

ORIGINAL ARTICLE

Role of C-reactive protein (CRP) and interleukin-6 (IL-6) level as predictors of multiple organ Failure in polytrauma patients.

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Abstract:

Background: The initial pathophysiological events immediately after the 'trauma' event has been found to play key role for future development of multiple organ failure (MOF).

Objective: This study was aimed to assess the role of C-reactive protein (CRP) and interleukin-6 (IL-6) as predictors of Multiple Organ Failure (MOF).

Methodology: This prospective study concluded 283 Polytrauma patients as sample who were treated in Department of Casualty of Sir Salimullah Medical College Mitford Hospital, Dhaka from January 2013 to January, 2018. Patients arriving within 24 hours of trauma, age ranging from 16-65 years, surviving more than 48 hours and with Injury Severity Score \geq 18 ('Polytrauma') were included. We excluded all patients with injury to CNS.

Result: A statistically significant difference was noted in average CRP levels between patients with and without MOF on all days. IL-6 concentration also followed decreasing trend being highest initially.

Conclusion: The most important parameters of MOF development are serum IL-6 concentration on the first day of hospitalization and the number of positive SIRS criteria on the fourth day of hospitalization.

Key words: Polytrauma, Multiple Organ Failure (MOF), CRP, IL-6

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Introduction:

With the advent of time though improvement of therapeutic concepts has decreased trauma related fatalities¹ still 'Organ Dysfunction' remains a frequent and severe complication during clinical course and the sole cause of high

mortality. Survival rate of 'Polytrauma' patients has improved but the frequency of development of organ dysfunction remains static.^{2,3}

To formulate a prudent combat strategy against the stress response of Polytrauma it requires to identify patients with a high risk for

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posttraumatic complications within very short interval after the assault. Polytrauma to date possess a great challenge for evaluation of clinical state and prognosis as many clinical parameters such as blood pressure, pH or heart rate failed to assess the posttraumatic situation.⁴

A tight correlation been noted between cytokine plasma level, development of MOF and mortality rate.⁵ Thus immune monitoring can be our answer to help in the selection of patients at risk for posttraumatic complications.

The aim of this study was to assess the kinetics of C-reactive protein (CRP) and interleukin-6 (IL-6) as predictors of MOF in Polytrauma cases.

Methodology:

This prospective study concluded 297 Polytrauma patients as sample who were treated in Department of Casualty of Sir Salimullah Medical College Mitford Hospital, Dhaka from January 2012 to January, 2016. Patients arriving within 24 hours of trauma, age ranging from 16-65 years, surviving more than 48 hours and with Injury Severity Score ≥ 18 ('Polytrauma') were included. We excluded all patients with injury to CNS. Development of MOF in the first 24 hour and lethal outcome in the first 48 hours made us to exclude 14 patients. The remaining 283 cases were followed up for next 10 days. Markers and mediators of inflammation (CRP & IL-6) were first assessed within 24 hours of injury and then consecutively on every day till the tenth day. Concentration of CRP was standardized with a normal value being < 9 mg/ml and reference range for IL-6 was 0–8 pg/mL.

The SAPS II has 17 variables, 12 of which assess physiology, age and type of treatment and 3 of which identify the presence of chronic diseases such as AIDS, metastatic cancer or hematologic malignancy. For the 12 physiologic variables, the poorest values in the first 24 hours upon admission (those with the highest number of points) were taken into account.

We determined the Injury Severity Score (ISS) from the formula ($ISS = \text{Abbreviated Injury Score} [\text{AIS}]^2 + \text{AIS}^2 + \text{AIS}^2$) where AIS^2 represents squared single highest scores from 3 regions of the body in the first 24 hours. We also applied the combined MOF/MODS score that defines organ damage according to the presence of 1 or more variables.^{1,6,7} Respiratory

failure was deemed present when mechanical ventilation was necessary for at least 72 hours, when $\text{PaO}_2/\text{FiO}_2 < 37.3$ kPa positive end-expiratory pressure (PEEP) was over 8 cm H_2O and when there was radiographically confirmed acute respiratory distress syndrome (ARDS) or a respiratory rate $\geq 5/\text{min}$ or $\leq 49/\text{min}$. Hepatic failure was defined as bilirubinemia over 51 $\mu\text{mol/L}$ for at least 48 hours. Renal insufficiency was defined as serum creatinine over 177 $\mu\text{mol/L}$ for at least 48 hours. Heart failure was defined as cardiac index $< 3.0 \times \text{min}^{-1} \times \text{m}^{-2}$, obligatory application of inotropic therapy, heart rate $\geq 54/\text{min}$, present ventricular tachycardia and/or fibrillation and mean arterial pressure ≥ 49 mm Hg or pH ≥ 7.24 . Hematologic insufficiency was defined as a platelet count < 20000 or a white blood cell count $< 1 \times 10^9/\text{L}$. We analyzed these parameters in all patients included in our study, and the worst results in the first 24 hours were taken into account when we qualified for the existence of organ insufficiency. The presence of at least 1 of the mentioned criteria during hospitalization defined existing organ damage. MOF duration was not significant because it represents an "all-or-nothing" event.

For statistical analysis help from a statistician was sought. χ^2 , Student's *t* test and the Mann–Whitney *U* test were used as deemed appropriate for intergroup comparisons. A logistic regression coefficient was used to investigate the correlation between the number of SIRS criteria per hospital days and the development of MOF. Values of $p < 0.05$ or $p < 0.01$ were considered significant. Each variable was assessed individually with univariate analysis as a resulting variable for MOF. Parameters that were found to be statistically significant predictors with univariate analysis were then included in a multivariate model.

Results:

The MOF patients' average age was 32.1 (standard deviation [SD] 1.9) years. Most patients had blunt injuries (192 patients, 67.84%), whereas 55 (19.43.9%) had open wounds. Most patients had triple (50.7%), double (27.3%) or single (19.7%) organ insufficiency. Only 8.7 % of patients had 4 or more insufficient organs. The male: female ratio was 4.05:1, which is common for traumatic injuries. The average ISS score was 21.79 ± 0.6 (SD), and the average SAPS II score was 41.12 ± 1.5 (SD).

Table-I
Demographic variables & General Data

Variable	MOF	No MOF	All Patients	p value
Patients	41	242	283	>0.05
Age (Mean ± SD)	32.1 ± 1.9	31.1±.9	35±3.9	
Sex (M : F)	5.1:1	3.9:1	4.05:1	
GCS	7.5 ± 1.9	10.1 ± 0.3	10 ± 0.4	>0.05
ISS(Mean ± SD)	27.9 ± 2.4	23.2 ± 1.1	21.79 ± 0.6	<0.01
Sepsis	15(36.56%)	192(79.34%)	207(73.15%)	<0.05
SAPS II (Mean ± SD)	23.8 ± 1.7	51.2 ± 2.3	41.12 ± 1.5	<0.01
Hospital Stay(Mean ± SD) Days	31.15 ± 3.1	23.56 ± 4.3	24.65 ± 2.7	<0.05
Mortality (%)	29(70.73)	24(9.91)	53(18.73)	<0.01

Table-I Shows the patients’ distribution according to MOF presence in relation to age, sex, duration of hospitalization, frequency of sepsis, ISS and SAPS II scores and mortality. A highly statistically significant difference was noted in survival between groups of patients with and without MOF.

Early MOF appearing in the first 72 hours after the injury, was present in 22 patients (53.6%), whereas 20 patients (48.78%) had late MOF appearing 72 hours after the injury. (Fig. 1)

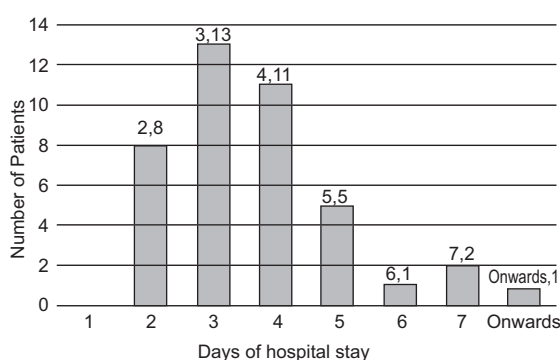


Fig.-1: Onset of MOF after injury in Polytrauma patients.

The number of SIRS variables was significantly different between the patient groups with and without MOF on day 5 of hospitalization, as shown in Fig. 2. Further, a significant correlation was found between SIRS determinants and the appearance and progression of MOF in the first 5 of 7 observed days.

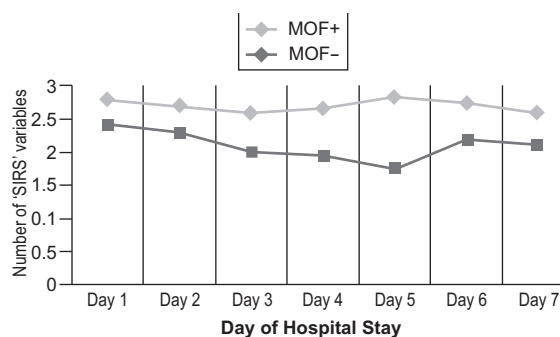


Fig-2: Number of positive SIRS variable per hospital days in Polytrauma patients with or without MOF.

Average CRP (mg/L) and IL-6 (pg/mL) on the first, second, third, seventh and tenth day after the injury are shown in Fig. 3 & 4. During the entire follow-up period, a statistically significant difference in average CRP level was noted between patients with and without MOF. Concentrations of IL-6 significantly varied on all days of hospitalization.

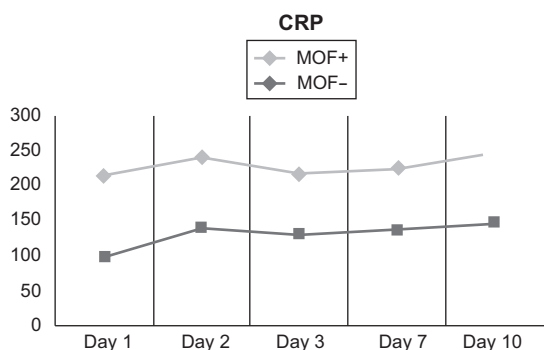


Fig-3: Average CRP (mg/L) with or without MOF following Polytrauma (Mann-Whitney U Test) White Star indicates p < 0.05

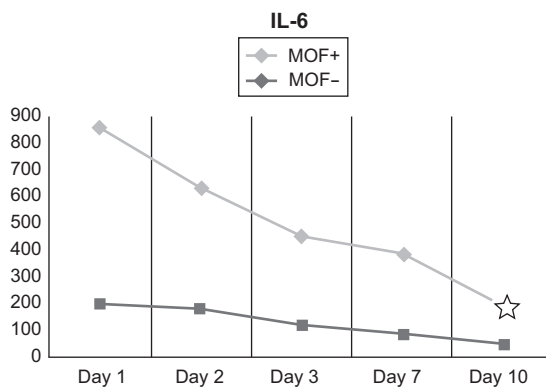


Fig-4: Average IL-6 (pg /mL) with or without MOF following Polytrauma (Mann-Whitney U Test)

White Star indicates $p < 0.05$

Discussion:

The high average ISS score in our group of patients reflects the inclusion of only Polytrauma patients in our study. MOF rate among these patients been found quite high in many studies. Most studies consider the period within 72 hours of admission to be the upper limit for diagnosis of early MOF. MOF appearing after 72 hours is diagnosed as late. In our study, out of 41 patients with MOF, 53.6% had the early form. These data only refer the onset of failure of the first damaged organ or system.

The mortality rate follows the increase in the number of affected organs. It varies from 11% in patients with single organ system failure to 62% in patients with failure of 2 systems, as reported by some authors.^{8, 9} Insufficiency of 3 or more organs almost always results in a lethal outcome.¹⁰

Apart from the order in which failures appear, their combination is also important. In a study of 1171 patients, lethal outcome after combined cardiac-respiratory failure occurred in 66.7% patients, after respiratory-hepatic failure, it occurred in 53.9%, and after hepatic-respiratory insufficiency, it occurred in 33.3%.⁵⁻¹³ In our study, 89% of patients with MOF had signs of respiratory failure, 28% had signs of renal failure and 32% had signs of cardiovascular decompensation, which is accompanied by an especially high mortality rate. Hepatic failure was also present in a significant number (34%),

but it usually appeared later and resolved more quickly.

In 81% of patients in our study, respiratory insufficiency appeared first, which is consistent with the findings of other authors.^{7,8,11} A smaller number of patients had renal failure (11%), cardiovascular insufficiency (5%) and cerebrovascular insufficiency (2%) as the first manifestation of MOF. Most of our patients had failure of 3 (50.7%), 2 (27.3%) or 1 (19.7%) organ system, and only 8.7% had 4 or more insufficient organs. The most frequent combination of organ failure in our patients was respiratory-renal failure and respiratory-hepatic failure. In patients with 3 or more affected organs, the most frequent combination was respiratory-renal-cardiovascular insufficiency, followed by respiratory-renal-hepatic failure.

The mortality rate in patients with MOF was high (70.73%). The average ISS value in our study was higher than reported by other authors in studies with similar mortality rates. In patients with failure of 2 organs, several studies reported a mortality rate of 42%,¹⁰ while another study reported a mortality rate of 35%.¹¹ The mortality rate in patients with 2 insufficient organs was higher in our study (83%) than that reported by other authors. However, all patients with single organ failure survived. Our lack of in depth knowledge and strategy to combat MOF in such cases might be the reason behind these dissimilarity.

All our patients with MOF had significantly higher CRP levels, compared with patients without MOF, indicating that CRP levels are a good early marker of morbidity in intensive care unit patients.

The plasma IL-6 level may be a marker of cytokine cascade and may reflect a complex inflammatory host response and the severity of disease (or injury).¹² The ratio of IL-6 to IL-10 may be a predictive factor in SIRS.¹³ Some authors always include cytokine status when distributing injured patients according to severity of the injury and expected outcome.¹³⁻¹⁵ According to these models, cytokine concentrations are classified in 4 groups with adequate prognostic significance (number of points).¹⁶ Almost one-half of the patients in our study (45%) belonged to the third (IL-6 > 250 pg/

L) and fourth (IL-6 > 500 pg/L) group, suggesting a bad prognosis. There are reports that IL-6 level on days 2 and 4 were significantly higher in MOF patients than in those without MOF.¹⁷

Some authors describe significant IL-6 increase on the first or even second day; however, most state that the window closes after 3 days, indicating that IL-6 levels have no prognostic value after that point.¹⁵⁻¹⁷

Conclusion:

IL-6 kinetics in the first days of hospitalization may suggest the development of MOF, even before clear clinical symptoms develop. The kinetics of CRP concentration differ significantly between groups, depending on MOF development, especially from the second to the seventh day of hospitalization.

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