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# Investigation of C-reactive Protein (CRP) in Never-Treated Depressed Patients

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**Abstract:**

***Introduction:*** The relationship between inflammatory markers and depression has been widely debated. C-reactive protein (CRP) is a candidate biomarker for studying such an association. We aim to measure the CRP levels of treatment-naive major depressive disorder (MDD) patients and compare them with those of previously treated MDD patients.

***Methods:*** This is a cross-sectional study. We recruited 120 patients with MDD; 47 (39.2%) were medication-naïve, while 73 (60.8%) had a history of receiving medication. High-sensitivity CRP in peripheral venous blood was assessed. Subjects were assessed using the Structured Clinical Interview for DSM-IV (SCID-I), the Beck Depression Inventory-II (BDI-II), the Hamilton Anxiety Rating Scale (HAM-A), and the Somatic Symptom Scale-8 (SSS-8).

***Results:*** Our results show a statistically significant difference between the two groups in serum CRP levels, with the drug-naïve group having a significantly lower mean CRP level than the group receiving medication. The CRP level was positively correlated with both the number of episodes ($p$ = 0.006) and the duration of illness ($p$ = 0.015) in MDD. However, it was not significantly correlated with depression severity or any of its clinical phenotypes.

***Discussion:*** These findings may suggest an underlying pathology of depression that could be either related to the natural course of depressive episodes or a response to antidepressant treatments.

***Conclusion:*** This study is one of the few studies to observe a significant difference in the level of CRP in treatment-naïve depressed patients in comparison to those who receive medications. Although the above data are preliminary, the significance of this finding warrants further investigation and replication.

**Keywords:** Major depressive disorder, C-reactive protein, Treatment-naïve, Inflammation, Biomarkers, Cross-sectional study.

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## 1. INTRODUCTION

Major depressive disorder (MDD) is currently the fourth leading cause of disability worldwide. Despite a range of effective treatments, more than 30% of patients do not achieve remission [1]. This could be explained by the clinical heterogeneity of the disorder and the lack of a complete understanding of its underlying pathological mechanisms [2].

Many hypotheses were proposed to explain MDD, including the well-established monoamine hypothesis, which assumes the depletion of neurotransmitters [3], the neurotrophic hypothesis, which attributes depressive symptoms to disordered neuroplasticity [4], and finally, the inflammatory hypothesis, which proposes that inflammatory cytokines affect the neurochemical, behavioural, and neuroendocrine processes resulting in depression [1, 5].

Growing evidence indicates an altered immunologic state in depression [6]. For example, depression is highly comorbid with chronic inflammatory diseases, such as rheumatoid arthritis or multiple sclerosis [4]. In addition, experimental administration of interleukins (IL-1β & IL-6) and tumour necrosis factor-alpha (TNF-α) exerts a depressive effect in humans [3].

Recent studies and meta-analyses show that inflammatory markers are upregulated in the peripheral and central nervous systems of individuals with depression compared to healthy controls [7-9]. This immune activation is notably present in MDD patients resistant to standard therapies and may signify a potential therapeutic target [10, 11]. Moreover, autopsy studies discovered increased expression of pro-inflammatory cytokine genes in MDD patients' frontal cortex [12].

The mechanism underlying this association between inflammation and depression, however, is not fully understood [13]. Pro-inflammatory cytokines are thought to cause depression *via* neuro–immuno–metabolic mechanisms. They activate the hypothalamus-pituitary-adrenal axis, disrupt neurotransmitter metabolism, particularly serotonin, and possibly impair neuroplasticity [4].

On the other hand, this could also be a bidirectional association, such that depression may also lead to inflammation. Psychological stress triggers the release of cytokines, which may initiate the acute-phase response and, in turn, trigger inflammation. Finally, the association might also be caused by a third factor that both elevates cytokine levels and induces depressive symptoms [13].

C-reactive protein (CRP) is a candidate biomarker for investigating inflammatory processes in MDD. CRP is an acute-phase protein that is used clinically as a marker of acute inflammation [7, 14].

A recent study attempted to classify MDD patients according to CRP levels into three categories: (CRP < 1 mg/L), denoting no inflammation; (1–3 mg/L), denoting elevated CRP; and (>3 mg/L), denoting low-grade inflammation. They demonstrated evidence supporting that these may constitute different immuno-metabolic phenotypes of depression. Specifically, the elevated CRP group exhibited a lack of antidepressant efficacy in prior randomised controlled trials involving anti-inflammatory treatments, with responses being predominantly observed in the low-grade inflammation group [10]. As such, the 'CRP > 3 mg/L' group exhibits distinct immune and metabolic activation compared to the 'CRP 1–3 mg/L' group, suggesting downstream consequences of low-grade inflammation. Consequently, immune-related depression may represent a heterogeneous condition with varied causal mechanisms and biomarkers [15].

Despite growing evidence linking inflammation to MDD, one important limitation in the existing literature is that most studies have included patients receiving antidepressant treatment, which may confound CRP levels and obscure the true relationship between inflammation and depression. In addition, the heterogeneity of MDD further complicates the interpretation of inflammatory markers. Treatment-naïve patients represent a more homogeneous group and provide a unique opportunity to examine the role of inflammation independent of medication effects. However, studies focusing specifically on this population remain scarce. Therefore, the present study aims to investigate CRP as a biomarker of inflammation in treatment-naive depressed patients, being a relatively homogeneous population of MDD.

## 2. MATERIALS AND METHODS

### 2.1. Participants

This study is a cross-sectional investigation conducted among 120 outpatients.

#### *2.1.1. Recruitment Site*

Patients were recruited from the Institute of Psychiatry at Ain Shams University Hospital and the Abbasia Hospital for Mental Health outpatient clinic from March 2020 to June 2021.

#### *2.1.2. Inclusion Criteria*

The study sample was selected *via* simple random sampling from a list of individuals regularly attending outpatient clinics at both hospitals who met the inclusion criteria: patients diagnosed with major depressive disorder (MDD) according to DSM-IV criteria using the SCID-I and aged 18-65 years. Finally, 120 participants were randomly selected to enter the study using a computer-based randomisation method. The status of patients who had previously received medications or were treatment naïve was determined, and patients were accordingly divided into two groups: treatment-naïve MDD patients and MDD patients who are currently depressed and are receiving medication.

#### *2.1.3. Exclusion Criteria*

Patients with other mood disorders (*e.g.*, bipolar disorder), other major psychiatric disorders, or patients with substance abuse (other than nicotine). Those with any medical disease resulting in increased C-reactive protein (CRP) were excluded; *e.g.*, patients with any infection

within 1 month before the study, patients with any inflammatory disease (*e.g.*, arthritis, asthma, or autoimmune diseases), patients who were on any medication that affects CRP (*e.g.* anti-inflammatory drugs), patients with recent surgeries, fractures, burns within 1 month before study, patients with malignancies, pregnant women or who were pregnant within 6 months before study, or women using oral contraceptive pills within 6 months before study.

We excluded other sources of inflammation to reduce confounding factors and more accurately attribute changes in CRP levels to depression rather than other inflammatory conditions. *i.e.*, we aim to study the subset of depression patients with elevated CRP and *without* current inflammation or infection.

#### *2.1.4. The Sample Size*

The sample size was calculated using Epi Info software (Centers for Disease Control and Prevention, Atlanta, USA). Based on previous studies examining differences in C-reactive protein (CRP) levels among patients with major depressive disorder, an expected moderate effect size was assumed. Using a confidence level of 95% ($\alpha = 0.05$) and a statistical power of 80% ($\beta = 0.20$), the minimum required sample size was estimated to detect a significant difference between two independent groups. The calculated sample size was then increased to account for potential missing data or exclusions, resulting in a final target sample of 120 participants.

### 2.2. Ethical Considerations

The Ain Shams Ethical Committee approved the study protocol. Before participating, each patient provided informed consent. The study's reporting adheres to the standards outlined in the Declaration of Helsinki.

Ethical approval number: FWA 000017585

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### 2.3. Procedure

#### *2.3.1. Clinical Assessment*

All study participants were asked to complete a comprehensive history sheet to record their socio-demographic data and clinical history.

#### *2.3.2. Biochemical Assessment*

- Participants fasted for 8 hours and refrained from intense physical activity for 72 hours before blood collection. Patients on psychotropic medications maintained their regular regimen on the assessment day.
- High-sensitivity technique for quantitative measurement of CRP: We detected CRP in an automated way using the Siemens Advia XPT apparatus, which utilises a random-access immunoassay system with an assay range of 0.1-50 mg/L and a sensitivity as low as 0.10 mg/L.
- The chosen cut-off levels for CRP have been applied in a previous study [16] and are based on the recommendations by the U.S. Centers for Disease Control and Prevention: CRP < 1 mg/L = low level of systemic inflammation; CRP 1–2.99 mg/L = average level of systemic inflammation; CRP 3–10 mg/L = high level of systemic inflammation; CRP > 10 mg/L = acute inflammation.

#### *2.3.3. Psychometric Assessment*

[1] The Structured Clinical Interview for *DSM*-IV Axis I Disorders (SCID I) was used to confirm the diagnosis of MDD and exclude patients with bipolar disorder, schizophrenia, and other disorders [17]. The SCID-I is a semi-structured diagnostic interview used to assess Axis I disorders. It begins with a section on demographic information and clinical background. There are 7 diagnostic modules focused on distinct diagnostic groups, such as mood, eating, and adjustment disorders. Both required and optional probes are provided, and skip-outs are used when no further questioning is warranted. It is considered the standard interview for verifying diagnoses in clinical trials and is widely used in other forms of psychiatric research. The Arabic version used in this research was translated and used in a previous Egyptian study [18].

[2] The Beck Depression Inventory-II (BDI-II) [19]: This is a self-reporting 21-item questionnaire for assessing the presence and severity of depressive symptoms. The score ranges from 0 to 63, with higher scores indicating greater severity of depression. In individuals with depression, scores range from 0–13 for minimal, 14–19 for mild, 20–28 for moderate, and 29–63 for severe depression [19]. The Arabic version was used [20].

The depressive symptoms were classified into two categories: “somatic” and “cognitive-affective.” [21]. This involved summating the subset of symptom scores indicative of somatic symptoms (including sadness, anhedonia, crying, agitation, apathy, indecisiveness, fatigue, sleep disturbances, irritability, appetite changes, concentration issues, tiredness, and sexual disinterest) alongside the subset representing cognitive-affective symptoms (such as pessimism, past failures, guilt, feelings of punishment, self-dislike, self-criticism, suicidal ideation, and worthlessness).

[1] Hamilton Anxiety Rating Scale (HAM-A) [22]: This is a 14-item version of the HAM-A instrument, designed to quantify anxiety symptoms. It has adequate reliability, validity, and sensitivity to change. The instrument has 14 items, each rated on a scale of 0 to 4, with a maximum aggregate score of 56. A threshold score of 14 indicates clinically significant anxiety, whereas scores of 5 or below are common in the general population. The Arabic version was used [23].

[2] Somatic Symptom Scale - 8 (SSS-8) [24]: This is a self-report questionnaire evaluating somatic symptom burden. The SSS-8 is a brief form of the Patient Health Questionnaire-15 (PHQ-15).

Each SSS-8 item is scored on a 5-point scale (0-4), yielding a total score between 0 and 32.

Somatic symptom burden is categorised as high (12-15 points), medium (8-11 points), low (4-7 points), and no to minimal burden (0-3 points), with a very high category (16-32 points). The scale underwent Arabic translation and subsequent back-translation for validation.

### 2.4. Statistical Analysis

All analyses were performed using SPSS 26. Quantitative variables were described using mean and standard deviation (SD), while qualitative variables were described using numbers and percentages. The Chi-square test ($\chi^2$) was used to assess the presence of a significant association between two categorical variables. Group means were compared for quantitative variables using an independent t-test. Spearman correlation coefficient was used to test the correlation between BDI-II, HAM-A, and SSS-8 scores and other continuous variables. The significance level was set at 0.05.

Scales used are available in the supplementary file.

## 3. RESULTS

Table 1 demonstrates the socio-demographic characteristics of the sample. Of all respondents, there were 47 patients (39.2%) who were medication-naïve, while 73 (60.8%) had a history of receiving medications. (57.4%) of the Naïve group were males (n = 27), and 42.6% were females (n = 20), while in the Medications group (42.5%) were males (n = 31), and 57.5% were females (n = 42), with the mean age of (29.3± 10.1) in the Naïve group, and (37.9± 11.3) in the Medications group.

**Table 1. Demographic data of the medication naïve depressed patients and MDD patients with a history of medications.**

| - | Naïve Group *n* = 47 (39.2%) | Medications Group *n* = 73 (60.8%) | *P*-value |
|---|---|---|---|
| **Age (years)** Mean±SD | 29.3± 10.1 | 37.9± 11.3 | ***0.000**[t] |
| **Gender** | | | |
| Females | 20 (42.6%) | 42 (57.5%) | 0.109[c] |
| Males | 27 (57.4%) | 31 (42.5%) | |
| **Marital Status** | | | |
| Single | 24 (51.1%) | 13 (17.8%) | ***0.001**[c] |
| Married | 20 (42.5%) | 51 (69.9%) | |
| Divorced/widow | 3 (6.4%) | 9 (12.3%) | |
| **Education** | | | |
| Illiterate | 3 (6.4%) | 13 (17.8%) | 0.079[c] |
| Primary | 4 (8.5%) | 10 (13.7%) | |
| Secondary | 13 (27.7%) | 24 (32.9%) | |
| High | 27 (57.4%) | 26 (35.6%) | |
| **Work Status** | | | |
| Unemployed | 25 (53.2%) | 35 (47.9%) | 0.575[c] |
| Employed | 22 (46.8%) | 38 (52.1%) | |

**Note:** SD: standard deviation.
[c]Chi-square test, [t] Independent-t-test.
*P*<0.05: significant.

In the naïve group, a total of 24 patients were single (51.1%), 20 were married (42.5%), and 3 were divorced/widowed (6.4%). In the medication group, 13 patients were single (17.8%), 51 were married (69.9%), and 9 were divorced/widowed (12.3%). 6.4% of the naïve group patients were illiterate (n = 3), 8.5% reached primary school (n = 4), 27.7% reached secondary school (n = 13) while 57.4% reached high education (n = 27). In the medication group, 17.8% were illiterate (n = 13), 13.7% reached primary school (n = 10), 32.9% reached secondary school (n = 24), and 35.6% reached higher education (n = 26). The Percentage of unemployed *versus* employed was (53.2% *vs* 46.8%) and (47.9%vs 52.1%) for the Naïve group and the Medications group, respectively.

The mean duration of illness among subjects was (3.2±4.2) years and (10.2±7.9) years for the Naïve group and Medications group, respectively. The mean number of episodes was (2±0.9) and (4.8±2.5) for the Naïve group and Medications group, respectively. (38.2%) and (35.6%) had a positive family history of psychiatric illnesses in the Naïve group and Medications group, respectively.

Regarding the medications used in the medications group, 40 (33.3%) discontinued their medications before admission, 16 (13.3%) were on SSRIs, 4 (3.3%) were on SNRIs, and 13 (10.8%) were compliant on other medications (tricyclic antidepressant, fluoxetine/olanzepine combination, or adjuvant anticonvulsant). For the naïve group *vs* the medication group, the mean BDI-II total scores were (42.2±8.2) and (40.3±7.7), the HAM-A total scores were (29.7±9.7) and (30.1±10.2), and the mean SSS-8 total scores were (17.7±6.6) and (17.9±6.4), respectively (Table 2).

On comparing the medication-naïve and medication groups, as shown in Table 1, there were significant differences between the two groups in age and marital status, with the medication-naïve group being younger (mean age 29.3±10.1 years) and having fewer married individuals. Otherwise, the groups did not differ significantly in other demographic characteristics.

Regarding clinical and laboratory data, Table 2 shows that the drug-naïve group had significantly less duration of illness and a smaller number of previous depressive episodes as compared to the medication group. In addition, the drug-naïve group had a significantly lower mean CRP level than the medication group (1.5±1.2 *vs* 2.7±4.1 mg/L). It is worth noting that almost all patients had CRP levels within the normal range, with a maximum of 5 mg/L, except for two patients (1.7%). Mean high-sensitivity CRP concentrations are shown in Table 2.

As shown in Table 3, CRP was statistically significantly positively correlated with both the number of episodes ($p$ =0.006) and the duration of illness ($p$ = 0.015) of MDD. Other variables, such as BDI-II, HAM-A, and SSS-8 scores, were not significantly correlated with CRP levels in patients (Table 3).

**Table 2. Clinical data of the medication naïve depressed patients and patients with a history of medications.**

| - | Naïve Group *n* = 47 (39.2%) | Medications Group *n* = 73 (60.8%) | *P*-value |
|---|---|---|---|
| **Duration of Illness (years)** | 3.2±4.2 | 10.2±7.9 | ***0.000**[t] |
| **Number of episodes** | 2±0.9 | 4.8±2.5 | ***0.000**[t] |
| **Positive Family History** | 18 (38.2%) | 26 (35.6%) | 0.702[c] |
| **Medication history**<br>Discontinued (before admission)<br>SSRI<br>SNRI<br>Other ^ | | 40 (33.3%)<br>16 (13.3%)<br>4 (3.3%)<br>13 (10.8%) | |
| **BDI-II total** Mean±SD | 42.2±8.2 | 40.3±7.7 | 0.220[t] |
| Mild | 4 (8.5%) | 9 (12.3%) | 0.740[c] |
| Moderate | 8 (17%) | 14 (19.2%) | |
| Severe | 35 (74.4%) | 50 (68.5%) | |
| Somatic subset Mean±SD | 10.3±2.2 | 9.9±2.4 | 0.881[t] |
| Cognitive-affective subset Mean±SD | 32.1±7 | 30.6± 6.4 | 0.390[t] |
| **HAM-A total** Mean±SD | 29.7±9.7 | 30.1±10.2 | 0.863[t] |
| No or Minimal | 2 (4.3%) | 4 (5.5%) | 0.725[c] |
| Mild | 0 (0%) | 1 (1.4%) | |
| Moderate | 12 (25.5%) | 14 (19.2%) | |
| Severe | 33 (70.2%) | 54 (74%) | |
| **SSS-8 total** Mean±SD | 17.7±6.6 | 17.9±6.4 | 0.845[t] |
| **SSS-8 severity** | | | |
| Low | 2 (4.3%) | 5 (6.8%) | 0.223[c] |
| Medium | 9 (19.1%) | 6 (8.2%) | |
| High | 5 (10.6%) | 14 (19.2%) | |
| Very High | 31 (66%) | 48 (65.8%) | |
| **CRP mg/L** Mean±SD | 1.5±1.2 | 2.7±4.1 | ***0.023**[t] |
| **CRP Groups** | | | |
| <1 mg/L | 25 (53.2%) | 30 (41.1%) | 0.394[c] |
| 1–2.99 mg/L | 15 (32%) | 25 (34.2%) | |
| 3-4.99 mg/L | 7 (14.9%) | 16 (21.9%) | |
| >5 mg/L | 0 (0%) | 2 (2.7%) | |

**Note:** Beck Depression Inventory-II (BDI-II), Hamilton Anxiety Rating Scale (HAM-A), Somatic Symptom Scale - 8 (SSS-8), SD: standard deviation. [c]Chi-square test, [t] Independent-t-test, *P*<0.05: significant.
^ was on a tricyclic antidepressant, fluxetine/olanzepine combination, or adjuvant anticonvulsant.

**Table 3. Correlation matrix between CRP levels in the studied sample, and no of episodes, duration of illness, BDI-II, HAM-A and SSS-8.**

| - | CRP |
|---|---|
| Number of episodes | 0.251** |
| *P*-value | **0.006** |
| Duration of illness | 0.221* |
| *P*-value | **0.015** |
| BDI-II total | -0.006 |
| *P*-value | 0.947 |
| BDI-II Mood | -0.099 |
| *P*-value | 0.281 |
| BDI-II Cognitive | -0.038 |
| *P*-value | 0.682 |
| BDI-II Psychomotor | 0.111 |
| *P*-value | 0.226 |
| BDI-II Vegetative | -0.018 |
| *P*-value | 0.845 |
| HAMA total | -0.067 |
| *P*-value | 0.467 |
| SSS-8 total | -0.054 |
| *P*-value | 0.555 |

**Note:** Beck Depression Inventory-II (BDI-II), Hamilton Anxiety Rating Scale (HAM-A), Somatic Symptom Scale - 8 (SSS-8). Spearman correlation was used. *P*<0.05: significant.

## 4. DISCUSSION

Several lines of evidence show that the immune system is implicated in the pathophysiology of MDD [25]. To the best of our knowledge, this is one of the few studies set out to assess CRP in depression in a sample of treatment-naive depressed patients in comparison to patients who are currently depressed and are receiving medication.

During the assessment of the current sample, we found a statistically significant difference between the two groups regarding serum CRP levels, with the drug-naïve group having a significantly lower mean CRP level than patients receiving medication. However, almost all patients had a CRP level within the normal range of 5 mg/L.

Many cross-sectional population studies have reported an association between CRP levels and depression in general [2, 13, 16, 26]. This was supported by recent meta-analyses, which confirmed that the levels of CRP and other inflammatory cytokines are higher in patients who are currently in a depressive episode compared with healthy controls [27]. It is worth noting that CRP levels are elevated in MDD patients compared with controls, yet remain within the normal range, consistent with our results. There is also evidence that individuals with MDD have altered expression patterns of immune-related genes compared with controls [15].

Nonetheless, there is an inconsistency regarding this association. For example, in a cross-sectional population-based study including 9300 participants, this association

disappeared after adjustment for confounding factors, such as chronic illness and body mass index (BMI) [28]. When studied longitudinally, a positive association between CRP and depression has also been reported by some [29] but not all studies [30].

The association between CRP and depressive disorder, therefore, remains indefinite. This inconsistency could be attributed to the heterogeneity of depressive disorder and the fact that almost all of the studied patients received antidepressant medications, which may act as a confounding factor.

The socio-demographic data in our sample revealed that most patients were young adults. Of all respondents, 47 patients (39.2%) were medication-naïve, while 73 (60.8%) had a history of receiving medications. There was a significant difference between the two groups regarding age and marital status, with the drug-naïve group being younger, and fewer of them were married. Otherwise, the groups did not differ in any other demographic characteristics.

Both groups were similar with respect to many clinical variables. However, as expected, the drug-naïve group had significantly less duration of illness and a smaller number of previous depressive episodes than the medication group. It is worth noting that the average severity of depressive episodes was moderate and severe in study participants. This is expected, given that the sample was collected from two tertiary psychiatric centres.

Our main finding was that the drug-naïve group had a significantly lower mean CRP level than the medication group. To the best of our knowledge, only a few studies have investigated CRP in treatment-naïve patients, using different methodologies.

The [31] study is the most comparable to ours. It investigated the level of CRP in subjects with MDD before and after antidepressant treatment, with 97.4% of their sample never receiving antidepressant treatment before enrollment. So, it is like comparing treatment-free MDD patients with themselves after receiving medications. In line with our findings, CRP levels increased significantly after six weeks of treatment, even after adjusting for age and gender. Being a prospective study, this may entail an association between receiving antidepressants and CRP elevation. Due to its cross-sectional design, our study cannot conclude such an association.

Second [25], studied CRP and cytokine levels from 50 unmedicated MDD patients during nonpharmacological treatment. However, they compared them to healthy controls. In their study, patients with MDD had higher baseline CRP levels than healthy controls. Cytokine plasma levels normalised during recovery from an acute depressive episode in MDD after non-pharmacological treatment. However, the plasma CRP level did not change [25].

However, in contrast to our findings [10], found that serum CRP levels were numerically higher in MDD patients (responding to medications), with a mean of 2 mg/L, than in unmedicated MDD patients (around 2.6 mg/L). Still, this difference did not reach statistical significance.

We then tried to investigate correlations between the CRP level in our sample and clinical data and phenotypes of depression, including the number of episodes, duration of illness, depression severity score as measured by BDI-II, symptom categories “somatic” and “cognitive-affective” subsets of BDI-II, anxiety symptoms assessed with HAM-A, and somatic symptoms by SSS-8 scores. The associations between CRP levels and both the number of episodes and the duration of illness in MDD were statistically significant, whereas associations with all other clinical phenotypes were not.

In agreement with our study [31], also found that the association between baseline CRP level and depression severity score was not significant in their sample, even after adjustment for age and gender. However, contrary to our results, the baseline CRP level in their sample was significantly associated with patients’ cognitive function. This discrepancy may be explained by the fact that [31] used standardised psychometric tests to assess cognitive performance, such as the Continuous Performance Test (CPT), the Finger-Tapping Test (FTT), and the Wisconsin Card-Sorting Test (WCST), while we used a self-reported subscale. That‘s why this correlation may not have been detected in our study.

Other studies indicate a link between elevated CRP levels and cognitive impairment [32, 33]. In a 12-year follow-up study [34], found that baseline CRP levels predicted cognitive symptoms of depression at follow-up.

Regarding the severity of depression, many previous studies have demonstrated the association between CRP levels and the severity of MDD [2, 16, 26, 35]. Some previous studies, however, found no significant association [11, 36, 37]. For example, in [15], the MDD patients with ‘CRP >3 mg/L’ show the highest severity of depression, as detected by HAMD-17 scores. The severity scores of the subjects were comparable to those of the ‘CRP <1 mg/L’ cohort, indicating that elevated CRP levels may not definitively correlate with increased depression severity. Inconsistent findings of the association between CRP levels and the severity of depression may be due to other confounding factors that may affect CRP levels in depressed patients, such as BMI, age, gender, and the use of antidepressant agents. Additionally, variations in sample size among studies may explain this inconsistency.

Regarding somatic symptoms, some studies have associated CRP levels in MDD patients with somatic symptoms [13]. For example, Green *et al*. (2021) showed that serum CRP levels correlate significantly with overall MDD symptom severity, particularly somatic symptoms. Inflammatory markers correlate with somatic symptoms of depression, such as fatigue and impaired sleep, rather than cognitive or psychological symptoms [7, 38]. These studies reported findings consistent with the sickness behaviour repeatedly demonstrated in animal models exposed to acute proinflammatory challenge [39, 40]. Regarding anxiety symptoms, and in contrast to our

results, some studies found evidence that state anxiety was related to CRP serum level [39].

The fact that in our sample, CRP levels were not correlated with any clinical data of depression, which was inconsistent with previous studies, might be caused by some factors, such as the type of depression, the disease severity, and medication status. In addition, these studies didn't include medication-naïve patients.

In agreement with our results [41], study performed in Pakistan initially found anxiety to be positively correlated with inflammatory parameters and general somatic symptoms to be negatively associated with inflammation. These correlations were not statistically significant in logistic regression.

The findings of our study suggest that CRP levels reflect the status of brain inflammation. This is further supported by the finding that CRP was significantly correlated with the duration and number of MDD episodes. Inflammation may impair brain function by reducing neurotrophic support, enhancing glutamatergic excitotoxicity, and modifying serotonin transporter activity [31].

Interestingly, susceptibility to MDD and CRP levels correlate with genetic variations in the CRP gene [42]. Furthermore, fluctuations in the inflammatory system occur during mood alterations in affective disorders [31]. Low-grade inflammation, indicated by high-sensitivity CRP, correlates with cerebral microstructural disintegration [43].

We think that's why it was not correlated to either the severity of depression or any of its symptomatic subsets, as this is a pathological process related to the disease itself, a trait rather than a state marker. This can be confirmed if we measure CRP levels in MDD patients in remission in comparison to those in depressive episodes.

A study by [44] studied state *vs*. trait immune alteration in MDD [44]. measured CRP levels and depression severity in patients with first-episode or recurrent MDD at hospital admission and after 6 weeks of treatment. They found that although both groups showed increased CRP levels compared with controls, baseline lymphocyte counts were elevated in the recurrent MDD group but not in the first-episode group, suggesting a potential role of adaptive immunity in chronic MDD. Although this study did not employ the same methodology as ours, it still supports the state-*versus*-trait immunity explanation.

The question of whether the elevated level of CRP in the medication group may be a result of the antidepressant treatment or not can be answered due to the absence of longitudinal data. Previous studies on antidepressants' effects on CRP levels yielded inconclusive results. Certain population-based studies indicated a correlation between antidepressant use and increased CRP levels, independent of mental illness symptoms and cardiovascular comorbidity [45]. Some other meta-analytic studies did not find any significant effect of antidepressant medication on CRP levels [1, 4], while others indicate a notable reduction in CRP levels post-antidepressant therapy [46, 47].

The findings of the present study have several important implications. First, the observation that CRP levels were significantly lower in treatment-naïve patients compared to those receiving antidepressant therapy suggests that inflammatory markers in MDD may not solely reflect the underlying disease process, but could also be influenced by treatment status or illness chronicity. This highlights the importance of considering medication exposure when interpreting inflammatory biomarkers in psychiatric research. Second, the positive association between CRP levels and both illness duration and number of depressive episodes supports the hypothesis that inflammation may be linked to the longitudinal course of depression, rather than its acute severity. This raises the possibility that CRP may function more as a trait marker rather than a state marker of depressive symptomatology. From a clinical perspective, these findings could have implications for personalised treatment approaches, including the potential role of anti-inflammatory strategies in selected subgroups. The significance of the raised level in the medication group compared to the drug-naïve group, however, warrants further investigation.

## 5. LIMITATIONS

Several important limitations must be acknowledged in interpreting these findings: first, the study's cross-sectional design may hinder causal inference. Second, longitudinal data would be preferred for understanding the temporal relationship between taking antidepressant medications and CRP level change in drug-naïve depressed patients. Moreover, we lacked CR*P*-values from healthy controls for comparison, making it difficult to draw a firm conclusion. The study did not examine variations in CRP across antidepressant subgroups. Finally, CRP is merely one of numerous peripheral inflammation markers. While it serves as an indicator of inflammatory activity, CRP may be affected by various current state factors, including recent infections, injuries, BMI, or chronic inflammatory conditions [7].

## CONCLUSION

In conclusion, this study is one of the few studies to observe a significant difference in the level of CRP in treatment-naïve depressed patients in comparison to those who receive medications. CRP was not associated with depressive symptom severity or any symptomatic subsets of depression, but was associated with the number of episodes and the duration of illness. Although the above data are preliminary, the significance of this finding warrants further investigation and replication. The question is whether antidepressants are associated with increased CRP levels or if this is a part of the patho-physiological mechanism of depression, *i.e*., a trait marker.

## AUTHORS' CONTRIBUTIONS

The authors confirm contribution to the paper as follows: H.H.E. and A.S.M.: Study conception and design; T.M.S.Z.: Data collection; M.S.E.A. and N.M.S.: Analysis and interpretation of results; M.A.R.S. and M.S.E.A.: Drafted the manuscript. All authors reviewed the results and approved the final version of the manuscript.

## LIST OF ABBREVIATIONS

| | | |
|---|---|---|
| CRP | = | C-reactive Protein |
| MDD | = | Major Depressive Disorder |
| SCID-I | = | Structured Clinical Interview for DSM-IV |
| BDI-II | = | Beck Depression Inventory-II |
| HAM-A | = | Hamilton Anxiety Rating Scale |
| SSS-8 | = | Somatic Symptom Scale-8 |
| TNF-α | = | Tumour Necrosis Factor-alpha |
| PHQ-15 | = | Patient Health Questionnaire-15 |
| CPT | = | Continuous Performance Test |
| FTT | = | Finger-Tapping Test |
| WCST | = | Wisconsin Card-Sorting Test |

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The Ain Shams Ethical Committee approved the study protocol. Ethical approval number: FWA 000017585. FMASU M D 101 / 2020.

## HUMAN AND ANIMAL RIGHTS

All human research procedures followed were in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013.

## CONSENT FOR PUBLICATION

Before participating, each patient provided informed consent.

## STANDARDS OF REPORTING

STROBE guidelines were followed.

## AVAILABILITY OF DATA AND MATERIALS

Data will be available upon request.

## FUNDING

None.

## CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

## SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's website along with the published article.

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