

Original Research Article

A comparative study of inflammatory marker highly sensitive C-Reactive Protein in depression patients exhibiting suicidal behaviour and depression patients without suicidal behaviour

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ABSTRACT

Background: Recent research have found a link between inflammatory pathway and suicidal behaviour. hs-CRP, IL, TNF have been shown to have significant alterations in suicidality, however multiple covariates influence this relationship. One of the main limitations of most of the studies is that they have evaluated the CRP in patients demonstrating suicidal behaviour but not in depression. No study has been conducted in Indian subpopulation with parameters of our study. Aims of the study was to compare hsCRP levels between depression patients with suicidal behaviour and without suicidal behaviour.

Methods: Authors compared 50 depression patients with suicidal behaviour and 50 depression patients without suicidal behaviour, diagnosed using ICD10. Hamilton Depression Rating Scale (HDRS-17), Suicide behaviour Questionnaire- Revised (SBQ-R), Beck Scale for Suicidal Ideation (BSSI) were applied for assessment of depression and suicidality. Highly sensitive CRP was measured using autoanalyzer.

Results: hsCRP levels were significantly high in depression patients with suicidal behaviour (4.12 mg/dl) than depression without suicidal behaviour (2.42 mg/dl). Duration of illness, HAM-D, BSSI and SBQ-R scores correlated positively with hsCRP levels.

Conclusions: Depression with suicidal behaviour patients have a significantly higher hs-CRP levels than depression without suicidal behaviour. Patients of depression with suicidal behaviour group have a strong positive correlation between hs-CRP levels and HAM-D, BSSI and SBQ-R scores.

Keywords: C-reactive protein, Inflammatory marker, Depression, Suicide

INTRODUCTION

Depression and suicide are serious intertwined problems. If left untreated, they can have dire outcomes. Both depression and attempted suicide have become more common in recent times and are of central concern to professionals in the fields of health, education and social services. It is characterized by persistent sadness of mood, markedly diminished interest or pleasure in activities, low energy levels and fatigue.¹ Suicide is a behemoth of a public health problem. More than 1,00,000 people die of suicide each year in the India, and 1 million

people die globally. Suicide is the 14th cause of death around the world and tragically the 2nd leading cause of death in young population 15-29 years of age. Early identification of suicidal behavior is vital for the prevention and meticulous treatment of suicide.²

Biochemical, psychological, behavioural risk factors are important in pointing the psychiatrist towards the right path, however, many times they produce a false positive or a false negative diagnosis. Multiple studies suggest that abnormal biology and genetic basis may be a risk factor for suicidality. Hence, a combination of bio-

psycho-social factors might more accurately predict suicidal behavior and be of key importance in finding at risk patients. It is thus of utmost importance to develop such biomarkers for suicidal behavior. A useful biomarker should not only reflect the psychopathology, in this case suicidal behavior, but it should also be measured in the least invasive manner possible.³

Having a psychiatric disorder, especially major depressive disorder (MDD), is another risk factor of suicide as 90% of suicide completers suffer from some form of psychiatric illness.⁴

Some inflammatory mediators, such as cytokines, are able to reciprocally interact with and are thought to be partially responsible for the dysregulations of the hypothalamic-pituitary-adrenal (HPA) axis and serotonergic system frequently observed in suicidal patients.^{5,6} Inflammatory markers might be linked to suicidality, among which hs-CRP play an important role. Many studies have demonstrated an association between suicidal behaviour and inflammatory markers primarily CRP.⁷⁻¹¹

However, one of the main limitations of most of the studies is that they have evaluated the CRP in patients demonstrating suicidal behaviour but not in settings of depression necessarily hence it was difficult to differentiate the altered inflammatory states that could be attributed to suicidality in depression or other causes. Another limitation of most of the above studies is the small sample sizes. Many of the studies had limitations in the form of using CRP instead of highly sensitive CRP. No study has been conducted in Indian subpopulation with the parameters of our study i.e. comparing depression patients with and without suicidal behaviour. The present study had taken real world depression patients in order to explore relationship between inflammation and suicidal behaviour.

METHODS

This was a cross sectional hospital-based study to compare the highly sensitive C-Reactive Protein (hs-CRP) among depression patients with and without suicidal behaviour conducted between January 2018 to December 2018 in M.G.M Medical College, Indore. The case group included depression patients exhibiting suicidal behaviour. The control group had depression patients without any suicidal behaviour or history of suicidal attempt.

Patients who met the diagnosis of depression as per International Statistical Classification of Diseases-10 (ICD-10 DCR) and were drug naïve or drug free for at least 3 months and aged between 18-65 years were included in the study.¹² Patients having any other major physical, endocrinology or psychiatric co morbidities, current scheduled use of, use of anti-psychotics, anti-

depressants, pregnancy were excluded. Any drugs or illness which may modify CRP levels were excluded.

After complete description of the study to the subjects, written informed consent was obtained from all participants. A detailed physical examination was done to rule out major medical or neurological illness. After that clinical assessment of patient group was done using Hamilton Depression Rating Scale (HAM-D), Beck Scale for Suicidal Ideation (BSSI), Suicide Behaviour Questionnaire (SBQ-R).¹³⁻¹⁵ Blood samples of all groups were drawn after explaining the procedure and were collected in a clot activator (red top) tube at MY Hospital Indore Dept. of biochemistry.

Post which serum was processed from the sample via centrifuge machine and the serum was analysed for hs-CRP with Automated analyser using Immunoturbidimetry method. Data collected was analysed using SPSS v23 and appropriate tests like students t-test, Pearson correlation, chi square were applied.



Figure 1: the recruitment, sampling, assessment process.

RESULTS

Table 1 shows in comparison to the depression without suicidal behaviour the depression with suicidal behaviour had younger age of onset (33.08 years), more male (52%), married (62%), Hindu faith (76%), unemployed (68%), urban (66%) locality-based subjects. However, there were lesser illiterate (18%) and low socioeconomic subjects (74%) in the suicidal group than the non-suicidal group.

Table 1: Sociodemographic variables of the patients.

| | | Depression with suicidal behaviour (N=50) | Depression without suicidal behaviour (N=50) |
|---------------------------|---|---|--|
| Age(mean) in years | | 33.08 years | 34.20 years |
| Males | | 26 (52%) | 21 (42%) |
| Females | | 24 (48%) | 29 (58%) |
| Marital status in %: | Married | 68% | 64% |
| | Unmarried | 20% | 26% |
| | Divorced | 4% | 4% |
| | Widowed | 2% | 0% |
| | Remarried | 6% | 6% |
| Religion in %: | Hindu | 76% | 68% |
| | Muslim | 24% | 32% |
| Education in %: | Illiterate | 18% | 22% |
| | Primary (5 th) | 32% | 32% |
| | Middle(8 th) | 20% | 22% |
| | High School | 12% | 10% |
| | Inter | 8% | 10% |
| | Diploma/Graduate/Post graduate Professional | 10% | 4% |
| Socioeconomic | Low | 74% | 76% |
| | Middle | 24% | 22% |
| | High | 2% | 2% |
| Occupation | Employed | 32% | 40% |
| | Unemployed | 68% | 60% |
| Family type | Nuclear | 66% | 54% |
| | Extended/ Joint. | 34% | 46% |
| Locality | Urban | 66% | 62% |
| | Rural | 34% | 38% |

Table 2: Clinical characteristics of the depression patients (continuous variables).

| Variables | Suicidal depression patients Mean±SD N=50 | Non-Suicidal depression patients Mean± SD N=50 | t value | p value |
|------------------------------------|---|--|---------|---------|
| Duration of illness (in months) | 5.58±2.50 | 5.10±2.30 | 0.991 | 0.324 |
| Age of onset of illness (in years) | 32.6±11.90 | 33.5±10.50 | -3.83 | 0.703 |
| HAM-D SCORES | 20.36±7.04 | 15.28±2.80 | 4.73 | 0.001 |
| BECK'S SSI SCORES | 19.70±6.37 | - | - | - |
| SBQ-R SCORES | 10.40±3.28 | - | - | - |

Table 2 shows the mean duration of illness of depression with suicidal behaviour patients was 5.58±2.5 months, while that of depression without suicidal behaviour patients was 5.10±2.30 months. The mean age of onset of illness of depression with suicidal behaviour patients was 32.6±11.9 years while the mean age of onset of illness of depression without suicidal behaviour patients was 33.5±10.5 years. Depression without suicidal behaviour patients had a mean HAM-D score of 15.28±2.80 while depression with suicidal behaviour patients had a mean HAM-D score of 20.36±7.04. t-test showed statistical

significance in HAM-D scores. The BSSI score in the depression with suicidal behaviour group was 19.7, while SBQ-R score was 10.4.

Table 3 displays comparison of hs-CRP levels between depression patient with suicidal behaviour and depression without suicidal behaviour patients. The mean hs-CRP for depression with suicidal behaviour was 4.12±4.95 mg/L which is considered as high value as per our criteria for cut off, while for depression without suicidal behaviour was 2.42±2.91 mg/L which is low and the

means differed significantly. Depression with suicidal behaviour patient group has shown higher hs-CRP mean than depression without suicidal behaviour group which was statistically significant. Table 4 describes the high and low hs-CRP counts which is defined by a cut off of 3mg/L as per literature and methodology in depression patients with and without suicidal behaviour. The chi square test was statistically significant implying that depression patients with suicidal behaviour have more hs-CRP samples in high group than depression without suicidal behaviour.

Cramer’s v = 0.257, moderate effect size

Table 5 displays various sociodemographic parameters of hs-CRP levels. None of the parameters for hs-CRP was statistically significant. The mean hs-CRP values were high in married subtype, Hindu religion, joint family type, rural locality and male gender. Despite there being a noticeable change in the various subtypes on applying students t test the results were not statistically significant.

Table 3: Comparison of hs-CRP between depression patients with suicidal behaviour and non-suicidal behaviour.

| hs-CRP (mg/L) | Depression with suicidal behaviour (N=50) | Depression without suicidal behaviour (N=50) |
|--------------------|---|--|
| Mean | 4.12 | 2.42 |
| N | 50 | 50 |
| Std. Deviation | 4.95 | 2.91 |
| Std. Error of Mean | 0.69 | 0.41 |
| Minimum | 0.12 | 0.15 |
| Maximum | 26.80 | 12.14 |
| Range | 26.68 | 11.99 |
| t value | 2.09 | |
| p value | 0.03* | |

*statistically significant

Table 4: Chi square test for hs-CRP samples (low and high) between depression with suicidal behaviour and depression without suicidal behaviour.

| | | hs-CRP result | | Total |
|-------------------------|----------------|----------------------------|---------------------------|-------|
| | | hs-CRP high (value >3mg/L) | hs-CRP low (value ≤3mg/L) | |
| Suicidal depression | Count | 22 | 28 | 50 |
| | Expected count | 16.0 | 34.0 | 50.0 |
| Non-suicidal depression | Count | 10 | 40 | 50 |
| | Expected count | 16.0 | 34.0 | 50.0 |
| Total | Count | 32 | 68 | 100 |
| | Expected count | 32.0 | 68.0 | 100.0 |
| Pearson chi-square | 6.61 | | | |
| p value | 0.01 | | | |
| Cramer’s V | 0.257 | | | |

Pearson chi-square value = 6.61, p= 0.01

Table 5: Comparison of hs-CRP levels between socio-demographic groups in depression patients with and without suicidal behaviour.

| hs-CRP mg/L | Variables | | Depression patients n =100 Mean±SD | t value | p value |
|----------------|-----------|--|------------------------------------|---------|---------|
| | | | | | |
| Marital status | Married | | 3.38±3.87 | 0.335 | 0.739 |
| | Others | | 3.08±4.57 | | |
| Religion | Hindu | | 3.53±4.56 | 1.24 | 0.216 |
| | Others | | 2.61±2.68 | | |
| Family type | Nuclear | | 3.14±4.19 | -0.403 | 0.688 |
| | Joint | | 3.48±4.08 | | |
| Locality | Urban | | 2.82±3.86 | -1.42 | 0.160 |
| | Rural | | 4.09±4.51 | | |
| Gender | Male | | 3.47±3.91 | 0.438 | 0.662 |
| | Female | | 3.11±4.32 | | |

Table 6: Correlation of hs-CRP with duration of illness and HAM-D scores in patients of depression with suicidal behaviour and depression without suicidal behaviour.

| | Duration of illness suicidal depression | | Duration of illness non-suicidal depression | |
|--------|---|-------|---|-------|
| | r | p | r | p |
| hs-CRP | 0.478** | 0.000 | 0.381* | 0.006 |
| | HAM-D suicidal depression | | HAM-D non-suicidal depression | |
| | r | p | r | p |
| | 0.618** | 0.000 | 0.133 | 0.357 |
| | BSSI | | SBQ-R | |
| | r | p | r | p |
| | 0.590** | 0.001 | 0.551 | 0.001 |

** . Correlation is significant at the 0.01 level (2-tailed).

* . Correlation is significant at the 0.05 level (2-tailed).

There is a statistically significant medium positive correlation between Duration of illness of depression and hs-CRP levels in depression with suicidal behaviour group, while the depression without suicidal behaviour group also had a statistically significant medium positive correlation between hs-CRP and duration of illness.

There is a statistically significant strong positive correlation between HAM-D scores and hs-CRP levels in depression with suicidal behaviour group, while the depression without suicidal behaviour group also had a small positive correlation between hs-CRP and HAM-D but it was not statistically significant.

There is a statistically significant strong positive correlation between BSSI and SBQ-R scores and hs-CRP levels in depression with suicidal behaviour group. Since the control group of depression without suicide behaviour did not have any suicidal behaviour the SBQ and BSSI scores are not applicable in the group.

DISCUSSION

The mean age of depression with suicidal behaviour group was 33.08±11.9 years while that of depression without suicidal behaviour group was 34.20±10.3 years, this implies that suicidality appears earlier in presence of depression.¹⁶ The number of female patients were higher in the depression without suicidal behaviour group (58%) than depression with suicidal behaviour group.¹⁷ Results suggest that males have higher suicidal behaviour than females. The married subjects were higher in depression with suicidal behaviour group (68%) than depression without suicidal behaviour (64%) groups.¹⁸ It was found that being married might have protective effect on suicidal behaviour due to better social and interpersonal support. The depression with suicidal behaviour group had higher preponderance of (76%) Hindu subjects which is in agreement of the local geographical distribution of the religion. Most participants in both depression with suicidal behaviour (32%) and depression without suicidal behaviour (32%) group were literate till primary

education, depression without suicidal behaviour group had more percentage of illiterates (22%).¹⁹ Low socio-economic income groups were found to be the majority in both depression with suicidal behaviour (74%) and depression without suicidal behaviour groups (76%).²⁰ The distribution of depression with suicidal behaviour group (66%) and depression without suicidal behaviour (62%) sample were urban dwelling in majority, while about one third sample in both groups belonged to rural background.²¹ The depression with suicidal behaviour group had higher composition of nuclear family (66%) than depression without suicidal behaviour group (54%).²¹ The sociodemographic results resonates with previous studies (Table 1).

The mean duration of illness of depression with suicidal behaviour patients was 5.58±2.50 months or 23 to 24 weeks. The mean duration of illness in depression without suicidal behaviour patients was 5.10±2.30 months or almost 21-22 weeks (Table 2). This is keeping with the mean duration of depression in most literature.²² We conclude that the depression with suicidal behaviour patients presented to the health-care settings later as compared to depression without suicidal behaviour patients which is alarming as suicidal behaviour is a psychiatric emergency and secondary to the psychomotor retardation seen in severe depression the suicidal behaviour patients could further hamper consultation. The mean age of onset of illness of depression without suicidal behaviour patients was 33.5±10.50. similar mean age has been found in multiple studies.²³⁻²⁵ The mean age of onset of illness of depression with suicidal behaviour patients was 32.6±11.90 years, previous studies have found mean age of onset to be around 39±5 years.²⁶

Depression without suicidal behaviour patients had a mean HAM-D score of 15.28±2.80 equivalent of moderate depression while depression with suicidal behaviour patients had a mean HAM-D score of 20.36±7.04 which corresponds to severe depression as per HAM-D (Table 2). This is in concordance with the current literature and classificatory system which suggest suicidality to be an indicator of severe depression. This

finding correlates suicidality to severity of depression, supplementing suicidal behaviour to be an indicator of severe depression, which is concordance with an earlier study which found severe depression as one of the factors significantly associated with suicide (OR=2.20, 95% CI=1.05-4.60), while another study reported the finding of severe depression was associated with a sensitivity of 87.3% and specificity of 63% for suicide attempt.²⁷⁻²⁹ Mean BECK'S SSI Score in depression with suicidal behaviour patients was 19.70 ± 6.37 while SBQ-R score was 10.40 ± 3.28 . SBQ-R scores more than 8 are suggestive of suicidal behaviour which is seen in our sample population (Table 2).

On comparing the hs-CRP values between depression patient with suicidal behaviour and without suicidal behaviour, depression with suicidal behaviour patient group has shown higher mean hs-CRP (4.12 ± 4.95 mg/L) than non-suicidal group of depression (2.42 ± 2.91 mg/L) which was statistically significant (Table 3). Similar results were replicated by other researchers who investigated CRP levels in 600 depressed inpatients who concluded risk of suicide attempts increased with higher levels of CRP.⁷ Another study on C-reactive protein and serum lipid levels among 122 inpatients found that higher levels of CRP were found in inpatients having recently attempted suicide compared with inpatients who had not attempted suicide.⁹ In a Korean study it was concluded that elevated levels of CRP were associated with an increased risk of suicidal ideation among a cross-sectional study in 4693 Korean adults aged 20-81.¹¹ Two other studies also found higher hsCRP values in depression patients with suicidal behaviour.^{30,31} The mean for suicidal group is above cut off for high category as per our study criteria which considers ≥ 3 mg/L as high level for hs-CRP. So, on the basis of mean hs-CRP as well we can say that hs-CRP can be an indicator for suicidal behaviour in depression patients.

Supplementing the above result for hsCRP non-parametric test of chi square was used which included the high and low hs-CRP counts which is defined by a cut off of 3mg/L as per literature and methodology in depression patients with and without suicidal behaviour (Table 4). The chi square test was statistically significant implying that depression patients with suicidal behaviour have more hs-CRP samples in high group than depression without suicidal behaviour. The Cramer's v score was 0.257 implying a moderate effect size.

The mean hs-CRP values were high in married subtype, Hindu religion, joint family type, rural locality and male gender without any statistical significance. However, our study did not find any statistically significant association of hs-CRP with any sociodemographic parameters (Table 5). On the contrary another study concluded Depression score was correlated to hs-CRP levels in women.³²

There is a statistically significant moderate positive correlation ($r=0.47$) between duration of illness of

depression and hs-CRP levels in depression with suicidal behaviour group, while the depression without suicidal behaviour group also had a statistically significant medium positive correlation ($r=0.38$) between hs-CRP and duration of illness. This is suggestive that hs-CRP correlates with duration of illness of depression in presence or absence of suicidal behaviour, although the suicidal behaviour group had a stronger correlation.

There is a statistically significant strong positive correlation between BSSI ($r=0.59$), SBQ-R ($r=0.55$) scores and hs-CRP levels in depression with suicidal behaviour group (Table 6). This finding is consistent with the inflammatory model utilized in the study it was hypothesized that hs-CRP would correlate positively with suicidal behaviour. Since BSSI and SBQ-R are indicators of suicidal behaviour as established by previous studies, hs-CRP correlates strongly with the suicidal parameters, hs-CRP could be an indicator of suicidal behaviour in depression patients.^{14,15,33}

There is a statistically significant strong positive correlation ($r=0.61$) between HAM-D scores and hs-CRP levels in depression with suicidal behaviour group, while the depression without suicidal behaviour group had a small positive ($r=0.13$) correlation between hs-CRP and HAM-D but it was not statistically significant (Table 6). It is suggestive that depression scores correlate positively with hs-CRP. Similar results were replicated in an earlier study who reported depression score was correlated to hs-CRP levels.³²

CONCLUSION

Depression with suicidal behaviour patients have a significantly higher hs-CRP levels than depression without suicidal behaviour. Not only the suicidal group mean hsCRP differ it had clinically relevant greater proportion of samples in the high hsCRP group (≥ 3 mg/L). We found that the patients of depression with suicidal behaviour develop the illness earlier and duration is longer than depression without suicidal behaviour. This finding is vital in cases where long standing depression can serve as a risk factor. A positive correlation between hsCRP, duration of illness, depression and suicidality was established. Interestingly there was no statistical association of hs-CRP with socio-demographic factors.

Few advantages of this study include being a case-control study, the advantage of both group containing depression patients eliminated any deviation arising due to other factors. Authors is a pioneer study in context of Indian population. Faster sample acquirement and analysis of serum samples obtained from suicidal and non-suicidal patients as delay may have resulted in dilution of strong association of inflammation and suicidality.

Thus hs-CRP an inflammatory marker can serve as a potential marker of suicidal behaviour in depression patients and such at risk patients may be identified prior

to suicidal attempt by high hs-CRP levels. There is a huge lacuna in the field of biomarkers for depression and suicide. This study is one of the few to take a leap towards this direction. Replication of current study with more ethnically diverse sample, larger sample and longitudinal design would be beneficial.

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