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C-Reactive Protein as an Indicator for Antidepressant Response in Late-Onset Depression: A prospective Study

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ABSTRACT

Introduction: Late-onset depression (LOD), often linked to immune dysfunction and vascular factors, presents distinct treatment challenges compared to early-onset depression. Predicting treatment outcomes remains difficult. We hypothesized that baseline levels of C-reactive protein (CRP), an inflammatory marker, may correlate with antidepressant response in individuals experiencing their first episode of LOD. **Methods:** This prospective study recruited subjects aged >60 years presenting with their first depressive episode (ICD-10 DCR criteria). Baseline assessments included clinical evaluation, serum CRP measurement (mg/L), and depression severity using the 17-item Hamilton Depression Rating Scale (HAMD-17). Participants received standard antidepressant treatment (Escitalopram) for 8 weeks, after which HAMD-17 was reassessed. Treatment response was defined as $\geq$50% reduction in HAMD-17 score from baseline. **Results:** Of 64 eligible participants, twenty-five participants (mean age 64.7$\pm$5.8 years; baseline HAMD-17 score 18$\pm$3) completed the 8-week follow-up. The overall antidepressant response rate was 24% (n=6 responders). Responders (n=6) had a mean baseline HAMD-17 score of 16$\pm$1.9, while non-responders (n=19) had a mean baseline score of 18.6$\pm$3.1. The mean baseline CRP level was significantly higher in non-responders (6.27 $\pm$ 1.58 mg/L) compared to responders (3.80 $\pm$ 1.40 mg/L) (p = 0.002). A significant negative correlation was observed between baseline CRP levels and antidepressant response (r = –0.588, p = 0.02). **Conclusions:** In this preliminary study of older adults with first-episode LOD, elevated baseline CRP levels were associated with a poorer response to an 8-week course of standard antidepressant therapy suggesting that systemic inflammation may be a potential predictive biomarker for treatment outcomes in this population.

KEYWORDS: C-reactive protein, Late onset depression, Antidepressant

INTRODUCTION

Depression is a leading global health concern, affecting over 264 million individuals and ranking as a major cause of disability worldwide.[1] Among older adults, late-onset depression (LOD)—defined as the first occurrence of depressive symptoms after the age of 60— is the second most prevalent psychiatric disorder, with an estimated prevalence ranging between 10% and 20%.[2–4] Compared to early-onset depression (EOD), LOD presents with unique etiological, clinical, and prognostic features, including greater cognitive impairment, higher rates of medical comorbidities, increased mortality risk, and diminished treatment responsiveness.[5–7]

Pharmacotherapy remains the mainstay of treatment for depressive disorders.[8] However, despite advances in antidepressant pharmacology, treatment outcomes remain suboptimal, especially in the elderly. Approximately two-thirds of patients fail to achieve full remission, as shown in large-scale studies such as the STAR*D trial[9, 10]. LOD, in particular, poses therapeutic challenges due to poor drug tolerance, a higher prevalence of side effects, and often a longer duration required to observe clinical improvement.[11, 12]

Inflammatory processes and vascular pathology have been implicated in the pathophysiology of LOD, giving rise to the conceptualization of ”vascular depression”.[13, 14] C-reactive protein (CRP), an acute-phase reactant and sensitive marker of systemic inflammation, has been studied extensively in cardiovascular and psychiatric disorders. Elevated CRP levels have been correlated with depressive symptom severity, particularly in older adults, and may influence antidepressant response via immunometabolic pathways.[14–16] Genetic variants of the CRP gene further support its potential role in the pathogenesis and progres-

sion of late-life depression. [17]

Despite this growing evidence, there is limited research evaluating CRP as a predictive biomarker for antidepressant treatment response in LOD. The present study aimed to assess whether baseline CRP levels are associated with treatment outcomes in patients with LOD, thereby exploring the utility of CRP as a biomarker to guide individualized antidepressant therapy.

METHODS

Study Design and Participants

This prospective cohort study was conducted at the Psychiatry Outpatient Department of MGM Medical College, Indore. Adults aged 60 years and older presenting with their first depressive episode were assessed for eligibility. Depression was diagnosed according to the ICD-10 Diagnostic Criteria for Research (ICD-10 DCR). [18] A total of 124 individuals were screened over a period of 6 months, of whom 46 met the eligibility criteria. Twenty-five participants completed 8-week treatment and follow up and were included in the final analysis (Figure 1).

Inclusion and Exclusion Criteria

Inclusion criteria

- Age >60 years.
- First episode of depression diagnosed using ICD-10 DCR.
- Initiation of a new course of antidepressant therapy.

Exclusion criteria

- Comorbid psychiatric disorders (e.g., bipolar disorder, schizophrenia).
- History of treatment-resistant depression.
- Concurrent use of other psychotropic medications or psychotherapy.
- Current use of anti-inflammatory medications.

All participants provided written informed consent, and the study protocol was approved by the Institutional Ethics and Scientific Review Board.

Clinical and Laboratory Assessment

At baseline, participants underwent a comprehensive clinical assessment, including medical history, medication use, blood pressure measurement, Mini-Mental State Examination (MMSE) [19], and stroke risk estimation using the Framingham Stroke Risk Score. [20] The risk score calculates risk based on predictors like age, blood pressure, diabetes, smoking, prior CVD, atrial fibrillation, ECG findings, and antihypertensive medication use. Confounding factor that may affect the CRP level were controlled by using of Framingham study score. [20]

Depression severity was measured using the 17-item Hamilton Depression Rating Scale (HAMD-17). [21, 22] The maximum score on HAMD-17 was 52, and scores of 0–7 were considered normal, 8–16 suggested mild depression, 17–23 suggested moderate depression, and scores over 24 were considered severe depression for the study. [21, 22]

Venous blood samples were collected under fasting conditions and analyzed for serum CRP levels using a high-sensitivity latex-enhanced immunoturbidimetric assay. The CRP reference range was $\leq$5 mg/L.

Treatment Protocol and Outcome Assessment

Participants received Escitalopram, initiated at 10 mg/day and titrated to a maximum of 20 mg/day based on clinical response and tolerability. No additional antidepressants or psychotropic agents were allowed during the study period. Depression severity was reassessed using HAMD-17 at the end of 8 weeks.

Treatment response was defined as a $\geq$50% reduction in HAMD-17 score from baseline to week 8. Non-response was defined as <50% reduction. [23] Participants were classified into responders and non-responders accordingly. Throughout the study, only one assessor conducted all of the evaluations. No formal category of partial responders was analyzed due to sample size limitations.

Statistical Analysis

Data were analyzed using SPSS version 21.0. Continuous variables were described using mean and standard deviation; categorical variables using frequencies and percentages. Between-group comparisons were performed using the independent samples t-test or Mann-Whitney U test, as appropriate. Categorical data were analyzed using the Fisher Exact test. Spearman's correlation was used to assess the relationship between baseline CRP levels and percentage reduction in HAMD-17 scores. Statistical significance was defined as $p < 0.05$.

RESULTS

Demographics Profile of study participants

Twenty-five participants completed the full 8-week study period and were included in the final analysis (Figure 1). The mean age of the analyzed sample (n = 25) was 64.7 $\pm$ 5.8 years. Females comprised 56% of the cohort. Of the 25 participants, 6 (24%) met the criteria for treatment response ($\geq$50% reduction in HAMD-17 score). The remaining 19 were classified as non-responders. No significant differences in socio-demographic variables-including age, sex, education, residence, or marital status were found between responders (n = 6) and non-responders (n = 19) (Table 1).

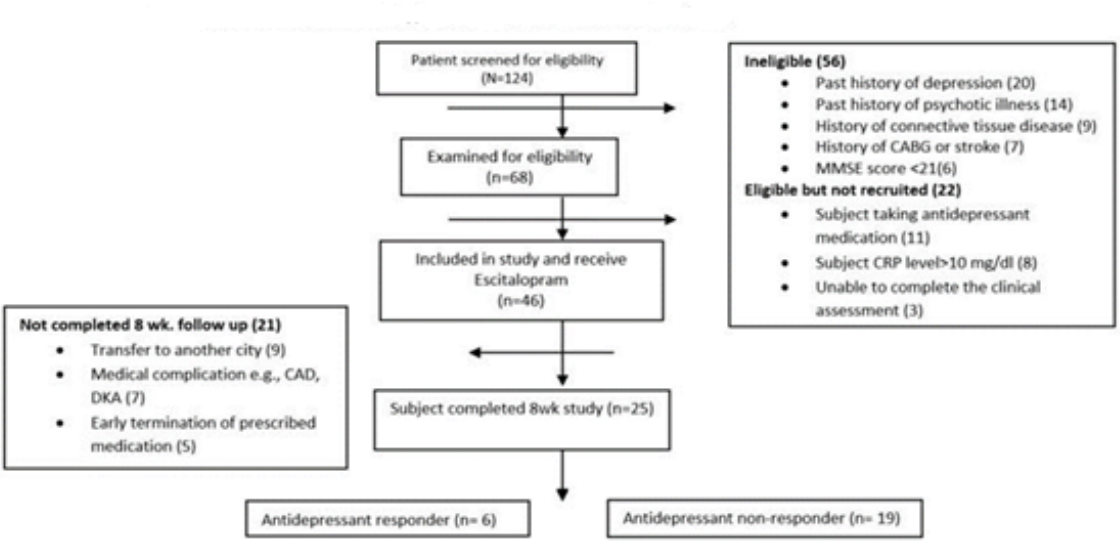

Figure 1: Flowchart of the study enrollment and participation

Variable	Non-Responders (n = 19)	Responders (n = 6)	p-value
Age, years [Mean (SD)]	65.13 ± 6.14	63.51 ± 4.83	0.56
Education, years [Mean (SD)]	3.41 ± 5.04	7.81 ± 4.93	0.07
Sex			
Male	8 (42%)	3 (50%)	0.42
Female	11 (58%)	3 (50%)	
Marital Status			
Married	16 (84%)	5 (83%)	0.64
Widowed	3 (16%)	1 (17%)	
Religion			
Hindu	14 (74%)	4 (67%)	0.37
Muslim	5 (26%)	2 (33%)	
Family Type			
Nuclear	11 (58%)	3 (50%)	0.57
Extended/Joint	8 (42%)	3 (50%)	
Residence			
Urban	14 (74%)	4 (67%)	0.37
Rural	5 (26%)	2 (33%)	

Table 1: Socio-demographic Characteristics of Responders and Non-Responders to antidepressant therapy

Clinical characteristics

Study sample baseline Hamilton depression severity rating score was 18 ± 3, shows moderate severity of depression. Medical co-morbidities were present in 60% of participants. No one using statin and anti-inflammatory drugs during participation in study.

ummarizes the baseline clinical characteristics of responders and non-responders to antidepressant therapy. No statistically significant differences were observed between groups in terms of age at onset, duration of illness, comorbid medical conditions, lifestyle factors, or vascular risk (as measured by the Framingham Stroke Risk Score). Cognitive function, as assessed by MMSE, was also comparable. However, responders exhibited significantly lower mean HAMD-17 scores at week 8 (7.50 ± 0.84) compared to non-responders (13.62 ± 1.11,p = 0.001), confirming treatment classification. Importantly, baseline CRP levels were significantly lower in responders (3.80 ± 1.40 mg/L) than in non-responders (6.27 ± 1.58 mg/L) (p = 0.002), supporting a negative association between systemic inflammation and antidepressant response.

A Spearman rank correlation analysis revealed a statistically significant negative correlation between baseline CRP levels and the percentage reduction in HAMD-17 scores, r(23) = –0.588, p = 0.02, indicating that higher CRP levels were associated with poorer treatment response.

DISCUSSION

Our prospective cohort study demonstrated a 24% antidepressant response rate in elderly patients with first-episode late-onset depression (LOD) treated with escitalopram, notably lower than the 50%–66% remission rates

Variable	Non-Responders (n = 19)	Responders (n = 6)	p-value $
Age at onset, years [Mean ± SD]	64.24 ± 6.31	62.34 ± 4.91	0.51
Duration of illness, months [Mean ± SD]	10.11 ± 8.13	9.70 ± 6.32	0.35
Family history of psychiatric illness	3	1	0.64
Family history of substance use	6	0	0.12
Precipitating factor present	2	0	0.41
Medical comorbidity	11	4	0.70
Alcohol use	1	1	0.37
Hypertension diagnosis	3	1	0.96
Diabetes mellitus	6	2	0.94
Cigarette smoking	2	0	0.41
Body Mass Index, kg/m^2 [Mean ± SD]	27.72 ± 3.93	26.42 ± 5.15	0.50
Framingham Stroke Risk Score [Mean ± SD]	6.17 ± 3.31	7.00 ± 3.01	0.74
MMSE Score [Mean ± SD]	24.84 ± 2.02	26.51 ± 2.78	0.11
HAMD-17 Score at baseline [Mean ± SD]	18.64 ± 3.12	16.00 ± 1.90	0.06
HAMD-17 Score at 8 weeks [Mean ± SD]	13.62 ± 1.11	7.50 ± 0.84	0.001*
CRP level at baseline, mg/L [Mean ± SD]	6.27 ± 1.58	3.80 ± 1.40	0.002*

$ Calculated using Mann-Whitney U test for continous variables (Age, HAMD scores, CRP etc.) and Fisher Exact test for categorical variables (Presence of comorbidities, alcohol use etc.)

*Statistically Significant. CRP = C-reactive protein; HAMD-17 = Hamilton Depression Rating Scale; MMSE = Mini-Mental State Examination.

Table 2: Baseline Clinical Characteristics of Responders and Non-Responders to antidepressant therapy

reported in broader adult populations.[9, 10, 24, 25] This is consistent with previous research showing that LOD often responds less well to antidepressant medications and may require longer treatment duration or higher doses to show improvement.[9, 11, 12, 26] This limited response may reflect age-associated pathophysiological changes [5, 6], including vascular compromise and neuroinflammatory processes, as proposed by the vascular depression hypothesis.[13, 14]

A primary finding was that baseline C-reactive protein (CRP) levels were significantly higher in non-responders (6.27 ± 1.58 mg/L) compared to responders (3.80 ± 1.40 mg/L; p=0.002), and that CRP correlated negatively with percentage reduction in HAMD-17 scores (r(23)=–0.588, p=0.02). These results support the "vascular depression" hypothesis, whereby systemic inflammation contributes to resistance to standard antidepressant therapy in late life.[13] This suggests that inflammation may play a role in poor treatment outcomes in LOD. Previous studies have also found that high CRP levels are linked to more severe depression and lower response to antidepressants, especially SSRIs.[15, 16, 27]

Interestingly, traditional vascular risk—as measured by the Framingham Stroke Risk Score—did not differ between responders and non-responders, suggesting that CRP may capture an inflammatory dimension of vascular pathology not fully reflected by conventional risk assessments.[28, 29] Furthermore, genetic investigations into CRP polymorphisms reinforce a potential causal link between inflammation and late-life depressive syndromes.[16, 17]

Importantly, our findings must be interpreted in the context of several limitations. First, the small sample size, particularly the low number of responders, limits the generalizability and statistical power of the results. Second, the lack of assessor blinding introduces the potential for bias. Third, although comorbidities were documented, the absence of detailed clinical workups may have underestimated underlying inflammatory or systemic conditions. Finally, the study was conducted in a tertiary care setting, potentially limiting applicability to primary care populations.

Despite these limitations, the study offers valuable insights into the pathophysiology of LOD and supports the integration of inflammatory markers like CRP into predictive frameworks for antidepressant response. Future research should aim to validate these findings in larger, multicentric cohorts, explore longitudinal changes in CRP levels with treatment, and investigate the interplay between CRP and other inflammatory or neurodegenerative markers.

CONCLUSION

Late onset depression is a significant concern for the geriatric population, as they are more vulnerable to the side effects of antidepressant medication, and their depression is less responsive to such medication. This study demonstrates

that elevated baseline levels of C-reactive protein (CRP) are significantly associated with reduced antidepressant response in patients with late-onset depression (LOD). The findings support the role of systemic inflammation as a potential biological contributor to treatment resistance in this population. Given its ease of measurement and clinical accessibility, CRP may serve as a useful biomarker for identifying individuals at higher risk of poor response to pharmacological treatment. Being able to predict antidepressant response in late onset depression can help in selecting appropriate therapeutic agents, determining the duration of antidepressant treatment, and predicting treatment outcomes. While these results are promising, the study's limitations—including a small sample size, lack of blinding, and limited generalizability—necessitate cautious interpretation. Further large-scale, prospective studies are warranted to validate the predictive value of CRP and to investigate whether anti-inflammatory strategies can enhance treatment outcomes in late-life depression.

DISCLOSURE

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