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Original Research Article

Association of Depression with IL-6 and CRP Levels Among COVID Recovered Patients: A Hospital Based Case Control Study

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Abstract

Introduction: Depression has been reported in patients suffered from COVID 19 (corona virus disease). Inflammatory markers like IL-6 and CRP have been also found raised in COVID 19 patients.

Aim: The objective of present study was to find out the association of serum IL-6 and CRP levels with depression in COVID 19 patients discharged from hospital.

Materials and Methodology: This Case control study included 30 patients of depression attending post COVID OPD after getting discharged from hospital and 30 post COVID patients without depression. Depression was diagnosed using PHQ-9 scores. A cutoff value of 10 was taken to diagnose depression upon PHQ-9 scale. Both groups were compared in relation to socio-demographic variables, serum IL-6 & CRP levels and other clinical variables.

Results: Serum IL-6 and CRP levels were significantly higher in post COVID patients with depression (IL-6=39.71 ± 46.39, CRP=43.66 ± 31.78) than those without depression (IL-6= 13.42 ± 18.98, CRP= 21.02 ± 25.36). Hospital stay was also greater in post COVID patients with depression.

Conclusion: Post COVID depression was significantly associated with IL-6 and CRP levels. Patients with raised level of these markers could be screened for early identification of depression and counseled preferentially for prevention of depression during post COVID period.

Key words: COVID, Depression, IL-6, CRP, Corona

Introduction

COVID-19 or Corona virus disease is caused by novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). [1] It is a negatively stranded RNA virus, which produce symptoms ranging from common colds to severe acute respiratory syndrome, and has been responsible for recent pandemic [2]. Though fatality rate had been relatively low, patients have developed various short to long term sequel even after recovery. These sequel ranges from mild weakness to fatal cardio/cerebro vascular disease. Neuropsychiatric sequel has also been reported by various studies. In the post-illness stage the prevalence of post-traumatic stress disorder was 32·2%, depression was 14·9%, that of anxiety disorders was 14·8%, insomnia was 12·1%, memory impairment was18·9% and fatigue was 19·3% [3]. Corona viruses could induce psychopathological sequel through direct viral infection of the central nervous system (CNS) or indirectly via an immune response [4]. Clinical, post-mortem, animal, in vitro, and cell culture studies demonstrated that corona viruses are potentially neurotropic and can induce neuronal injuries [5]. Not withstanding possible brain infiltration, "cytokines storm" involved in the immune response to corona viruses may cause psychiatric symptoms by precipitating neuro-inflammation [6]. In addition to the immunological mechanisms, fear of illness, uncertainty of the future, stigma, traumatic memories of severe illness, and social isolation experienced by patients during the COVID-19 are significant psychological stressors that may interact in defining psycho-pathological outcome [7,8].

The etiology of major depressive disorder (MDD) is complex, with psychological, biological as well as environmental components[9]. Cytokines, which are a heterogeneous group of polypeptides, may be the key players in the immune activation which has been repeatedly described in MDD and stress reactions [10]. Elevated serum levels of IL-6 has been found in many COVID- 19 patients. Thus our study is aimed to find out any association of serum IL-6 and CRP levels with depression in COVID 19 patients discharged from hospital.

Methodology

A case control study was conducted at Post COVID clinic of hospital attached to a Medical College of Western India. Ethical approval was taken from the research review board and ethical committee of the institution (NO. MC/3454). Patients aged 18 years and above, of either gender, who had been discharged from hospital after recovery from COVID and attending the post COVID OPD within one month of recovery / discharged from hospital, were included in study. Diagnosis of depression was made by a trained psychiatrist using PHQ-9 scale [11]. A cut off value of 10 on PHQ-9 was used for diagnosis of depression. A total of 30 patients with depression were consecutively taken as 'Cases'. Consecutive next Eligible patients presenting to Post COVID OPD after each Case, having PHQ-9 score of less than 10 were taken as 'Controls'. Patients with a history of Neuro-psychiatirc illness prior to COVID disease, patients with serious medical condition, unstable physical condition were excluded from the study. Recent corona virus disease was confirmed by the medical records of patients. A written informed consent was taken from all participants prior to inclusion in the study.

Socio-demographic data and clinical data including IL-6 and CRP levels were gathered by interviewing the patients and reviewing the medical reports of the patients. If multiple reports were available then the maximum value of IL-6 and CRP was taken. After

recording the data, the two groups (post COVID patients with depression and post COVID patients without depression) were compared upon sociodemographic data, clinical data and PHQ-9 scores.

Statistical Analysis

Categorical variables were expressed as frequency and percentage and were analyzed using Chi square test / Fischer's Exact test as applicable. Quantitative variables were summarized as mean and standard deviation and were analyzed independent samples t test. A p value ≤ 0.05 was considered statistically significant. All statistical analysis was done using Epi info version 7.2.1.0. statistical software.

Results:

Most of the post COVID patients with depression were males (70%). Mean age of Cases with depression (53.9 years) was slightly higher than those without controls (46.2 years), but the difference was not statistically significant (p>0.05). Both the groups were similar in relation to their socio-demographic characteristics (Table 1).

Mean CRP levels during COVID was significantly higher (p=0.003) in Cases with depression (43.66 mg/dl) as compared to controls (21.02 mg/dl). Mean IL-6 levels were also significantly higher (p=0.006) in Cases with depression (39.71 pg/l) as compared to controls (13.42 pg/l) without depression (Table 2).

Table 1: Comparison of socio-demographic profile of the study groups

		Cases (n=30)	Controls (n=30)	Total (n=60)	Test statistic	P value
Gender	Male Female	21(70%) 9 (30%)	20 (66.6%) 10 (33.3%)	41 (68.3%) 19 (31.6%)	χ^2 =0.078 at 1 df	0.781
Locality	Rural Urban	18 (60%) 12 (40%)	16 (53.3%) 14 (46.6%)	34 (56.6) 26 (33.3)	χ^2 =0.272 1 df	0.602
Age (mean±SD) in years		53.9 ± 16.1	46.2 ± 15.1	50.0 ± 15.9	t=1.92 at 58 df	0.06

χ^2 =Chi square; df=degree of freedom

Table 2: Comparison of clinical variables among the two groups

	Cases (n=30)	Controls (n=30)	t value (at 58 df)	p value
CRP levels (in mg/l)	43.66 ± 31.78	21.02 ± 25.36	3.05	0.003*
IL-6 levels (in pg/l)	39.71 ± 46.39	13.42 ± 18.98	2.873	0.006*
Hospital stay (days)	8.43 ± 3.61	6.93 ± 2.36	1.905	0.062
PHQ-9 Scores	15.17 ± 4.3	4.76 ± 2.14	11.87	<0.001*

Discussion

Present study was conducted with the objective to find out the association between depression and serum CRP & IL-6 levels in recovered COVID patients. A total of 60 post COVID participants were included in study among which 41 were male and 19 were female. Similar to our study Raimondi F et al., also found higher prevalence of hospitalization in males in COVID [12].

In present study it has been found that serum CRP and IL-6 levels were significantly higher in post COVID patients with depression (CRP=43.66 ± 31.78 mg/l and IL-6=39.71 ±

46.39 pg/l) than patients without depression (CRP=21.02 ± 25.36 mg/l and IL-6=13.42 ± 18.98 pg/l). These findings are consistent with previous studies. One such study including 96 convalescent COVID-19 patients among which 42 patients had depressive symptoms found level of CRP was significantly higher in the self reported depression group compared with the normal group (0.2 ± 0.3 vs 0.1 ± 0.1 mg/dL; $p < 0.05$). However, IL-6 levels were not significantly different between the two groups[13] While an another study comparing serum CRP and IL-6 levels in 88 depression patients and 86 control subjects, found significantly higher levels of IL-6 in patients with depression [14].

This study further strengthens the role of inflammatory markers in pathogenesis of depression. Previous studies have described significant role of inflammatory markers in depression [15]. The exact mechanisms linking inflammation to depression are still unclear, but include effects of psychological stressors, sensitization of cells to neurotoxicpeptides, oxidative and nitrosative stress, autoimmune response to oxidatively and nitrosatively damaged molecules, lower omega-3 andantioxidants. [16]

Present study also provides evidence for the neuropsychiatric sequel of COVID and sought the role of neuro-inflammation in depression. It implies that early treatment may prevent the complication and neuropsychiatric sequel like depression.

This study also purposes the importance of early identification and treatment of depression. The vice versa hypothesis that depression may aggravate the inflammatory condition may also be true. In that condition treatment of depression with antidepressants may be useful in COVID progression also.

Limitations

Present study includes baseline IL-6 and CRP levels. Further studies measuring current and follow up IL-6 and CRP levels are necessary to establish proper causal relationship. Present study has the inherent limitations of a case control study. Also this is a hospital based study including patients who required hospital admission during COVID, which may have higher incidence of depression and difference characteristics than patients not requiring admission.

Conclusion

Serum levels of IL-6 and CRP were found to be significantly associated with depression in discharge patients of COVID. These findings provide insight about the neuropsychiatric sequel of COVID, and strengthen the evidence for the inflammatory hypothesis of depression. Further studies with follow up serial measurement of inflammatory markers and depression severity would give more insight into the inflammatory hypothesis.

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