and was statistically significant at *P*< 0.01, indicating a fair discriminatory ability. The optimal cut-off value

Table 2 — Mann-Whitney U Test to compare the differences in serum hs CRP (pg/L) and IL-1β (pg/L) between MDD and Control group

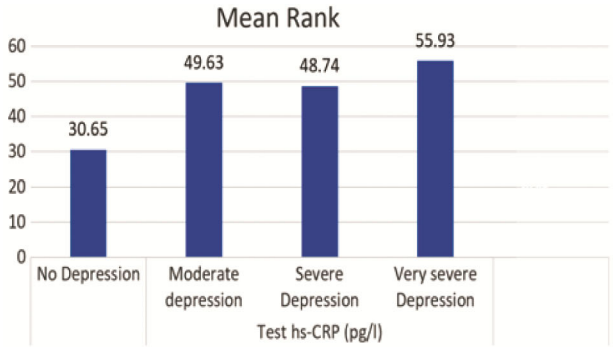
Inflammatory markers	N	Case (n=40)	Control (n=40)	Test: Man-Whitney U Test		
Serum hs-CRP (pg/L)	80	3335.7	3164.7	*U* = 406	z= -3.804	**P*=0.0001
Serum IL-1β (pg/L)	80	14.5	14.7	*U* = 711	z= -0.858	*p*=0.391

U = Mann Whitney U, z = Standardized Test Statistic (**P*< 0.05 significant)

Table 3 — Kruskal Wallis H test for hs-CRP and IL-1 β in between cases (levels of depression) and controls

Inflammatory markers	Mean rank				X^2(3)	*p* value
	Cases			Control		
	Moderate depression	Severe depression	Very severe depression	No depression		
hs-CRP (pg/L)	49.63	48.74	55.93	30.65	14.9	.002*
IL-1 β (pg/L)	39.22	46.44	41.71	38.28	1.55	.670

(**P*< 0.05 significant)



	P value
No depression vs moderate depression	*0.042
No depression vs severe depression	*0.034
No depression vs very severe depression	*0.044
Moderate depression vs severe depression	>0.05
Severe depression vs very severe depression	>0.05
Moderate depression vs very severe depression	>0.05

Fig 1 — Mean rank of hs-CRP (pg/L) differences in between moderate depression, severe depression, very severe depression and no depression

Table 4 — ROC curve analysis of serum hs-CRP and IL-1β in distinguishing patients with Major Depressive Disorder (MDD) from healthy controls

ROC analysis	hs-CRP	IL-1β
Area under curve (AUC) (CI –95%)	0.746 (0.638 – 0.854)	0.556 (0.427-0.684)
p-value	<0.01*	>0.05
Cut- off (pg/L)	3284.450	21.749
Sensitivity	65%	27.5%
Specificity	77.5%	100%

*P-value <0.05 significant

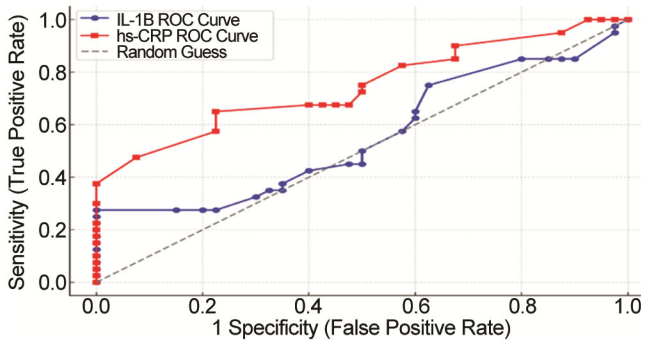


Fig. 2 — Receiver Operating Characteristic (ROC) curves for serum hs-CRP and IL-1β in discriminating Major Depressive Disorder (MDD) patients from healthy controls

identified was 3284.45 pg/L, yielding a sensitivity of 65% and specificity of 77.5%. In contrast, IL-1β demonstrated a much lower AUC of 0.556 (95% CI: 0.427–0.684), non-significant at $P>$ 0.05, suggesting poor discriminatory power. Although the cut-off value of 21.74 pg/L showed 100% specificity, the sensitivity was only 27.5%, limiting its utility as a standalone marker. The ROC plot further illustrates that the hs-CRP curve lies well above the diagonal line of random guess, while the IL-1β curve hovers near it, supporting these findings.

Discussion

The descriptive analysis of this study demonstrates that patients with MDD presented at an average age of 34 with a female preponderance; a pattern consistent with global findings where depression is more common among women because of biological and psychosocial factors[15]. Most study participants had a normal BMI, aligning with studies suggesting that depression occurs across all weight categories and is not limited to obesity or underweight groups[16]. Ethnically, most MDD patients belonged to the Sikkimese Nepali community, followed by Bhutia and other groups, reflecting the demographic composition of the region. Studies exploring ethnicity and depression signify that cultural norms, stress exposure, and community-specific risk factors contribute to the observed distribution rather than true biological differences[17]. Therefore, the ethnic pattern observed in this study appears consistent with the local population representation rather than indicating ethnicity as a disease determinant.

Upon testing for differences between the two groups for the inflammatory markers, the study demonstrated that the median value for hs-CRP (3335.7 pg/L) was significantly higher in participants with MDD than in healthy controls (3164.7 pg/L). Additionally, the mean ranks of hs-CRP were different between the severity of depression groups based on HAM-D score and the controls (Tables 1 & 2, and Fig. 1); however, the difference within subgroups was not statistically significant. In line with the study's initial BMI observation, where the majority of participants had a normal weight, it is important to consider the potential confounding effect of the small proportion of obese participants (3, 7.5%) present in the MDD group. While obesity is a known determinant of chronic inflammation, the overall BMI distribution between the MDD and control groups was not statistically different ($P=$ 0.581). Furthermore, a 2024 large-scale National Health and Nutrition Examination Survey (NHANES) study by Miller *et al*[18] found that BMI did not significantly moderate the association between depressive symptoms and hs-CRP levels. This suggests that the observed elevation in hs-CRP observed here likely reflects the inflammatory pathophysiology of MDD itself, rather than being solely a byproduct of adiposity. This independent association is supported by a growing body of case-control evidence where patients with depression consistently exhibit higher CRP levels alongside elevated clinical severity scores[19].

Systematic reviews also found that the majority of studies reported elevated CRP levels in depressed patients compared to controls, and this elevation was associated with increased symptom severity[20,21]. A cross-sectional study by Ji Y *et al*. found that higher hs-CRP levels were significantly linked to increased depressive symptoms[22]. However, contrasting results have also been reported. For instance, the study by Nishuty *et al*., involving 88 individuals with MDD and 86 age, gender, and BMI-matched controls, found that mean serum CRP levels were lower in patients than controls, with no significant difference ($P>$ 0.05)[23]. Such discrepancies in the literature could be attributed to variations in study design, sample size, methodology, and environmental or genetic factors.

The median values for IL-1β (pg/L), on the other hand, were not statistically significant between MDD and healthy controls, nor between the severity of depression groups based on HAM-D scores and the controls. A cumulative meta-analysis in 2015 found that there was no association between IL-1β levels and MDD[24]. Similarly, other meta-analyses showed that the difference in IL-1β levels between patients with depression and healthy controls was not significant[25]. Studies from Taiwan and Japan have also reported no significant difference in serum or plasma IL-1β levels between MDD and non-MDD participants prior to treatment, consistent with the present findings[26,27]. Conversely, Osimo *et al*. conducted a meta-analysis of 26 studies comprising 1000 depressed individuals and 949 controls, which revealed significantly elevated IL-1β levels in the depressed group[21]. Thomas AJ *et al*. also found significantly higher IL-1β levels in major depressive patients compared to healthy controls, along with a strong association between IL-1β and depression severity[28]. Diniz *et al*. similarly reported increased serum IL-1β levels in elderly depressed patients compared to non-depressed participants[29]. These variations may reflect differences in participant demographics, including age, ethnicity, and comorbid conditions.

The ROC analysis in this study (Table 4, and Fig. 2) indicated that hs-CRP had a fair ability to distinguish individuals with Major Depressive Disorder from healthy controls, showing moderate accuracy with good sensitivity and specificity at the identified cut-off. In contrast, IL-1β demonstrated poor discriminative power, with low sensitivity despite high specificity, suggesting limited usefulness as a standalone diagnostic marker in this context. These findings align with previous systematic analyses that have highlighted CRP as a more reliable inflammatory biomarker in depression than IL-1β[30]. Osimo *et al*. reported that elevated CRP levels are consistently associated with MDD and may also relate to treatment response[21] Similarly, Haapakoski *et al*. emphasised the more robust and consistent association of CRP with depressive symptomatology compared to IL-1β, whose levels tend to vary widely and may reflect acute inflammatory states rather than chronic low-grade inflammation typically seen in MDD[24].

Conclusion

hs-CRP shows potential as an adjunct inflammatory marker in assessing depression. However, the cross-sectional design of this study precludes any causal inference between inflammatory markers and disease progression .The poor discriminatory performance of IL-1β suggests a limited role in the peripheral inflammatory profile of depression. Future research should concentrate on longitudinal monitoring of biomarker changes before treatment, during treatment, and remission to better understand their dynamic changes. Additionally, a composite biomarker approach that combines inflammatory markers with clinical scales like the HAM-D may enhance diagnostic accuracy and treatment strategies.

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Conflict of interest

All authors declare no conflict of interest

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