Prognostic Value of an Early Soluble L-Selectin (sCD62L) Assay for Risk Assessment in Blunt Multiple Trauma: A Metaanalysis

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Background: After severe trauma, decreased plasma concentrations of the soluble adhesion molecule L-selectin (sCD62L) have been linked to an increased incidence of lung failure and multiorgan dysfunction syndrome (MODS). Individual studies have had conflicting results, however. We examined multiple studies in an attempt to determine whether early sCD62L concentrations are predictive of major complications after severe trauma.

Methods: We performed a systematic review of six electronic databases and a manual search for clinical studies comparing outcomes of multiply injured patients (Injury Severity Score ≥16) depending on their early sCD62L blood concentrations. Because of various outcome definitions, acute lung injury (ALI) and adult respiratory distress syndrome (ARDS) were studied as a composite endpoint. Weighted mean differences (WMDs) in sCD62L concentrations were calculated between individuals with and without complications by fixed- and random-effects models.

Results: Altogether, 3370 citations were identified. Seven prospective studies including 350 patients were eligible for data synthesis. Published data showed the discriminatory features of sCD62L but did not allow for calculation of measures of test accuracy. Three of four studies showed lower early sCD62L concentrations among individuals progressing to ALI and ARDS (WMD = −229 μg/L; 95% confidence interval, −476 to 18 μg/L). No differences in sCD62L concentrations were noted among patients with or without later MODS. Nonsurvivors had significantly lower early sCD62L plasma concentrations (WMD = 121 μg/L; 95% confidence interval, 63–179 μg/L), but little information was available on potential confounders in this group.

Conclusions: Early decreased soluble L-selectin concentrations after multiple trauma may signal an increased likelihood of lung injury and ARDS. The findings of this metaanalysis warrant a large cohort study to develop selectin-based models targeting the risk of inflammatory complications.

Severe trauma leads to 2 million years of potential life lost before age 65 annually in the United States (1). Advances in preclinical resuscitation and rapid transferal to high-volume centers have improved the chance of early survival (2), but today, inflammatory conditions such as acute lung injury (ALI),5 adult respiratory distress syndrome (ARDS), multiorgan dysfunction syndrome (MODS), and their associated complications determine outcomes.

The clinical problem arising at the trauma bay is to triage patients in a timely manner based on proper diagnostic work-ups and emergency surgery. Surgery in...
patients at high risk for inflammatory complications may do more harm than good. It is now widely accepted to shorten operating times in these patients. Examples for damage-control strategies include abbreviated laparotomy to stop bleeding and external fixation for long bone fractures instead of intramedullary nailing (3, 4).

There are few clinical and laboratory tests available that can predict the probability of inflammatory mediated “second-hit” damage in trauma patients. There is experimental and clinical evidence that patients who had encountered severe trauma develop a less severe state of systemic inflammatory response syndrome (5, 6). In the acute phase, polymorphonuclear leukocytes become primed and vulnerable, whereas apoptosis is inhibited. Thus, secondary insults such as reamed intramedullary nailing may easily trigger adverse immunologic reactions.

Clinical examination alone often produces a reliable idea of the presence of diseases and injuries, and when it does, it is straightforward to assume that patients with more severe injuries are at higher risk for lung injury or MODS. In this case, extra tests are of little value if they only confirm the clinical judgment. In contrast, absent physical findings rarely exclude the condition of interest, especially in case of endogenous susceptibility to inflammation-associated risk.

Importantly, there are distinct groups of patients in whom initial clinical assessment and established imaging and laboratory tests fail to predict further progress. For example, it is difficult to identify potential candidates for early reamed or unreamed nailing vs external fixation of long bone fractures in case of accompanying chest injury. Some of these patients will benefit from early intramedullary fracture stabilization by improved oxygenation during ventilatory support (7–10), whereas others may rapidly progress to acute lung failure or ARDS (11–13). For example, scheduling vulnerable patients for primary nailing (because of falsely underestimating their risk) produces more harm than postponing early nailing, whereas choosing external fixation in nonsusceptible patients (because of falsely overestimating their risk of developing inflammatory complications) rather than primary nailing exposes those patients to additional procedures. It is therefore important to develop rapid and easy diagnostic tests that, if they give negative results, confidently exclude an individual’s tendency toward an excessive inflammatory response to planned surgical interventions. Emergency physicians will need tests with high sensitivity (i.e., low false-negative rates) available at the point of care to triage injured patients to the safest and most effective treatment possible, given their individual biological risk profiles.

In addition to physiologic scales and examination, several studies suggested that new molecular markers may give the emergency physician added discriminatory power. Supplementing diagnostic work-ups with profiles of inflammatory mediators may improve patient management decisions. The circulating selectin molecules gained attention as promising candidates to reach this goal. They are the earliest known inductors of leukocyte tethering at endothelial surfaces and are key mediators of whole-body inflammation. The leukocyte isoform L-selectin (CD62L) is an 80-kDa molecule produced on the surfaces of resting human neutrophils.

L-Selectin has been defined as a neutrophil-rolling and lymphocyte-homing receptor (14, 15). Together with the endothelial selectin isoform (E-selectin), binding of L-selectin to its endothelial ligands induces high-velocity rolling and initial loose contact of leukocytes to the vessel wall (16–18). Selectins show high affinity to O-glycans of CD34, mucosal addressin cell adhesion molecule-1 and glycosylation-dependent cell adhesion molecule-1, the latter being the currently best-characterized L-selectin ligand (17, 19, 20). L-Selectin-dependent leukocyte–leukocyte interaction further accelerates rolling, which is mediated by the sialomucin P-selectin glycoprotein ligand-1 (21, 22). Shown in Fig. 1 is a sketch of the adhesion steps mediated by L-selectin, with later firm attachment and diapedesis accomplished by members of the integrin family.

After capture on the endothelial surface, a unique metalloproteinase (L-selectin sheddase) cleaves the extra-cellular L-selectin domain from the leukocyte membrane (23, 24). The soluble molecule sCD62L contains the functional lectin and epidermal growth factor domain and distributes rapidly into the circulation. It has been suggested that circulating sCD62L serves as a biological buffer system to prevent inadequate migration of leukocytes (15).

Several researchers reported associations between low concentrations of sCD62L measured in specimens obtained at the accident site or shortly after hospital admission and later lung failure (25), nosocomial infections (26), and poor survival prognosis (27). However, these studies did not allow for robust inferences because of small sample sizes, different reference intervals, cutoff values, and fortunately, low event rates.

Lack of scientific knowledge and the need for further

![Fig. 1. Early steps of leukocyte adhesion and migration and interactions between leukocyte membranes and the endothelial surface are mediated by selectins and selectin ligands.](image)

GlyCAM-1, glycosylation-dependent cell adhesion molecule-1; PSGL-1, P-selectin glycoprotein ligand-1; ICAM-1, intercellular adhesion molecule-1.
research are best identified by a systematic literature search among different databases and without limits made for language. This prevents selective reading and interpretation of the available data on the topic of interest. Metaanalytic synthesis of quantitative information may provide a reasonable idea of the size and direction of expected effects.

Fryback and Thornbury (28) proposed six levels to appraise diagnostic research: technical measures, accuracy, influence on diagnostic thinking (i.e., the difference between prior and posterior odds of disease), influence on therapeutic decisions, patient outcomes, and societal benefits. The first two steps describe the efficacy of a diagnostic test. Noting different plasma concentrations of a biochemical marker among individuals at high and low risk demonstrates the idea. Beyond a plain difference, an accurate test demands few false-negative results among high-risk individuals and few false-positive results among low-risk individuals.

We set out to clarify the diagnostic value of early soluble L-selectin (sL-selectin) plasma concentrations in trauma patients, following the first two steps in the Fryback–Thornbury hierarchy (28). We wanted to evaluate whether sL-selectin differs in individuals with uncomplicated and complicated clinical progress (level I) and to define its diagnostic accuracy (level II).

Materials and Methods

We conducted a systematic review of prospective clinical studies that examined the diagnostic efficacy of early sL-selectin concentrations in patients with blunt or penetrating multiple injuries.

Two reviewers (D.S. and K.B.) traced studies in MEDLINE, EMBASE, and the Cochrane CENTRAL register of controlled trials. We scanned the web services of the German Institute of Medical Documentation (DIMDI), the Lippincott Williams & Wilkins publisher’s database, and SpringerLink for relevant articles beginning with the first citation of L-selectin (alias LECAM-1, LAM-1, LEU8, and others) in 1983 (29, 30) until January 2004.

We completed our retrieval strategy by cross-referencing the bibliographies of individual articles, a manual search across key journals, and a free internet search using the Google search engine. No limits were applied to language.

The search algorithm included MeSH and its equivalents in other databases (for example, the EMTREE keywords used in EMBASE): multiple trauma, L-selectin, multiple organ failure, shock, respiratory distress, outcome, prognos*, diagnos*, sensitivity, specificity, and accuracy. The text words CD62L, blunt trauma, and polytrauma supplemented key terms.

Eligible studies provided a sL-selectin assay performed at the emergency department shortly after admission. We did not account for sequential measurements. We requested follow-up of participants throughout their hospital stay and recording of relevant endpoints (ALI or ARDS, MODS, and survival).

A first appraisal of potentially eligible studies revealed various definitions of ALI, ARDS, and MODS (31–35). We regarded lung injury and MODS as common outcomes, irrespective of the definition used in particular trials. We planned sensitivity analyses to study the influence of disease classification on the diagnostic value of L-selectin. We excluded laboratory work and studies performed on healthy volunteers. Studies that correlated sL-selectin loads with injury severity or the Glasgow Outcome Scale but did not present information on morbidity or mortality were also excluded. We contacted individual authors by e-mail and asked for unpublished information.

Two reviewers (D.S. and K.B.) abstracted mean sCD62L values and standard deviations assembled from early plasma samples of patients with and without later complications. We recorded demographic and injury characteristics, outcomes, and other study features (for example, the manufacturer of the test and handling of specimens) on a data abstraction form. We independently assessed methodologic standards by an abbreviated version of the recently developed Quality Assessment of Studies of Diagnostic Accuracy included in Systematic Reviews (QUADAS) tool (36). We assembled nine methodologic standards considered relevant for the chosen scenario (Table 1). Of note, the sL-selectin assay shares diagnostic and prognostic features. Its diagnostic properties may signal a high risk for inflammatory complications and the need for delayed definite repair of fractures and visceral injury. On the other hand, it may indicate a poor chance of survival that will be unaffected by maximum surgical and critical care.

Without accepted clinical, laboratory, or radiologic reference standards indicating the risk for lung failure or organ dysfunction, the later onset of any of these compli-

<table>
<thead>
<tr>
<th>Table 1. Methodologic standards derived from the QUADAS tool (14).</th>
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<tbody>
<tr>
<td><strong>Item</strong></td>
</tr>
<tr>
<td>1. Was the spectrum of patients representative of the patients who will receive the test in practice?</td>
</tr>
<tr>
<td>2. Were selection criteria clearly described?</td>
</tr>
<tr>
<td>3. Was the execution of the index test described in sufficient detail to permit replication of the test?</td>
</tr>
<tr>
<td>4. Was the execution of the reference standard described in sufficient detail to permit its replication? (That is, did the definition of lung failure, ARDS, and MODS follow common recommendations?)</td>
</tr>
<tr>
<td>5. Were the index test results interpreted without knowledge of the results for the reference standard?</td>
</tr>
<tr>
<td>6. Were the reference standard results interpreted without knowledge of the results of the index test?</td>
</tr>
<tr>
<td>7. Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?</td>
</tr>
<tr>
<td>8. Were uninterpretable/intermediate test results reported?</td>
</tr>
<tr>
<td>9. Were withdrawals from the study explained?</td>
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</table>
cations represented the proper reference test for this analysis. Clearly it was not reasonable to judge the interval between performing the index test (sL-selectin) and confirmation by outcome as an indicator of methodologic quality, as recommended by QUADAS.

Verification bias is an important bias in diagnostic research that occurs if only positive results of the index test are corroborated by a reference test. Again, we did not assign relevance to this issue because the outcome equated the reference test in this study. We scored quality items as yes, no, or unclear. Inconsistencies between raters were solved by informal consensus.

**METAANALYSIS**

We calculated the weighted mean difference (WMD) in sL-selectin plasma concentrations with their 95% confidence intervals (CIs) between participants with and without later complications. Random-effects modeling accounted for within- and between-study variability. Where suitable, we explored publication bias (i.e., a lack of small studies reporting small or null effects) by funnel plot asymmetry (37). We also planned to merge measures of diagnostic accuracy by summary ROC according to the method of Moses et al. (38). STATA 8.0 statistical software was used for all analyses.

**Results**

**SYSTEMATIC REVIEW**

Altogether the most sensitive searching strategy revealed 3370 citations. Fig. 2 depicts the study selection procedure according to the Quality of Reporting Meta-Analyses (QUOROM) guidelines (39).

Seven inception cohort studies enrolling 507 injured individuals met the eligibility criteria for this work (25–27, 40–43). Data synthesis was possible for 350 participants with an Injury Severity Score (ISS) ≥16 who underwent early sCD62L testing. Study populations comprised 74.1% men (95% CI, 66.7–81.4%) with a mean age of 37.4 years (95% CI, 33.5–41.2 years) and a mean ISS of 33.4 (95% CI, 24.8–41.9).

Individual study profiles and outcome definitions are summarized in Table 2. Published data were supplemented by unpublished information and individual patient data from two study authors. The demographic details of the source populations are listed in Table 3.

One author (25) provided added information of mean and SD sCD62L values, whereas others did not respond to our queries.

Protocols, specimen processing, and follow-up policies were similar across the studies. Five investigators used identical ELISAs (R & D Systems). All studies allowed for evaluating early sL-selectin assays in a representative sample of patients. In addition to injured cases and healthy controls, comparisons involved consecutive samples of injured individuals with and without inflammatory complications, defined by ALI, ARDS, or MODS. All studies precisely indicated selection criteria and outcomes.

No study reported handling of indefinite results or verified results in an independent cohort of patients.

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**Fig. 2. QUOROM flow chart of the trial selection procedure.**
Table 2. Study profile.

<table>
<thead>
<tr>
<th>Authors (Ref.)</th>
<th>Included</th>
<th>Evaluated</th>
<th>MODS</th>
<th>Lung Injury and ARDS</th>
<th>Follow-up, days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donnelly et al. (40)</td>
<td>82</td>
<td>52</td>
<td>MODS</td>
<td>Murray et al. (31)</td>
<td>&gt;30</td>
</tr>
<tr>
<td>Kerner et al. (27)</td>
<td>51</td>
<td>50</td>
<td></td>
<td>Goris et al. (34)</td>
<td>12</td>
</tr>
<tr>
<td>Rainer et al. (25)</td>
<td>216</td>
<td>56</td>
<td></td>
<td>American College of Chest Physicians (33)</td>
<td>28</td>
</tr>
<tr>
<td>Seekamp et al. (43)</td>
<td>80</td>
<td>65</td>
<td></td>
<td>Denver MOD Score</td>
<td>14</td>
</tr>
<tr>
<td>Stengel et al. (26)</td>
<td>70</td>
<td>70</td>
<td></td>
<td>American-European Consensus Conference on ARDS (32)</td>
<td>30</td>
</tr>
<tr>
<td>Siemiatkowski et al. (42)</td>
<td>44</td>
<td>34</td>
<td></td>
<td>American College of Chest Physicians (33)</td>
<td>12</td>
</tr>
<tr>
<td>Gando et al. (41)</td>
<td>66</td>
<td>58</td>
<td></td>
<td>Murray et al. (31)</td>
<td>Unclear</td>
</tr>
</tbody>
</table>

Table 3. Demographic characteristics.

<table>
<thead>
<tr>
<th>Authors (Ref.)</th>
<th>Males, %</th>
<th>Mean age, years</th>
<th>Mean ISS</th>
<th>Mortality, %</th>
<th>MODS, %</th>
<th>ARDS, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donnelly et al. (40)</td>
<td>78.0</td>
<td>38.1 (32.8–43.4)</td>
<td>31.4</td>
<td>25.0 (12.7–41.2)</td>
<td>50.0 (35.5–64.5)</td>
<td>15.4 (6.9–28.1)</td>
</tr>
<tr>
<td>Kerner et al. (27)</td>
<td>73.2</td>
<td>37.5 (36.2–38.8)</td>
<td>14.3</td>
<td>26.7 (15.8–40.3)</td>
<td>17.9 (8.9–30.4)</td>
<td></td>
</tr>
<tr>
<td>Rainer et al. (25)</td>
<td>62.2</td>
<td>32.6 (29.6–35.6)</td>
<td>28.4</td>
<td>20.0 (9.6–34.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seekamp et al. (43)</td>
<td>80.0</td>
<td>33.6 (29.1–38.2)</td>
<td>42.4</td>
<td>22.2 (11.2–37.1)</td>
<td></td>
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</tr>
<tr>
<td>Stengel et al. (26)</td>
<td>70.6</td>
<td>40.9 (35.7–46.0)</td>
<td>38.6</td>
<td>32.4 (17.4–50.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Siemiatkowski et al. (42)</td>
<td>80.4</td>
<td>41.5 (40.6–42.2)</td>
<td>26.0</td>
<td>22.4 (12.5–35.3)</td>
<td>53.4 (39.9–66.7)</td>
<td>10.3 (3.9–21.2)</td>
</tr>
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</table>

* Values in parentheses are the 95% CI.
In trauma care, many interventions take place between admission, staged surgery, intensive care, rehabilitation, and ambulation. One might think of a perfect model that predicts remote outcomes on a small set of items routinely assessed at the emergency department. Claiming to have this perfect model, or a perfect single predictor (known as the "magic bullet") (44), is desirable but probably unrealistic. Concerning survival, anatomic and physiologic scoring scales such as the ISS and Trauma and Injury Severity Score (TRISS) meet some of these predictive features. Nevertheless, they fail to explain ~10% of the variability in survival probability (45–47). Although simplification preserves clinical practicality of a statistical model, it introduces uncertainty into outcome predictions.

A major perspective of trauma outcome research goes beyond survival prognosis and toward variables contributing to morbidity. TRISS and others show, at best, minor to moderate accuracy in predicting inflammatory complications. Biochemical and molecular markers are considered key parts of models narrowing risks of morbidity, not only to explore some of the residual variance, but to guide doctors in scheduling patients to individualized treatment strategies. There is conflicting evidence on the predictive role of many circulating mediators. Several interleukins and chemokines have gained clinical importance in quantifying the posttraumatic inflammatory state (48–51). They may be helpful in identifying patients at high risk for developing systemic inflammatory response syndrome or ARDS.

Unfortunately, sample sizes in published studies of inflammatory mediators have been small, and false-negative associations between individual mediator profiles and outcomes might have occurred because of a type II, or beta, error. The statistical power of a study \((1 - \beta)\) refers to the chance of detecting a certain effect dimension. Clearly this is driven mainly by the sample size. Small studies with large variance are less likely to detect small effects. Although their average predictive value may point toward a distinct benefit or harm with a certain intervention or exposure, its broad distribution among
study participants still makes it compatible with a null, or statistically nonsignificant, effect. Metaanalysis is a promising tool to overcome some of these limits. Totaling data increases the precision of estimates and might reveal associations between inflammatory mediator blood concentrations and outcomes that are likely to be missed by a single small study. By increasing sample sizes, metaanalyses enable more reliable subgroup analyses.

We summarized data from all available clinical studies that correlated circulating plasma L-selectin with outcomes for multiple-trauma patients. Pooled results suggest different risks of developing remote organ injury with high and low early sL-selectin loads after blunt trauma. However, studies provided little information on patient profiles and treatments. For example, no adjustments were possible for dilution by fluid resuscitation and transfusion, which may contribute to the reported lower sL-selectin values among nonsurvivors.

As a main finding, circulating sL-selectin concentrations were lower in patients later progressing to lung failure and ARDS, with confidence limits close to statistical significance at the two-sided 5% level. With a mean (SD) physiologic sL-selectin value of 1.6 (0.8) µg/L (15), a 14% decrease in trauma patients at high risk for lung failure is likely to be beyond measurement errors. Manufacturers report a lower detection limit of 0.3 µg/L with current human sL-selectin ELISAs, whereas intra- and interassay variation has been reported to be <5% (52).

In the presence of statistical diversity, pooling of data is clearly controversial. Although random-effects modeling captures some of the unexplained variance, combined estimates must be interpreted with caution, and control for confounding by multivariate adjustment is necessary.

Some other limits of our study merit further discussion. For example, although we made efforts not to miss relevant clinical work and to avoid language bias, the small study sample prevented formal testing for funnel plot asymmetry. In addition, measures of test accuracy are lacking, weakening inferences from the published data, although sL-selectin seemingly discriminates between patients with different risks for inflammatory mediated sequels. The sharpness of this distinction remains unclear because false-positive and -negative results have not yet been quantified. Current studies merely reach conclusions about the efficacy of risk assessment by sL-selectin at the first level of the Fryback–Thornbury (28) hierarchy.

Finally, one might argue with our focus on early sL-selectin concentrations. Other soluble fragments of adhesion molecules, such as sP- and sE-selectin, or soluble intercellular adhesion molecule-1, in plasma and bronchoalveolar lavage fluid have been suggested as predictors for the onset and outcome of inflammatory pulmonary complications as well (42, 48, 53, 54), and combining these tests may increase the discriminatory power of a prognostic model. However, collecting almost complete information by systematically exploring a broad range of data sources needs to narrow the molecule of interest. Our results may stimulate other researchers to construct search algorithms for studies of other inflammatory markers. It will be interesting to aggregate data from different metaanalyses to gain unbiased insight into the predictive role of certain components of the immunologic network in the scenario of severe trauma.

Kerner et al. (27) showed that circulating sL-selectin concentrations remained stable up to 144 h after injury, despite remarkable changes in cellular activation. Other authors noted a similar behavior of sCD62L in sepsis (55). Thus, sequential measurements may strengthen the diagnostic and prognostic value of biomarkers. However, molecular markers showing predictive ability only by multiple assays hardly serve the needs of emergency physicians for an early sensitive test that eases triaging at the point of care. One might consider low sCD62L values a surrogate of a particular immunoreaction associated with a higher likelihood of leukocyte priming, second hit damage, and sustained leukocyte activity.

Metaanalysis cannot compensate for weaknesses of the source data or prove hypotheses. We set out to summarize the best available clinical evidence about sL-selectin in blunt severe trauma and to stabilize effect estimates. This may be helpful for creating hypotheses and sample size calculations in future studies.

In conclusion, sL-selectin represents a potential ingredient of future morbidity models in trauma. Our analysis warrants further research on the diagnostic accuracy and prognostic implications of sCD62L assays on a larger scale before continuing to the potential impacts on treatment decisions. Because of the projected sample size and the possible number of confounders, this demands many clinical collaborators and multivariate adjustments.

The ESPRIT (Early Selectin Assays to Predict the Risk for Inflammatory complications after Trauma) Investigators include the authors as well as the following: Norbert Haas, MD, PhD; Olaf Ahlers, MD; Frank Perschel, MD; and Edmund A. Neugebauer, PhD.

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