Interleukin-6 and serum lactate as biomarkers in predicting morbidity and mortality among patients with polytrauma and multiple trauma

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Background: Following major trauma, exaggerated immune response occurs due to stress of injury (first hit) which is further amplified by surgical procedures performed during the period (second hit). This is brought about by pro and anti-inflammatory cytokines of which interleukin-6 (IL-6) has been found to be reliable and the first cytokine to be elevated following injury. Serum lactate which is a byproduct of anaerobic metabolism in hypo perfused cells has been found to be a potent marker to predict outcome. Since these biomarkers have not been widely studied among the Indian population, this study was conducted to assess the levels of IL-6 and serum lactate to predict morbidity and mortality in polytrauma and multiple trauma patients.

Methods: This prospective observational study was conducted at Mahatma Gandhi Medical College and Research Institute, Pondicherry after Institutional review board approval and included 30 patients with polytrauma and multiple traumas satisfying inclusion criteria. Blood samples were collected to assess IL-6 and lactate levels at admission (day zero), 24 hours after the first sample (day one) and on fifth day following injury (day 5). The patients were monitored daily using the Sequential Organ Failure Assessment (SOFA) scoring. Statistical analysis was performed using SPSS software.

Results: Males were predominant and the mean age of the study participants was 43.80 years. Twentythree patients suffered from multiple trauma and seven patients suffered from polytrauma. There was a statistically significant relationship between Injury Severity Score, SOFA score, serum lactate and IL-6 levels. IL-6 and serum lactate levels independently correlated with the development of Multiple Organ Dysfunction Syndrome (MODS) and a cut off score of 102.9 pg was obtained for IL-6 which was predictive of MODS with a sensitivity of 75% and specificity of 91.7%.

Conclusions: In our study, the levels of IL-6 and serum lactate were high in patients who died or developed MODS and their levels correlated with each other in predicting morbidity and mortality. Hence, IL-6 and serum lactate can be used as biomarkers to predict morbidity and mortality in polytrauma and multiple trauma patients.

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Introduction

Polytrauma is ranked fifth worldwide among the top 10 causes of morbidity and mortality, and 98/10,000 individuals die following major trauma despite adequate medical treatment (1). The Berlin study conducted in 2014 has defined polytrauma as a condition where in the "Abbreviated Injury Score is greater than 3 in at least 2 body regions; Injury Severity Score (ISS) is greater than or equal to 16 with one of the five physiological parameters namely: hypotension (systolic blood pressure less than 90 mmHg), loss of consciousness (Glasgow Coma Scale <8), acidosis (base excess less than 6), coagulopathy [international normalized ratio] (INR) >1.4] and age greater than 70 years" (1). Rendy et al. defined multiple trauma as a condition wherein the "AIS is greater than 3 in at least one body region with ISS greater than or equal to 16 without significant physiological disarray (2). Following major trauma, an exaggerated immune response is triggered because of the stress of injury (first hit), which is further amplified by surgical procedures performed during this period (second hit) (3). This process is facilitated by proand anti-inflammatory cytokines, of which interleukin-6 (IL-6) is considered a biomarker for predicting morbidity and mortality in patients with multiple injuries because it is one of the first cytokines to be elevated following injury (4). Similarly, lactic acid, which is a byproduct of anaerobic metabolism due to hypoperfusion of the major organ systems, is a potent marker for predicting morbidity and mortality, especially when studied serially. Multiple Organ Dysfunction Syndrome (MODS) was defined as a condition occurring due to initial inflammatory phase following polytrauma or multiple trauma, characterized by reversible physiological abnormalities with the dysfunction of two or more organs that occurs simultaneously leading to longer stays in the intensive care unit (ICU) or mortality in severe cases (5).

Anatomical and physiological scoring systems are being routinely used in emergency and critical care units to predict the onset of MODS, although these systems depend on the anatomical and physiological parameters that are prone to interobserver variability (4). According to Meccariello et al. in his study, an ideal outcome score system should be simple, all inclusive, reliable and reproducible and should be able to provide prognostic information based on the outcomes of different fracture patterns to help a surgeon to improve preoperative planning and treatment to improve outcomes in patients with multiple injuries (6). Previous studies performed using inflammatory markers such as mean platelet volume and erythrocyte sedimentation rate could not reliably predict outcomes even when used with the anatomical and physiological scoring systems (7,8). Hence, we assessed the levels of IL-6 and serum lactate in patients with polytrauma and multiple trauma and evaluated their role as biomarkers for predicting morbidity and mortality in these patients. Further, we calculated the cutoff value of IL-6 to predict morbidity, which has not been extensively studied in the Indian subcontinent (3,6). Thus, this study provides insights into the use of IL-6 and serum lactate as biomarkers to predict morbidity in patients with polytrauma and multiple trauma in South India.

Methods

This prospective, observational study was conducted at Mahatma Gandhi Medical College and Research Institute, Pondicherry, between January 2020 and September 2021 after Institutional Review Board approval. A total of 34 patients with polytrauma or multiple trauma who presented to the Emergency Department within 24 hours of injury with an injury severity score of >16 at presentation and who were willing to stay in the hospital for at least five days were included in the study. One patient who was aged less than 18 years, and one patient with history of chronic steroid use, one patient suffering from chronic liver disease and one patient with chronic kidney disease were excluded from the study. The patients satisfying the inclusion criteria were assigned to a single group after measuring the Injury severity score wherein the Abbreviated Injury Score (AIS) was calculated and the codes were grouped into 6 body

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regions namely head and neck, face, chest, abdomen, extremities and external injuries. Only the highest AIS severity score in each body region was considered and the sum of the squared AIS scores for the three most severely affected regions was taken as Injury severity score. Patients with two or more organ systems involvement were considered as Polytrauma patients and patients with one or more organ system involvement or patients with more than one long bone injury were considered as multiple trauma patients (7). An informed and written consent was obtained from the patients or their attender. IL-6 levels were assessed by collecting two millilitres of venous blood in an ethylene diamine tetraacetic acid (EDTA) (Lavender) vacutainer on day zero (time of presentation), day one (24 hours after the first sample), and day five (the fifth day following injury). The samples were centrifuged at 2,500 rpm (revolutions per minute) for 15 minutes to separate plasma from the underlying cellular components and then stored at -70 °C at the Central Interdisciplinary Research Facility. The samples were then collectively assessed using an enzyme linked immunosorbent assay (ELISA) kit (Abbkine, SynergyTM, Chennai, India). The serum lactate levels were assessed by collecting a drop of blood by using a lactometer (Lactospark, SensacoreTM, Hyderabad, India), which is an amperometric biosensor that calculates the level of lactate within 5 seconds on day zero, day one and day five. The patients were monitored daily using the Sequential Organ Failure Assessment (SOFA) score which is a physiological score comprising 6 variables, each representing an organ system that is assigned a point value from zero (normal) to four (8). The patient was considered to have developed MODS if SOFA score was more than four on any given time during the study period (9). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). and was approved by institutional ethics committee (ECR/451/Inst/PO/2013/RR-19).

Statistical analysis

Statistical analysis was performed using SPSS version 19.0 (IBM SPSS, USA) software with regression modules installed. Descriptive analyses were performed, and their results for continuous variables are expressed as the mean and standard deviation. Analysis of variance was performed to determine the variability of IL-6 and serum lactate levels between different days. Multivariate analysis using a correlation coefficient matrix was performed to determine the association between IL-6, serum lactate, injury severity score, and SOFA score. Univariate analysis was performed to determine the correlation between the variables and the development of MODS. Receiver operating characteristic (ROC) curve analysis was used to determine the association between IL-6 and MODS and to determine the cut-off value of IL-6 to predict MODS.

Results

Of the 30 patients, 28 were men and two were women, with a mean age of 43.80 years (range, 30-60 years), and 60% of the study participants had no comorbidities. Among the study participants, seven patients suffered from polytrauma as defined by the Berlin definition, and 23 patients suffered from multiple trauma as defined by Rendy et al. in his study (1,2). The mean injury severity score at the time of presentation was 32.03 (range, 17-54 years). The SOFA score was measured serially, and the results are shown in Table 1. IL-6 levels were assessed using the Abbkine Synergy kits that have a normal value range of 12-92 pg/mL and a significant value of greater than 200 pg/mL. Of the 30 patients, four patients developed MODS and two patients died during the study period. As shown in Table 2, IL-6 levels were higher than the normal range in all patients with polytrauma and 25% of patients with multiple trauma. Serum lactate levels were also increased in patients with polytrauma (more than 2 mmol/L), as described in Table 2.

The variation in the IL-6 and serum lactate levels between different days was not statistically significant. Multivariate analysis using the correlation coefficient matrix showed a statistically significant correlation between the IL-6 level, serum lactate level, injury severity score, and SOFA score. Furthermore, the IL-6 levels were significantly correlated with the serum lactate levels on day zero, day one and day five. The univariate analysis to determine the correlation between the study variables and the development of MODS showed a significant correlation between the IL-6 and serum lactate levels, with the development of MODS as described in Table 3. Variables such as age, gender, vitals at presentation, injury severity score, and SOFA score did not exhibit a significant correlation with the development of MODS. ROC curve analysis showed that the levels of IL-6 and serum lactate predicted morbidity with the sensitivity of 75% and 91.6%, respectively, and specificity of 88% and 86.8%, respectively (Table 4, Figure 1). The specificity of both IL-6 and serum lactate in predicting morbidity increased on day five as seen in Table 4. ROC curve analysis also yielded an IL-6 cut-off

Table 1 Correlation	a of Injury	y Severit	ty Score, S	OFA Score,	interleuk	in-6 and se	erum lacta	te levels on	days 0, 1 ar	1d 5					
Social Sector		lnju	Iry Severit	y Score			SOFA sco	re		Inte	erleukin-6 ((bd)	S	erum lactat	Ð
20016	Lay	Day 0	Day 1	Day 5	Day 1	Day 2	Day 3	Day 4	Day 5	Day 0	Day 1	Day 5	Day 0	Day 1	Day 5
Injury Severity	Day 0	-	0.977**	0.968**	0.468	0.572*	0.658*	0.596	0.669**	0.618**	0.748**	0.609*	0.623**	0.652**	0.655**
Score	Day 1		-	0.998**	0.489	0.525*	0.576*	0.519**	0.616	0.665**	0.807**	0.624**	0.621**	0.621**	0.655**
	Day 5			-	0.466	0.467*	0.503	0.505**	0.620**	0.632	0.822**	0.624**	0.574*	0.588*	0.666**
SOFA score	Day 1				-	0.937**	0.822**	0.783**	0.611*	0.126*	0.293	0.122	0.755**	0.653**	0.557*
	Day 2					-	0.888**	0.876**	0.672**	0.298*	0.447*	0.168	0.791**	0.772**	0.628**
	Day 3						-	0.949**	0.842**	0.372**	0.486	0.323	0.777**	0.761**	0.679**
	Day 4							÷	0.893**	0.255	0.326	0.370	0.719**	0.692**	0.748**
	Day 5								÷	0.365**	0.446*	0.632**	0.643**	0.607*	0.819**
Interleukin-6 (pg)	Day 0									-	0.904**	0.825**	0.374*	0.489*	0.485*
	Day 1										÷	0.701**	0.556*	0.656**	0.542*
	Day 5											-	0.337	0.337	0.673**
Serum lactate	Day 0												÷	0.932**	0.852**
	Day 1													-	0.809**
	Day 5														-
*, correlation is sigr	nificant a	t P valu	e <0.05; * [*]	, correlatio	n is signif	icant at P	value <0.	01. SOFA,	Sequential	Organ Fail	ure Assess	ment.			

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 Table 2 Correlation between patient's vitals, Injury Severity Score,

 SOFA score and MODS

Variable	MODS	No MODS
Patients (n)	4	26
Age, mean ± SD (years)	40.75±8.23	44.27±2.81
Sex (M:F)	3:1	23:3
Pulse, mean \pm SD	118.5±4.99	104.88±3.29
Oxygen saturation, mean \pm SD	89.52±6.61	94.35±1.05
Injury Severity Score, mean ± SD	I	
Day 0	44.25±3.33	30.15±1.90
Day 1	45.75±2.25	30.52±2.15
Day 5	46.75±1.89	29.71±2.07
SOFA score, mean \pm SD		
Day 1	3.75±1.38	1.46±0.33
Day 2	3.25±1.44	0.96±0.22
Day 3	2.00±1.23	0.88±0.26
Day 4	2.00±1.23	0.46±0.19
Day 5	2.00±0.82	0.50±0.26

SOFA, Sequential Organ Failure Assessment; MODS, Multiple Organ Dysfunction Syndrome.

Table 3 Correlation betw	een interleukin-6, s	erum lactate and MODS
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value of 102.9 pg to predict morbidity.

Discussion

Trauma related injuries are often complex in nature requiring patients to stay in the hospital for extended periods of time, often involving specialist care within an ICU resulting in extensive physiological and psychological burden on the patient and his bystanders (10). Over recent years, therapeutic concepts of patients with major trauma have improved but organ dysfunction still remains a frequent complication since the concept of "Second hit" or "Third hit" of polytrauma is still not completely understood (11,12). In the present study, 30 participants who were mainly young and middle-aged men were included with the mean age of the study participants being 43.8 years which is in concordance with other Indian studies (11,12). However studies conducted in Western countries in contrast, reported that elderly patients represented 47.8% of his population (13,14). This difference in age is probably because of the high incidence of high-velocity injuries due to road traffic accidents in the young and middle-aged populations who are a part of the productive workforce in developing countries such as India (11,12).

Variable	Day	MODS, mean ± SD	No MODS, mean \pm SD	Significance (P)
Interleukin-6	Day 0	122.58±36.70	73.38±18.74	<0.001
	Day 1	126.43±37.18	60.83±15.88	<0.001
	Day 5	88.22±34.00	45.71±13.13	<0.001
Serum lactate	Day 0	4.58±0.53	2.66±0.32	<0.001
	Day 1	4.20±0.59	2.62±0.27	<0.001
	Day 5	4.03±0.42	1.93±1.06	<0.001

MODS, Multiple Organ Dysfunction Syndrome.

Table 4 Sensitivity and	l specificit	y of interleukin-6	6 and serum lacta	te on days 0,	1 and 5 in	predictin	g morbidit	y and mortality
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Variable	Day	Area under the curve	Std. error	Lower bound	Upper bound	Cut off value	Sensitivity	Specificity
Interleukin-6	Day 0	0.692	0.148	0.402	0.983	106.56	0.750	0.846
	Day 1	0.745	0.137	0.476	1.000	129.16	0.750	0.880
	Day 5	0.771	0.139	0.499	1.000	67.50	0.750	0.917
Serum lactate	Day 0	0.885	0.061	0.766	1.000	3.75	1.000	0.808
	Day 1	0.860	0.083	0.697	1.000	3.90	0.75	0.880
	Day 5	0.953	0.042	0.871	1.000	2.90	1.000	0.917

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Figure 1 Validity of interleukin-6 and serum lactate on days 0, 1, and 5 in predicting morbidity. Diagonal segments are produced by ties. ROC, receiver operating characteristic.

We did not find a significant correlation between the patient's vitals at presentation [pulse, blood pressure (BP), oxygen saturation (SPO₂)] with morbidity and mortality which was justified by Montoya *et al.* in his study which concluded that while blood pressure and shock index predicted the efficacy of initial resuscitation, they could not significantly predict the prognosis of polytrauma and multiple trauma patients (15).

Various patterns of injury among the study participants ranging from multiple closed fractures of the extremities to involvement of two or more organ systems such as head, chest and open injuries to extremities were studied by us and we observed that patients with higher Injury severity scores on admission had a higher incidence of morbidity and mortality which was also observed by Oktafianto *et al.* and Rendy *et al.* in their respective studies (2,16). However, we found no significant correlation between the anatomical scores and physiological scores alone with the development of MODS, which is consistent with the findings of other studies (17,18). This is because the response of every individual to the stress of trauma is unique, and the response to treatment also varies among individuals due to different factors (17). We observed that the levels of IL-6 predicted the development of MODS in our study. Patients with IL-6 levels greater than 102.9 pg had a higher probability of having MODS, which required further intervention. The cut-off value in this study was lower than those reported in studies conducted abroad (721.7 pg) (3). This may be because the ELISA kit used for the detection of IL-6 in our study had a range of 2-400 pg. In the present study, serum lactate levels could predict MODS both independently and in association with IL-6 This finding suggested that serum lactate might be considered an independent biomarker to predict morbidity and mortality in patients with trauma in developing countries such as India where the routine assessment of IL-6 levels is expensive and time consuming. This study has some limitations. The sample size of the present study is smaller than that of other similar studies because of the reduction in incidences of trauma due to the coronavirus disease 2019 (COVID-19) pandemic during the study period. In addition, due to logistic reasons, blood samples for IL-6 level determination obtained from the study participants were stored in a deep freezer and were collectively analyzed retrospectively rather than on a realtime basis, unlike other studies.

Conclusions

In this study, the levels of IL-6 and serum lactate were high in patients who died or developed MODS, and the levels of both IL-6 and serum lactate significantly correlated with each other to predict morbidity and mortality. In our kit, an IL-6 cut-off value of more than 102.9 pg denoted a higher risk of the development of MODS. Therefore, we concluded that IL-6 and serum lactate can be considered biomarkers for predicting morbidity and mortality in patients with polytrauma and multiple trauma.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jxym. amegroups.com/article/view/10.21037/jxym-22-22/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics committee (ECR/451/Inst/PO/2013/RR-19) and informed consent was taken from all the patients.

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