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# Prognostic value of plasma interleukin 6 levels in severe traumatic brain injury

**Afeefah Jamsheed[1], Suhail Sidiq[2], Abdul Qayoom Lone[3], Zaffar Amin[4]**

*[1]Postgraduate Resident, [3]Professor, Department of Anesthesiology and Critical Care, [2]Associate Professor, Department of Critical Care Medicine, [4]Professor, Department of Immunology and Molecular Medicine, Sher-I-Kashmir Institute of Medical Sciences, Srinagar, Jammu and Kashmir, India*

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## ABSTRACT

**Background:** Traumatic brain injury (TBI) results in a significant morbidity and mortality. Several inflammatory mediators are released after TBI. Some studies have shown inconclusive association between interleukin-6 (IL-6) and outcome following TBI. **Aims and Objectives:** The aim of the present study was to investigate the role of plasma IL-6 levels as a possible prognostic marker in patients with severe TBI. **Materials and Methods:** A total of 47 male patients with isolated severe TBI were included in a prospective observational study. Plasma IL-6 levels was measured at admission, 24 h and 48 h. Association of IL-6 levels with mortality and functional outcome were studied. The Glasgow outcome scale was used to assess functional outcomes. **Results:** Mean age was 44.4 years. Overall mortality of 42.6% was noted. Higher mortality was noted for patients beyond 50 years of age. Mean IL-6 levels at the time of admission was 306.285 pg/mL and 167.830 pg/mL at 24 h while 99.033 pg/mL at 48 h of admission Mean IL 6 levels were higher in patients with lower Glasgow coma scale (GCS), with a significant statistical association of GCS with IL-6 levels at admission and 24 h ($P<0.001$). 38 (80.85%) patients underwent surgical intervention. No statistical correlation was noted between IL-6 levels and mode of management. Significant IL-6 levels were seen in patients with worse clinical course at admission, 24 h and 48 h ($P<0.0001$). A level of 78 pg/mL was the appropriate cutoff to differentiate patient mortality as per receiver operating characteristic curve with Sensitivity of 1 and specificity of 0.8. **Conclusion:** IL-6 plasma concentrations are likely to be a useful parameter for assessing prognosis in severe TBI.

**Key words:** Glasgow outcome scale; Interleukin-6; Traumatic brain injury

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## INTRODUCTION

Traumatic brain injury (TBI) is a silent public health epidemic mainly involving the productive age group.[1] Sixty-nine million people suffer TBI each year, with the Southeast Asian and Western Pacific regions having maximum incidence.[2] Many survivors live with major disabilities, resulting in significant socioeconomic burden. In 2010, the economic impact of TBI in the United States was estimated to be $76.5 billion.[3]

Prognostication of critically ill patients has long been a concern.[4] Scoring system such as APACHE has significantly improved prognostication in general intensive care unit (ICU) patients. However prognostic assessment of severe TBI may range from clinical indicators (e.g., disease severity, vital signs, intracranial pressure, cerebral perfusion pressure) to radiological imaging (CT, MRI) and electroencephalogram, however utility of many of these modalities is limited in critically ill patients.[5] Furthermore, they reveal little or no information regarding secondary injury processes such as excitotoxicity, neuroinflammation, blood–brain barrier breakdown, ischemic damage and cell death. It would be beneficial if an endogenous molecule could be identified to have an expression profile. The ideal biomarker for prognostication in TBI patients should be readily accessible, early predictive and both sensitive and specific for the short- and long-term outcome.[6]

**Address for Correspondence:**
Dr. Suhail Sidiq, Associate Professor, Department of Critical Care Medicine, Sher-Kashmir-Institute of Medical Sciences, Srinagar, Jammu and Kashmir, India. **Mobile:** +91-9419408781. **E-mail:** sidiqsuhail@gmail.com

Amongst several inflammatory cytokines released post-TBI, interleukin-6 (IL6) is a key protein released by microglia, astrocytes, and neurons.[7,8] IL-6 is often undetectable under physiological conditions, its acute release in response to TBI is widely recognized,[4] with peak serum levels observed at 2–8 h after injury and easily detectable by existing assays.[9] Therefore, it may potentially fulfils the essential criteria of a prognostic biomarker for neurological outcomes and help in decision making regarding treatment leading to an optimal outcome.

### Aims and objectives

The aim of present study was to investigate the role of plasma IL6 levels as a possible prognostic marker in patients with severe TBI.

## MATERIALS AND METHODS

This prospective, hospital-based observational study was conducted in the Department of Anaesthesiology and Critical Care at a tertiary care center during 2020–2022. Informed consent was obtained from the patient's relatives who were apprised about the purpose of this study after approval from the institutional ethical committee. Male patients with age >18 years admitted with severe TBI (Glasgow coma scale [GCS] 3–8) and transferred to the ICU within 24 h of the head injury were enrolled in this study. A sample size of 47 male patients with severe TBI was taken having 95% power of study. Female patients were excluded from the study as there is some outcome difference following severe TBI in comparison to males.[10] Polytrauma patients, patients with spontaneous subarachnoid haemorrhage or infratentorial lesions or history of neurological or psychiatric disease were excluded from the study. Patients with need for any other emergency surgery upon admission to the hospital were excluded. On admission to the trauma emergency room, patients were initially evaluated, resuscitated and underwent emergency surgery if indicated. All the patients were managed as per the institutional protocol in accordance with recent TBI guidelines. Blood samples for IL-6 were taken at 0, 24, and 48 h after admission. Sample processing and data analysis was performed according to the manufacturers instructions. The following variables of interest were noted: age, GCS on admission, mechanism of injury, management (surgical or conservative), serum IL-6 levels, clinical outcomes (mortality and/or functional outcome). The Glasgow outcome scale (GOS) was used to access functional outcome that categorized patients: 1-Dead, 2-Vegetative state, 3-Severe disability, 4-Moderate disability and 5-Good recovery. Relationship between IL-6 levels and outcome as per GOS were analysed. Primary end point was in-hospital mortality. Secondary end points were functional outcome.

For IL-6 quantification, 5 mL blood samples from each patient were collected, and plasma was isolated immediately. The blood samples were obtained at admission, 24 and 48 h. Those who died had the blood samples collected up to that occurrence. The material was centrifuged and supernatant stored at −20°C. IL-6 ready to use kits were procured from Beckman coulter USA and serological IL-6 levels were estimated using chemiluminescence DXI800. As compared to ELISA, chemiluminescence has higher sensitivity and unlike ELISA does not require multistep manual processing.

### Statistical methods

Statistical analysis was performed by using SPSS software. All the categorical variables were shown in the form of frequency and percentage. Furthermore, continuous variables were analyzed by proper statistical tests and reported as mean and standard. $P<0.05$ was considered statistically significant. Receiver operating characteristic (ROC) was used to determine the threshold value.

## RESULTS

Forty-seven male patients had a mean age of 44.4 years. Maximum patients belonged to the age group of 20–30 years 27.6% (n=13), followed by 40–50 years 23.4% (n=11), 60–70 years 19.1% (n=9), 30–40 years 14.8% (n=7), and 50–60 years 8.5% (n=4), 70–80 6.38% (n=3).

Motor vehicular accidents (MVA) were the most common mode of injury in 26(55.3%) cases, while as in 21 cases (44.7%), fall from height was the mode of injury. MVA constituted the predominant mode of injury in younger age groups, while fall from height was more predominant in older age groups.

The most common injury was traumatic subarachnoid hemorrhage 29.7 % (n=14), followed by multiple intracranial injuries on CT (Combination of SAH, SDH and Contusions) 23.4% (n=11). Diffuse axonal injury 12.7% (n=6), Cerebral contusions 12.7% (n=6), Epidural hemorrhage 10.6% (n=5), cerebral edema 4.2% (n=2), intraventricular hemorrhage 4.2% (n=2), multicompartment hemorrhage 2.1% (n=1).

The mean GCS of all patients was 5.25. There was a significant association of IL6 levels with GCS on admission and 24 h; however, no association GCS and IL6 levels at 48 h (Table 1).

38 (80.85%) patients underwent surgical intervention (decompressive craniectomy/craniotomy/bone elevation/EVD insertion) while 9 (19.14%) were managed

**Table 1: GCS and IL-6 levels at admission, 24 and 48 h**

| GCS | n | Mean | SD | Minimum | Maximum | P-value |
|---|---|---|---|---|---|---|
| IL-6 admission | | | | | | |
| 3 | 12 | 608.58 | 410.291 | 154 | 1598 | |
| 4 | 2 | 1023.50 | 812.46 | 449 | 1598 | |
| 5 | 4 | 130.75 | 62.19 | 98 | 224 | <0.0001* |
| 6 | 8 | 208.62 | 129.86 | 77 | 440 | |
| 7 | 14 | 160.31 | 137.18 | 65 | 490 | |
| 8 | 7 | 87 | 23.00 | 55 | 122 | |
| Total | 47 | 306.28 | 356.58 | 55 | 1598 | |
| IL-6 24 h | | | | | | |
| 3 | 9 | 319.52 | 298.33 | 114 | 998 | |
| 4 | 1 | 876 | 711.2 | 876 | 876 | |
| 5 | 4 | 93.75 | 42.22 | 63 | 154 | |
| 6 | 8 | 156.75 | 115.57 | 32 | 339 | <0.0001* |
| 7 | 14 | 102.14 | 67.08 | 32 | 266 | |
| 8 | 7 | 58 | 27.87 | 21 | 99 | |
| Total | 43 | 167.83 | 204.14 | 21 | 998 | |
| IL-6 48 h | | | | | | |
| 3 | 7 | 181.75 | 224.38 | 49 | 687 | |
| 4 | 1 | 242 | 154 | 242 | 242 | |
| 5 | 4 | 69.5 | 40.583 | 32 | 123 | 0.15 |
| 6 | 7 | 129.85 | 125.65 | 11 | 330 | |
| 7 | 14 | 72 | 60.39 | 16 | 209 | |
| 8 | 7 | 36 | 25.95 | 11 | 89 | |
| Total | 40 | 99.03 | 120.86 | 11 | 687 | |

GCS: Glasgow coma scale, IL: Interleukin

conservatively. Among surgical group 18.4% had good recovery (GOS 5), while 22.2% had GOS 5 in the non-surgical group. Mean IL-6 levels of 321.40 pg/mL, 175.70 pg/mL, and 97.53 pg/mL were noted in the surgical group at the time of admission 24 and 48 h, respectively. Mean levels of IL6 in non-surgical group was 242.44 pg/mL at admission and 138.07 pg/mL, 105.03 pg/mL at 24 and 48 h, respectively. No statistical correlation was noted between IL-6 levels and the mode of management (surgical or conservative).

The overall mortality of 42.6% was noted. Higher mortality was noted for patients beyond 50 years of age, with maximum mortality noted in the age group of 70–80 years (100%). Least mortality was noted in the age group of 40–50 years (27.3%). Good recovery was noted in the age groups of 20–30 and 30–40 years. The Glasgow outcome score of various age groups is depicted in Figure 1.

In our study, mean IL-6 levels at the time of admission was 306.285 pg/mL and 167.830 pg/mL at 24 h while 99.033 pg/mL at 48 h of admission.

In our study of 47 patients, mean IL-6 levels at the time of admission, 24 h and 48 h in non-survivors (GOS=1) was significantly higher than survivors (GOS >1) (P=0.0001, 0.002, and 0.006, respectively) (Table 2).

Mean IL-6 levels with different grades of GOS at admission, 24 and 48 h were found to be statistically

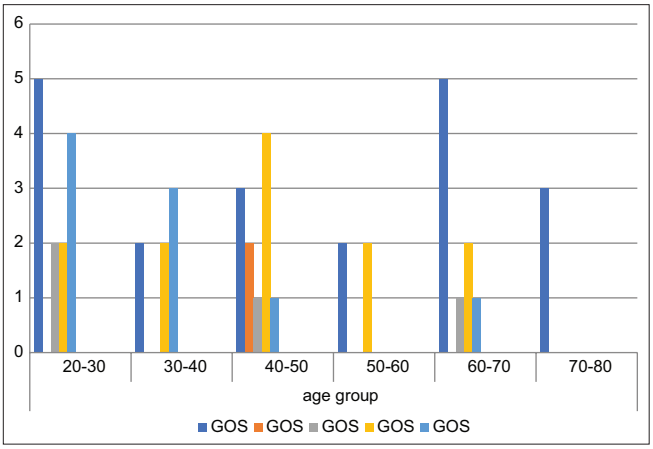


**Figure 1:** Different age groups and outcome

significant (P<0.0001, 0.002, and 0.002, respectively) (Table 3).

IL-6 levels of 78 pg/mL were found as the appropriate cut off to differentiate patient mortality as per ROC curve with sensitivity of 1 and specificity of 0.8.

## DISCUSSION

The physical and cognitive disability resulting from TBI have significant economic burdens.[11] Despite some prognostic value of the clinical and radiological investigations at present, there are no definite biomarkers known to predict patient outcomes in routine clinical practice.[6] The levels

of circulating mediators such as cytokines, hormones, and adhesion molecules have been checked for prognosis assessment and compared with existing scoring systems.[12] IL-6 is a pleiotropic cytokine produced by various cell types after stimulation or hypoxia/ischemia.[13,14] There is some evidence that IL-6 plasma levels correspond to infarct volume after cerebral ischemia, suggesting a hypoxia-induced local production in association with the extent of brain injury.[4] There are still some unanswered questions and controversies surrounding IL-6 role in TBI. Some studies have shown IL-6 can be neuro protective, while others suggested it could be a marker of poor outcome.[15] There is also variability in studies regarding the time course and patterns of IL6 elevation. So further research is necessary to fully understand the cytokine's role in TBI. Moreover, IL-6 has been studied in context of TBI for many years, but IL-6 in TBI has not been studied in our subset of population. As expression of IL-6 is dependent on genetic factors, findings in one population may not be necessarily valid in another population. Most of the studies analysed IL-6 with ELISA, we used chemiluminescence for quantification. Chemiluminescence has higher sensitivity unlike ELISA. IL-6 quantification was not readily available before COVID-19 pandemic, however post Covid era IL-6 quantification is readily available, so further research is needed to fully establish its utility and determine how this an easily available bedside investigation can be best integrated into clinical practice.

**Table 2: IL6 levels on admission, 24 and 48 h in non-survivors and survivors**

| GOS | n | Mean | SD | P-value |
|---|---|---|---|---|
| IL6 at admission | | | | |
| Equal to 1 | 20 | 565.700 | 421.983 | |
| >1 | 27 | 114.126 | 68.771 | <0.0001* |
| IL6 at 24 h | | | | |
| Equal to 1 | 16 | 323.544 | 270.967 | |
| >1 | 27 | 75.556 | 34.655 | 0.002* |
| IL6 at 48 h | | | | |
| Equal to 1 | 13 | 204.023 | 166.811 | |
| >1 | 27 | 48.481 | 30.099 | 0.006* |

GOS: Glasgow outcome scale, IL: Interleukin

The patients in our study were exclusively male cohort. Many studies included patients of both genders; however, we only included male patients in our study as there is an outcome difference in TBI between the genders.[10] We wanted to overcome this bias compared to other studies. The mean age of patients was 44.4 years. Maximum patients belonged to the age group of 20–30 years (27.6%) followed by 40–50 years (23.4%). TBI incidence is high in working age groups. Kamal et al., reported majority of cases in the age group of 21–40 years (50.24%).[16] Yang et al., reviewed 13495 patients and mean age reported was 40.8 years.[17]

The most common mechanism of injury in our study cohort was MVA (55.3%), followed by fall from height (44.7%). This differs from published literature on the epidemiology of TBIs, in which fall is the most common cause of injury.[2]

Mean GCS of 47 patients was 5.25. We observed a significant correlation of IL-6 levels at admission (P<0.0001) and 24 h (P<0.0001) with GCS at admission. These results indicate that lower GCS at admission is associated with higher mean IL-6 levels however, no such

**Table 3: Mean IL6 levels at admission, 24 h, 48 h and GOS**

| IL6 and GOS | n | Mean | SD | Min. | Max. | P-value |
|---|---|---|---|---|---|---|
| IL6 at admission | | | | | | |
| Dead | 20 | 565.70 | 421.983 | 154 | 1598 | |
| Veg state | 2 | 249 | 197.98 | 109 | 389 | |
| Severe disability | 4 | 124.75 | 65.77 | 69 | 220 | <0.0001* |
| Moderate disability | 12 | 114.83 | 44.167 | 55 | 221 | |
| Good recovery | 9 | 78.48 | 11.51 | 65 | 99 | |
| Total | 47 | 306.28 | 356.58 | 55 | 1598 | |
| IL6 at 24 h | | | | | | |
| Dead | 16 | 323.54 | 270.96 | 112 | 998 | |
| Veg state | 2 | 112 | 9.89 | 105 | 119 | |
| Severe disability | 4 | 77.25 | 29.17 | 46 | 113 | |
| Moderate disability | 12 | 84.83 | 39.88 | 21 | 164 | 0.002* |
| Good recovery | 9 | 54.33 | 20.36 | 32 | 92 | |
| Total | 43 | 167.83 | 204.14 | 21 | 998 | |
| IL6 at 48 h | | | | | | |
| Dead | 13 | 204.02 | 166.81 | 49 | 687 | |
| Veg state | 2 | 91 | 26.87 | 72 | 110 | |
| Severe disability | 4 | 37 | 21.46 | 16 | 67 | 0.002* |
| Moderate disability | 12 | 54.41 | 32.75 | 11 | 103 | |
| Good recovery | 9 | 36.22 | 21.59 | 17 | 78 | |
| Total | 40 | 99.03 | 120.86 | 11 | 687 | |

GOS: Glasgow outcome scale, IL: Interleukin

statistical correlation was noted with plasma IL-6 collected at 48 h. McClain et al., reported elevated IL-6 plasma levels following severe head injury and levels decreased faster in patients with higher GCS scores than in those with lower scores, indicating a correlation with the severity of injury.[18] However, Venetsanou et al., studied 75 patients with severe or moderate TBI, showed that higher serum IL-6 levels were associated in non-survivors versus survivors but no statistically significance of IL-6 with GCS.[19]

Comparison of outcomes between the operated and non-operated group with respect to IL-6 levels and mortality, no statistical significance was found. This finding could be due to the small number of cases in the non-operated group. Higher number of surgically managed patients in our study was likely due to the inclusion of only severe TBI, while many comparative studies included mild and moderate TBI patients.[17] Aman et al., measured serum levels at admission and post-operatively in their cohort of 40 surgically managed patients. They demonstrated a significant reduction in serum IL-6 levels after surgical intervention (mean reduction 190.6 pg/mL).[20] However no such findings could be established in our study.

Out of 47 patients, higher mortality (>50%) was noted for patients beyond 50 years of age, with maximum mortality in the age group of 70–80 years (100% mortality), although this cohort comprised of only three patients. Least mortality was noted in the age group 40–50 years (27.3%). However, this data were not statistically significant to determine any correlation of age with IL-6 levels or neurological outcome.

We observed that the mean concentration of IL-6 levels was significantly higher in non survivors as compared to survivors. Our results demonstrate that severe brain injury produces a condition with increased plasma levels of IL-6 that showed a high positive predictive value for mortality. When analyzing the mean value of IL-6 at admission, 24 h and 48 h in the poor and favorable groups, a significant difference was observed ($P<0.0001$), suggesting that the highest IL-6 levels are seen in patients with worse clinical course. The results in our current analysis provide evidence that early elevation in mean IL-6 levels 566 pg/mL at admission, followed by 323 pg/mL at 24 h and 204 pg/mL at 48 h after severe brain injury correlates with subsequent mortality ($P<0.001$, 0.002, and 0.006, respectively). Plasma IL-6 levels at admission varied with the range from 55 to 1598 pg/mL. Although IL6 has been studied for many years still it is not fully clear how to use IL-6 in clinical practice. We found a threshold value of 78 pg/mL at admission as appropriate cut off for increased mortality as per ROC curve with sensitivity of 1 and specificity of 0.8. Further studies with sizable patient population may be necessary to validate this threshold level in our population.

Feng et al., studying 30-day mortality in patients with severe TBI, reported drastically significant IL-6 levels in non-survivors as compared to survivors.[21] Similar results were also demonstrated by Venetsanou et al., where they studied 30-day mortality in patients of TBI, and mean IL-6 levels at admission were significantly higher in non-survivors compared to survivors.[19] However, some studies have shown no significant association of IL-6 with outcome.[22,23]

In our prospective study, we could emphasize that patients with a worse GOS have a much more impressive inflammatory IL-6 response shortly after the acute event ($P<0.001$). Higher IL6 levels at admission, 24 h and 48 h corresponded to significant fall in GOS ($P<0.0001$, 0.002, and 0.002, respectively). Lustenberg et al., in their study, concluded that IL-6 on admission showed a stepwise increase with worsening GOS in patients with isolated TBI and in patients with concomitant extracranial injuries.[24] Deepika et al., studied graphical representation of the univariate association between serum IL-6 values and 6 month GOS and found significantly higher levels in the unfavourable outcome group at days 3 and 10.[25]

### Limitations of the study

This study is limited by the relatively small sample, therefore, the literature would benefit from larger studies. we did not adjust for age differences and can therefore not make any conclusions on how age may have altered the inflammatory response. Ours was an exclusively male cohort; the immunological sequelae need to be further evaluated and compared in females with TBI. We studied short-term outcomes in these patients, long term relation of IL6 with outcome needs to be evaluated in our population. The method of IL6 level estimation varies in the published literature (ELISA, immunofluorescence, chemiluminescence), which differ in sensitivity and specificity; hence, standardization is required to remove any discrepancies. Patients in the study were exclusively severe TBI cases, thus, generalization of our findings to the wider TBI population may be limited. Complications/polytrauma/Covid 19 infection/other neurological diseases have been shown to significantly impact IL-6 concentrations therefore represent important confounders. However, we focused on a population of patients without any significant extra-cranial injuries and the relevance of serum IL-6 concentrations in the context of cofounders and its specificity in TBI needs evaluation.

## CONCLUSION

These results show that IL-6 plasma concentrations are likely to be a useful parameter for assessing prognosis. The results of this analysis suggest that early elevation in

plasma IL-6 to a level of 78 pg/mL at admission or greater is associated with increased mortality in our population. Further studies with sizable patient populations are necessary to verify the usefulness of early IL-6 plasma concentrations for short-term prognostication. Ability to stratify a severe TBI patient cohort in the post traumatic phase with biomarkers, clinical and radiological tools will enable the focussed management of such patients with early identification, prevention and management.

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**Authors Contribution:**
**AJ**- Implementation of study protocol, data collection, interpretation of data; **SS**- Concept, design, manuscript preparation, revision and editing, final approval; **AQL**- Concept, design, drafting the work; **ZA**- Laboratory support, statistical analysis, revising work for intellectual content.

**Work attributed to:**
SKIMS Soura, Srinagar, Jammu and Kashmir, India.

**Orcid ID:**
Suhail Sidiq - https://orcid.org/0000-0003-3544-0148
Afeefah Jamsheed - https://orcid.org/0000-0002-8426-7786
Abdul Qayoom Lone - https://orcid.org/0009-0003-2378-2527
Zaffar Amin - https://orcid.org/0000-0001-9269-9303

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