Correlation Between IL-6 Levels and the Systemic Inflammatory Response Score: Can an IL-6 Cutoff Predict a SIRS State?

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Background: **Recently, increasing emphasis is being placed upon assessment of the inflammatory status of the patient. Serum inflammatory cytokines, particularly IL-6, have been used as an adjunct to this assessment. Another method uses a combination of simple laboratory and clinical data to provide an assessment of the patient's current level of systemic inflammation, the SIRS. The aim of this study was to investigate, in a group of adult trauma patients, the relationship between the interleukin-6 (IL-6) concentration, the systemic inflammatory response score (SIRS) and outcome.**

Methods: **In patients with femoral shaft fracture, serum IL-6 levels and clinical parameters were recorded prospectively on admission and on days 1, 3, 5, and 7. Clinical course, the SIRS score and complications were documented. Nonparametric tests were used to assess relationships between variables and receiver operator characteristic (ROC) curves were used to examine their predictive values. Significance was assumed at the $p < 0.05$ level.**

Results: **Forty-eight patients were included in the final analysis, with a median new injury severity score (NISS) of 31.5 (range, 9–75). The presence of a "SIRS state" detected early (day 1 and 3) positively correlated with the IL-6 measurement from the same period ($p < 0.001$). ROC curve analysis revealed elevated IL-6 to be significantly diagnostic of a SIRS state ($p < 0.001$) at all times. Early (days 0 and 1), an IL-6 value above 200 pg/dL diagnosed a SIRS state with an 83% sensitivity and a 75% specificity (area under ROC curve 0.76, $p < 0.0001$). Both a SIRS state and an IL-6 > 300 pg/mL was associated with a significantly increased risk of complication (pneumonia, MOF, death). Both systems were found to be significantly diagnostic of these complications using ROC curve analysis.**

Conclusions: **The IL-6 concentration and SIRS score are useful adjuncts to clinical evaluation of the injured patient. In the early phase, they are closely correlated with the NISS and each other. A cutoff value of 200 pg/dL was shown to be significantly diagnostic of a SIRS state. Significant correlations between adverse events and both the IL-6 level and SIRS state are demonstrated.**

Key Words: **Polytrauma, Trauma, Interleukin 6, IL-6, Systemic inflammatory response, SIRS, Femur, Fracture, Mortality.**

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Although advances in critical care have lead to decreased mortality in trauma victims, early intervention to prevent progression to organ failure remains of paramount importance.[1] Current understanding of host trauma response continues to include a "two-hit" model, the first hit being the initial traumatic insult with the second hit delivered by ongoing physiologic derangement and early surgical interventions.[1–3] Poor results from trials of immune modulatory therapies have lead to increased emphasis on limiting the second-hit by rapid correction of physiologic abnormalities and the adoption of a damage control approach where appropriate.[4–6] Objective, quantitative measurements of inflammatory status are therefore important for clinical assessment and research purposes.[7–10] Various laboratory parameters have been employed for this purpose including the pro- and anti-inflammatory cytokines,[7,9,11] and more established markers of inflammation.[10,12,13] Interleukin-6 (IL-6) has perhaps been the most useful and widely employed of these, partly due to its plasma half life and relatively consistent pattern of expression.[14] A pattern of clinical response in patients suffering systemic inflammation is also recognized and the systemic inflammatory response score (SIRS) has been developed for objective assessment of this.[15–17] A combination of simple, widely available, laboratory and clinical measurements are used (Leukocyte count, temperature, pulse rate, and respiratory rate) giving a score of 0 to 4, with a score of 2 or more declaring the patient as suffering systemic inflammation (SIRS state).

Though both laboratory and clinical systems have previously been correlated with injury severity and adverse outcome,[16–19] little work has examined their relationship in detail. A study was undertaken to evaluate the relationship between clinical and laboratory assessment of inflammatory status, particularly:

- Is an IL-6 cutoff able to predict the SIRS state at certain points in the clinical course?
- Do these two measurements essentially assess the same thing or can they be complimentary?

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Do early abnormalities in these two measurements relate to later complications?

MATERIALS AND METHODS

Patient Population and Treatment

Approval was obtained from the local medical ethics committee. Consecutive adult patients (aged 16–70 years) admitted primarily to our two units with diaphyseal femoral fracture (AO classification 32-)[20] were recruited. Informed consent was obtained from the patient or their family as appropriate, those in agreement being enrolled. Patients with comorbid medical conditions that might alter their response to trauma were excluded, these included those with systemic inflammatory conditions (inflammatory arthropathy, inflammatory bowel disease), diabetes mellitus, and those undergoing systemic steroid or immune modulatory drug therapy. All patients were treated according to existing unit protocols; standard AO/ASIF techniques of fracture fixation were employed.[21] Early fracture stabilization was undertaken, either by primary, antegrade, reamed, intramedullary nailing, or external fixation, as determined by the patients overall clinical condition. It is both our units policy to treat patients with severe multiple injuries and those who are hemodynamically unstable using damage control principles, according to previously published criteria.[22] Where initial external fixation was undertaken, as part of a damage control approach, exchange to an intramedullary device was undertaken within the first 2 weeks where possible, as dictated by the patients physiologic state.[23] Three doses of broad spectrum antibiotics were given as standard to cover operative procedures. The patients were subsequently cared for on the ward or intensive care unit as appropriate, again according to standard unit protocols.

Sample Schedule/Analysis and Data Collection

Peripheral venous blood samples were drawn on admission preoperatively (day 0) and on postoperative days 1, 3, 5, and 7. No arterial or central venous samples were used. A commercially available enzyme-linked immunosorbent assay kit (R&D Systems, Minneapolis, MN) was used to estimate serum IL-6 concentrations. The patients IL-6 concentrations were not known to the treating physicians at the time and therefore did not influence clinical decision making. Relevant physiologic and laboratory parameters to allow calculation of the SIRS were also recorded at these time points, these being pulse, temperature, leukocyte count, respiratory rate, and arterial CO_2 concentration. These laboratory estimations were performed in the hospital laboratories using standard techniques. The SIRS score was calculated as originally described,[15] a point being scored for each of a pulse greater than 90 beats per minute, a white cell count below 4 or above 12, core temperature below 34°C or above 38°C, a respiratory rate above 20 (or a $Paco_2$ below 33 mm Hg). This gave a score of 0 to 4; the patient was defined as in a SIRS state where more than one of these criteria was abnormal giving a SIRS score of 2 or more.

Upon discharge, the patients' notes were reviewed to record their clinical course and complications suffered for the whole of their inpatient stay. The abbreviated injury scale was used to quantify the severity of individual injuries suffered and The New Injury Severity Score (NISS) was used as an estimate of overall injury magnitude.[24] Because the study was particularly concerned with systemic complications, pneumonia, adult respiratory distress syndrome (ARDS), multiple organ failure (MOF) and death were specifically recorded as well as the length of critical care treatment received (this being intensive care or high dependency unit stay). Pneumonia was diagnosed where positive sputum or bronchoalveolar lavage culture results were obtained or a clinical diagnosis was made, supported by typical radiographic changes leading to antibiotic administration. ARDS was diagnosed based upon typical radiographic appearances (bilateral lung infiltrations) alongside increased oxygen demand (decrease of the Horowitz ratio <200) in the absence of infection.[25] Multiple organ failure was diagnosed based upon Marshall's criteria where more than a single organ system failed.[26] Death was recorded where mortality occurred because of any cause during in-patient stay.

Statistical Analysis

Data were collated on a personal computer; statistical analysis was undertaken using SPSS (Chicago, IL)[27] and Analyze-it computer software.[28] Continuous variables were assessed for normality, as most variable sets were non-normally distributed or ordinal, nonparametric tests were used to assess for significant differences between groups throughout. The χ^2 test was used to assess for differences in dichotomous variables between groups. Spearman's rank correlation coefficients were used examine the data for significant relationships between variables. Receiver operator characteristic (ROC) curves were used to examine the predictive qualities of the IL-6 and SIRS scores, Hanley and McNeil's[29,30] method being used to assess for significant differences between the area under different ROC curves. Because of the relatively small sample size, complication data were analyzed as a dichotomous state being present or absent depending on whether the patient suffered any of these systemic complications at any time during their clinical course.

To examine the effect of combining markers of inflammatory status (SIRS score and IL-6) with the NISS, these parameters were mathematically transformed in order that they were of similar magnitude. These transformed values were used only for the final ROC analysis considering the effect of using parameters together, at all other points, including other ROC analysis, the unmodified values were used. Natural logarithms of the IL-6 were used and the NISS was transformed linearly to give a result from 0 to 4. Values under consideration were summed to give a single combined score. The validity of this method was assessed by comparing ROC curves obtained for each value before and after trans-

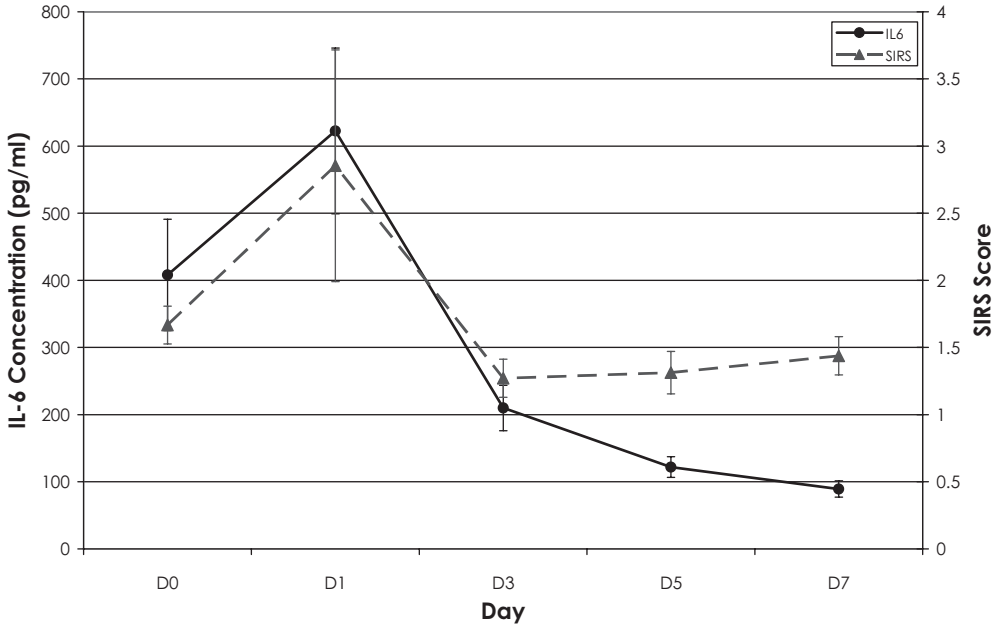

Fig. 1. *Mean recorded values for IL-6 concentration and SIRS score for all patients.*

formation which were identical. Statistical significance was assumed at the $p < 0.05$ level throughout.

RESULTS

Demographics, Overall Injury Pattern, Treatment, and Complications

Fifty patients were recruited to the study; two were excluded from final analysis after transfer to another hospital before the completion of the 7-day study period. Thirty-seven of the remaining 48 patients were male (77%), the median age was 28 years (range, 16–67). All were the victims of blunt trauma. The median NISS was 31.5 (9 – 75), eight patients (16%) had suffering femoral fracture in isolation. There were 11 (23%) patients with significant head, 27 (56%) significant thoracic, and 14 (29%) significant abdominal injuries (abbreviated injury scale grade 2 or worse). Fifteen femoral fractures were open (31% overall, 5 grade I, 3 grade II and 7 grade III Gustillo and Anderson).

Twenty-five (52%) of the patients were treated according to damage control protocols and underwent initial emergency stabilization of their femoral fractures by external fixation, all being converted to intramedullary fixation at less than 2 weeks. The rest were treated by primary, reamed intramedullary nailing. The median length of stay in critical care facilities was 15 days (range, 0–73 days). Forty-eight percent of patients suffered systemic complications during their initial inpatient treatment. Six had ARDS (13%), 17 pneumonia (36%), 12 MOF (25%), and 2 patients died (4%).

Inflammatory Parameters

Figure 1 shows the mean results recorded for the SIRS score and IL-6 at each time period. Both were elevated on admission, peaking on day 1 before falling below admission levels by day 3. Patients with multiple injuries had a higher IL-6 and SIRS score on admission compared with those with isolated injuries (Median, IL-6 229 vs. 114, SIRS 2 vs. 0.5 Mann-Whitney U $p < 0.01$). NISS was found to positively correlate with early inflammatory response as measured using both the IL-6 and the SIRS score (Spearman's Rank rs 0.33, $p < 0.05$ and rs 0.44, $p < 0.001$, respectively for values recorded on admission). A small number of patients had some missing IL-6 values. This amounted to less than 5% of the data overall and none from admission or postoperative day 1. No SIRs data were missing from the final data-set. Missing data points were excluded from analysis.

Correlation Between SIRS and IL-6

Table 1 displays Spearman's rank correlation coefficients between IL-6 concentrations and both the SIRS score

Table 1 Spearman's Rank Correlation Coefficients Between IL-6 and SIRS Score and IL-6 and SIRS State

Day	SIRS Score		SIRS State	
	rs	*p*	rs	*p*
Individual data				
0	0.52	0.0005	0.45	0.0032
1	0.18	0.2194	0.38	0.0071
3	0.25	0.0885	0.2	0.1845
5	−0.07	0.6766	−0.07	0.6515
7	0.25	0.1381	0.14	0.4155
Cumulative data				
0	0.52	0.0005	0.45	0.0032
0 and 1	0.35	0.0009	0.42	<0.0001
0, 1, and 3	0.36	<0.0001	0.39	<0.0001
0, 1, 3, and 5	0.29	<0.0001	0.31	<0.0001
All	0.26	0.0001	0.25	0.0003

Table 2 **Area Under Receiver Operator Characteristic Curves (AuROC) for Diagnosis of SIRS State by IL-6 Concentration**

Day	AuROC	*p*	95% CI of Area
Individual data			
0	0.763	0.0003	0.612–0.914
1	0.756	0.0001	0.621–0.891
3	0.62	0.0731	0.458–0.782
5	0.542	0.3236	0.361–0.723
7	0.58	0.2047	0.389–0.771
Cumulative data			
0	0.763	0.0003	0.612–0.914
0 and 1	0.759	<0.0001	0.661–0.858
0, 1, and 3	0.728	<0.0001	0.643–0.812
0, 1, 3, and 5	0.678	<0.0001	0.6–0.757
All	0.642	<0.0001	0.568–0.715

(0 to 4) and the SIRS state (SIRS score <2 or 2 or more, Yes or No). The cumulative data adds pairs of results from each day starting with the admission values. Taking the data as a whole (bottom row) a significant relationship is present, this relationship being stronger closer to admission (higher rs statistic). Taking individual days, significant correlation is only seen on admission for the SIRS score and also on day 1 for the SIRS state.

Is the IL-6 Concentration Diagnostic of a Simultaneous SIRS State?

Table 2 displays the results for the area under the ROC curves examining the diagnostic efficacy of IL-6 concentration for a SIRS state on that day. Taking individual data it can be seen that the IL-6 concentration was significantly diagnostic of the SIRS state on admission and day 1, significance was approached on day 3. Using the cumulative data to increase the number of data pairs, the IL-6 was found to be diagnostic of the SIRS state when all the data were included, though again a stronger relationship was seen when only data from earlier in the admission was considered alone. Examining the ROC curves allows us to set an IL-6 concentration cutoff for diagnosis of the SIRS state. A cutoff of 200 pg/mL diagnoses the SIRS state with 66.7% sensitivity and 82.4% specificity on admission. Similar power is observed when day 1 data are included, with the sensitivity cumulatively falling as more data from later in the clinical course is added, until only 44.3% sensitivity is achieved when all the data are considered together. The specificity of the test is however maintained with 77.8% achieved when the data are considered as a whole.

Outcome and Complications

The median SIRS score was significantly higher on admission and day 1 in patients who went on to suffer systemic complications (Fig. 2). The IL-6 was significantly higher from admission until day 5 in those patients with subsequent complications (Fig. 3). Median critical care stay was significantly higher in those with a SIRS score of 2 or more on admission or day 1 (Fig. 4) and in patients with an IL-6 concentration greater than 200 pg/mL on admission and days 1 and 3 (Fig. 4). Systemic complication rates were significantly higher in those in a SIRS state on admission or day 1

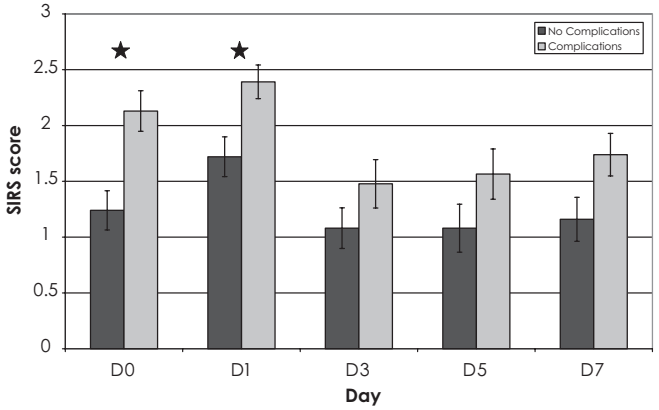

Fig. 2. *Mean SIRS scores recorded for patients grouped by presence or absence of complications. ⋆, $p < 0.05$.*

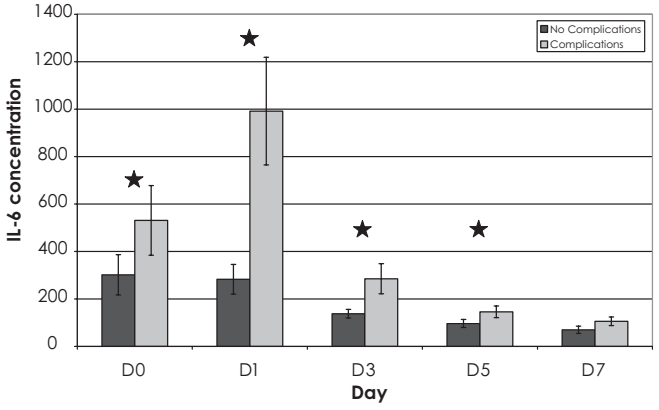

Fig. 3. *Mean IL-6 concentration for patients grouped by presence or absence of complications. ⋆, $p < 0.05$.*

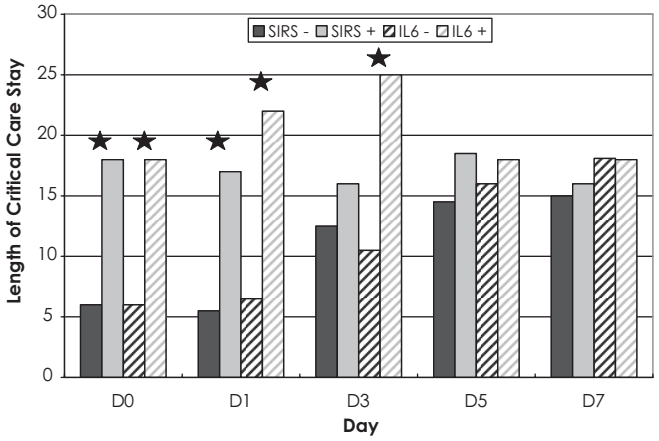

Fig. 4. *Length critical care stay, divided by inflammatory state determined by SIRS 2 or more and IL-6 200 pg/mL or more. ⋆, $p < 0.05$.*

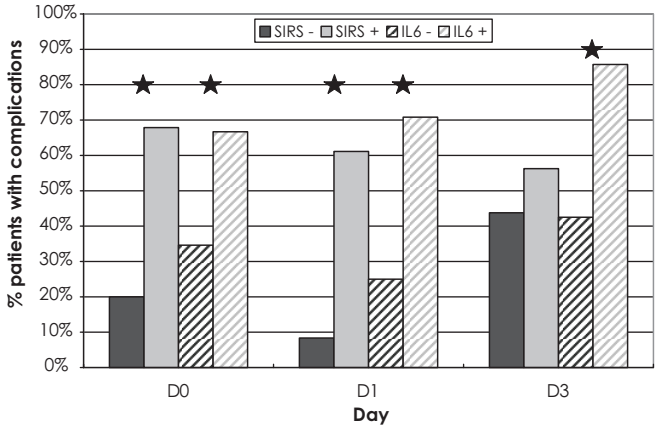

Fig. 5. *Rates of systemic complications, divided by inflammatory state determined by SIRS 2 or more and IL-6 300 pg/mL or more. ⋆, $p < 0.05$.*

Table 3 Results of Receiver Operator Curve Analysis for Prediction of Complications Based Upon Early Elevation of SIRS Score or IL-6 Concentration

Variable	AuROC	*p*	95% CI of Area
Individual systems			
D0 SIRS	0.789	<0.0001	0.648–0.931
D0 IL-6	0.708	0.0060	0.546–0.870
D1 SIRS	0.720	0.0015	0.575–0.865
D1 IL-6	0.771	<0.0001	0.630–0.913
NISS	0.736	0.0007	0.59–0.881
Combinations			
D0 IL-6 and SIRS	0.804	<0.0001	0.664–0.944
D1 IL-6 and SIRS	0.812	<0.0001	0.689–0.935
D1 SIRS, IL-6 and NISS	0.84	<0.0001	0.725–0.955

and in those with an IL-6 concentration greater than 200 pg/mL as measured on admission and days 1 and 3 (Fig. 5) (See Appendix).

ROC Prediction of Complications

Both the SIRS score and IL-6 were significantly predictive of systemic complications occurring at any time in the patients stay when measured on days 0 and 1 (ROC analysis, Table 3). Similar results were obtained using the NISS. An IL-6 cutoff of 300 pg/mL it was able to predict complications patients with a sensitivity of 77% and specificity of 58% on admission and 72% and 78% on day 1. Results obtained by mathematically combining the systems are also shown. All are statistically significant predictors of complications and offer improvement over the single systems alone, though, in this relatively small series, statistical significance is not reached. Using the system combining both the assessments of inflammatory response with the NISS, it is possible to select a cutoff that will predict complications with a sensitivity of 82.6% and specificity of 84.0%.

DISCUSSION

This data describes the relationship between a clinical and a laboratory assessment of posttraumatic inflammatory status in a series of typical blunt trauma patients with femoral shaft fractures. In adults, these fractures are usually the result of high-energy trauma and are associated with a high incidence of multiple injury and complication. Both the IL-6 and SIRS score were found to be positively correlated with overall injury severity as measured by the NISS, in accordance with previous studies.[31–33] Both the IL-6 and SIRS score have previously been correlated with the severity of various types of insult including burns and elective surgery.[16,34,35]

Early in the clinical course, the IL-6 and SIRS were closely related. An IL-6 cut off of 200 pg/dL was found to provide a good discrimination in predicting the SIRS state and on days 0 and 1, being able to diagnose the SIRS state with 83% sensitivity and 75% specificity (area under ROC curve 0.83, $p < 0.0001$). Later in the patients' course, this association diminishes, though when one considers the data set as a whole a positive relationship is still demonstrable using both the Spearman's ranks correlation coefficient and area under the ROC curve (both $p < 0.0001$). Interestingly, it is the sensitivity of the test which deteriorates with time, while the specificity of a 200 pg/mL IL-6 cutoff is maintained at almost 80% when data from all time points is considered. Put another way, as time passes, it is increasingly likely that a patient with IL-6 below 200 pg/mL might still show clinical signs of inflammation (SIRS state) but it remains unlikely that those who do have an elevated IL-6 will not. This may be due to the short period of IL-6 expression, with a SIRS state continuing after concentrations have fallen in some patients. It is recognized that IL-6 release is one part of a complex cascade of inflammatory mediator expression leading to the characteristic inflammatory response, which is being measured here by the SIRS score.[3,36]

Several series have reported similar patterns of IL-6 expression after trauma. Similar initial SIRS response pattern has been described following femoral shaft fracture in patients with a NISS above 20, the SIRS score positively correlated with injury severity.[37] Nast-Kolb et al.[7] found in a series of 66 patients with severe multiple injuries that IL-6 levels peaked at 16 hours to 32 hours post-admission with decline to sub-admission levels during the first week. In survivors, this peak was less pronounced and prolonged compared with those who suffered multiple organ failure and those who died. This series represented the very severe end of the injury severity spectrum with 75% of patients suffering multiple organ failure and 16% mortality. Gregoric et al.[38] described positive correlation between the admission IL-6 and SIRS score on admission as well as severe abnormalities in a multiple organ failure score in a series of 35 patients with multiple, blunt injury.

An abnormal inflammatory response as measured using both the IL-6 and SIRS score was positively associated with

later systemic complications and length of stay in critical care facilities. This was most apparent on admission and day 1 post-op. Patients suffering complications had significantly higher mean IL-6 concentrations and SIRS scores at these times, and those with Il-6 concentrations higher than 200 pg/mL or a SIRS score of 2 or more suffered a significantly higher rate of complications. Similarly, length of stay in critical care units was significantly longer for those with SIRS scores of 2 or more on admission and day 1 whereas the difference between those with and IL-6 above or below 200 pg/mL continued to be significantly different at all considered time points. Both systems were able to predict complications with greater efficacy than the NISS, as quantified by the area under ROC curves, though the difference did not reach statistical significance.

Several previous works have identified a similar relationship between both the IL-6 and SIRS scores early after trauma and later complications.[7,17,18,39,40] Other studies have been unable to describe such a relationship,[33,41,42] the reasons for this are not clear, though it may partly be related to the selection criteria used. In general, larger series have identified a positive correlation with early abnormalities in the inflammatory response and complications, consistent with the findings in the current series. Most series include a wide range of injury patterns at the more severe end of the spectrum, whereas patients in the current series had suffered significant extremity injury and represented the full spectrum of overall injury severity. This may account for the better discrimination than found in some series. Bone has been identified as an important source of IL-6[43] and it may be that by including only patients with long bone fracture, a group is selected in whom IL-6 is more consistently elevated in relation to injury. In a previous study examining the relationship between IL-6 levels and complication in patients with severe injuries, a cutoff of 500 pg/mL was found to correlate with adverse outcome, significantly higher than in the current series.[8] In any situation, using a numerical variable as a diagnostic test, increasing the cutoff will trade specificity for sensitivity. In the current series, increasing the IL-6 cutoff for prediction of complications to 500 pg/mL resulted in a sensitivity of 80% and specificity of 60% on day 1 and 82% and 36% on admission. A 300 pg/mL level was found to give better discrimination.

Combining these measures of inflammatory status with the NISS, improved diagnostic efficacy, this improvement approaching but not reaching statistical significance ($p = 0.08$ for the difference in efficacy between combined scores and single scores). Such an approach, combining a marker of overall injury severity and measurements of physiologic response, is not dissimilar to methods used in the revised trauma score and the trauma injury severity scores. These systems were developed using complex mathematical analysis on large numbers of patients. Also, with a relatively small data-set it is difficult to draw more meaningful conclusions, but it is illustrated that combining a measure of the overall injury severity with a measure of the host inflammatory response appears to improve prediction of complications in the patients considered.

The series is relatively small and limited to blunt trauma patients who have suffered femoral fracture. This may explain why differences in the values recorded for both IL-6 and SIRS scores were not significant later in the patient's course. A much larger and more inclusive series of patients is required to undertake further analysis, but this study supports the view that it could be possible to improve current systems used for triage, allocation of resources and determination of treatment protocols by including a measure of early inflammatory response in the calculation. It would be interesting to record these parameters for a longer period of time and more frequently to investigate their temporal relationship with complications. Could a preclinical rise in the IL-6 concentration herald imminent deterioration, stimulating early intervention and preventing consequent adverse outcome? It is difficult to draw conclusions on this directly using the presented data. However, our current approach is to triage patients with a high IL-6 or raised SIRS score on admission to a high dependency nursing environment and to have a low threshold for adopting a "damage control" approach to their management. Patients with rising or persistently elevated inflammatory estimates are investigated for missed injuries, ongoing hemorrhage, and complications.

CONCLUSION

The relationship between a clinical and laboratory estimate of systemic inflammation has been described in a series of blunt trauma patients with extremity injury. An IL-6 concentration of greater than 200 pg/dL was able to diagnose the SIRS state effectively early in the clinical course. Both systems were able to predict later complications with similar efficacy to the NISS. Combining the measures of inflammation with the NISS offered improved diagnostic efficacy, approaching statistical significance even in this relatively small series. The authors feel this approach warrants further investigation.

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