High plasma IL-18 identifies high-risk ARDS patients not identified by latent class analysis sub-phenotyping: a secondary analysis of the SAILS and HARP-2 studies

Andrew R Moore  
Stanford University

Shaun M Pienkos  
Stanford University

Pratik Sinha  
Washington University in St. Louis

Jiazhen Guan  
Harvard Medical School

Cecilia M O’Kane  
Queen's University of Belfast

Joseph E Levitt  
Stanford University

Jennifer G Wilson  
Stanford University

Manu Shankar-Hari  
The Queen's Medical Research Institute

Michael A Matthay  
University of California

Carolyn S Calfee  
University of California

Rebecca M Baron  
Brigham and Women's Hospital

Daniel F McAuley  
Queen's University of Belfast

Angela J Rogers  
ajrogers@stanford.edu  
Stanford University

Research Article
Abstract

Background: Both latent class analysis (LCA) assignment based upon a panel of plasma biomarkers and interleukin-18 (IL-18) plasma level have been shown to predict prognosis and treatment response in Acute Respiratory Distress Syndrome (ARDS). Interleukin-18 is a measure of inflammasome activation and plays a distinct role in inflammation that is not captured by the biomarkers used in LCA assignments. We hypothesized that elevated IL-18 would provide additive prognostic and therapeutic information to previously published LCA assignments in ARDS, identifying additional “high-risk” patients not captured by LCA who could be eligible for inclusion in future precision medicine-focused trials.

Methods: IL-18 and a panel of protein markers used for LCA had been previously measured in plasma from 683/745 patients in the Statins for Acutely Injured Lungs from Sepsis (SAILS) and 511/540 patients in the Hydroxymethylglutaryl-CoA reductase inhibition with simvastatin in Acute lung injury to Reduce Pulmonary dysfunction (HARP-2) trials. We tested the association between high IL-18 (>800 pg/mL) and LCA class assignment using McNemar’s test and evaluated the association of each subgrouping as well as treatment with 60-day mortality using Fisher’s exact test. We assessed 60-day mortality in each combination (high/low IL-18, hypo-/hyper-inflammatory LCA class, and treatment/placebo) using Kaplan-Meier survival analysis. We evaluated the correlation between the log₂ transformed IL-18 level and LCA biomarkers using Pearson’s correlation coefficient.

Results: 33% of patients in SAILS and HARP-2 were discordant by IL-18 level and LCA class. Elevated IL-18 identified a high-risk group of individuals previously classified as hypo-inflammatory by LCA in both SAILS (OR 3.3, 95% CI 1.8-6.1, p<0.001) and HARP-2 (OR 2.1, 95% CI 1.2-3.8, p = 0.009). IL-18 was only moderately correlated with LCA biomarkers with r of 0.17-0.47.

Conclusions: High Plasma IL-18 level provides additional prognostic information to LCA sub-phenotypes in two large ARDS cohorts.

Background

Acute Respiratory Distress Syndrome (ARDS) is a life-threatening condition defined by acute hypoxemic respiratory failure and bilateral pulmonary edema not primarily of cardiac origin [1, 2]. ARDS is seen in approximately 25% of mechanically ventilated patients in the ICU and carries a mortality of over 30% [3, 4]. Despite its prevalence, the majority of clinical trials have shown medications targeting the disorder to be ineffective [5, 6]. This may relate to the heterogeneous nature of ARDS, and researchers have increasingly attempted to identify subsets of patients with ARDS who might benefit from therapies [7–9]. Latent class analysis (LCA) is a statistical methodology that sub-classifies subjects based on baseline characteristics, irrespective of outcomes. This methodology has successfully identified two classifications of ARDS patients in several independent ARDS cohorts: a lower-risk, hypo-inflammatory subgroup and a high-risk, hyper-inflammatory subgroup[10–12]. The hyper-inflammatory subgroup has
been shown in all cohorts to experience higher mortality, and in several secondary analyses, have been shown to respond preferentially to therapeutics or interventions [12–14].

Interleukin-18 (IL-18) is a cytokine within the IL-1 family that is activated through the inflammasome pathway and has been associated with a variety of disease states [15, 16]. IL-18 elevation has previously been shown to be associated with mortality in ARDS [17–19]. To date, however, IL-18 has rarely been included in “conventional” measures of inflammation in ARDS and has not been used as a class-defining variable in the LCA algorithm. As IL-18 may reflect inflammasome activation, distinct from other pro-inflammatory cytokines, we hypothesized that it would provide additional prognostic and therapeutic information. In this study, we utilized previously analyzed plasma samples in the Hydroxymethylglutaryl-CoA reductase inhibition with simvastatin in Acute lung injury to Reduce Pulmonary dysfunction (HARP-2) trial [20] and the Statins for Acutely Injured Lungs from Sepsis (SAILS) trial [21] to evaluate whether IL-18 provides additive and/or distinct information to previous LCA sub-phenotype analyses.

Both SAILS and HARP-2 evaluated statins in patients with ARDS [20, 21]. In each trial, statins failed to show benefit compared to placebo across the cohort as a whole, however uncertainty remains as to whether there were specific sub-groups who may have benefited from therapy. Retrospective analysis of the SAILS trial failed to show a mortality benefit to rosuvastatin in high-risk subgroups as defined by either LCA or IL-18 levels[10, 17]. However, in secondary analyses of HARP-2, both the hyper-inflammatory LCA subgroup and patients with IL-18 levels ≥ 800pg/mL experienced lower mortality when they received simvastatin relative to those that received placebo [13, 19]. There is interest in future biomarker-guided randomized trials of simvastatin in high-risk ARDS patients, increasing the importance of understanding the overlap in classification by these two methods. We hypothesized that IL-18 level would identify additional high-risk patients within the hypo-inflammatory LCA subgroup (i.e., in those not identified as high risk by LCA class) that might benefit from inclusion in future clinical trials.

Methods

Study Design

We performed a secondary analysis of the SAILS and HARP-2 trials. SAILS was a multi-center, randomized controlled clinical trial in North America evaluating rosuvastatin versus placebo in patients with acute sepsis-induced ARDS [21]. Patients were randomized 1:1 to rosuvastatin or placebo with the treatment group receiving a 40mg loading dose followed by 20mg per day until 3 days after discharge from the ICU, day 28, or death. HARP-2 was a multi-center, randomized controlled clinical trial performed in the United Kingdom and Ireland evaluating simvastatin vs placebo in patients with ARDS from any cause [20]. Patients were randomized 1:1 to receive simvastatin or placebo stratified by study site and vasopressor requirement, with the treatment group receiving 80mg daily until day 28, discharge from critical care, or death. In both studies, eligible patients were defined as those receiving mechanical ventilation through an endotracheal tube, with a partial pressure of arterial oxygen (PaO2) to the fraction of inspired oxygen (FIO2) ratio of 300 or less, bilateral infiltrates on chest radiography consistent with
pulmonary edema, and lack of evidence of left atrial hypertension. Further details regarding the individual studies can be found in the original publications [20, 21].

**Interleukin-18 and latent class analysis measurement and subgrouping**

Total IL-18 levels in the plasma samples from the SAILS trial were measured in duplicate by enzyme-linked immunosorbent assay (ELISA; RayBiotech, Norcross, GA; Cat# ELH-IL-18-001) using the manufacturer's protocol. Average values of the duplicates were \( \log_2 \) transformed for analysis [17]. Total IL-18 levels in the plasma samples from the HARP-2 trial were measured in duplicate by ELISA (Duoset, R&D Systems) according to manufacturer's instructions [19]. The mean of duplicate values was used for analysis.

Latent class analysis assignments were previously performed for patients in both SAILS and HARP-2 [10, 13]. In both cohorts, LCA was performed using baseline demographic, clinical, and biomarker data. Importantly, both clinical and biomarker data differed between the two groups, with HARP-2 having fewer variables relative to SAILS (and other prior LCA studies). Biomarkers used in SAILS included the biomarkers in prior latent class analyses of ARDS - soluble intercellular adhesion molecule-1 (ICAM-1), interleukin-6 (IL-6), interleukin-8 (IL-8), soluble tumor necrosis factor receptor-1 (sTNFr-1), plasminogen activator inhibitor-1 (PAI-1), protein C - along with the new addition of C-reactive protein (CRP). Biomarkers in HARP-2 included IL-6 and soluble TNFr-1. IL-18 level was not used in LCA assignment for either study.

**Statistical Methods**

We included patients in SAILS and HARP-2 that had complete IL-18 and latent class analysis data available. Baseline characteristics were described. In accordance with prior analyses, patients were categorized based on low versus high IL-18 (< 800 pg/mL versus \( \geq 800 \) pg/mL) [17, 19] and hypo- versus hypo-inflammatory LCA class[10, 13], providing 4 subclassifications. We tested the association between high IL-18 and LCA class using McNemar's test. We assessed 60-day survival in each of the 4 combinations using log-rank test.

Given the differences in assays used for IL-18 measurement, we performed a sensitivity analysis. Prior analyses of IL-18 in SAILS showed that approximately 20% of patients were above the 800 pg/mL cut-off [17]. Based on this, we used a pre-defined top quintile cut-off to identify patients with high IL-18 in both SAILS and HARP-2. We then repeated the above analyses using this cut-off.

To evaluate the relationship between IL-18 and the individual inflammatory markers used in prior latent class analyses of ARDS, we calculated Pearson's correlation coefficient of \( \log_2 \) - transformed IL-18 level and each biomarker used in latent class analyses (IL-6, IL-8, ICAM-1, sTNFr-1, PAI-1, and protein C) in the SAILS and HARP-2 studies.
Results

Subjects

Of the 745 patients recruited to SAILS and the 540 patients recruited to HARP-2, 683 (92%) and 511 (95%) respectively had complete IL-18 data that were included in the analysis. Baseline characteristics for each cohort are outlined in Table 1. On average, the HARP-2 cohort was more ill than the SAILS cohort, with a higher percentage of moderate-severe ARDS and a higher percentage of vasopressor use. Mortality was similar between the two cohorts (Table 1).

<table>
<thead>
<tr>
<th></th>
<th>SAILS (n = 683)</th>
<th>HARP-2 (n = 511)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age (IQR)</td>
<td>55 (42–65)</td>
<td>54 (42–66)</td>
</tr>
<tr>
<td>% Female</td>
<td>51%</td>
<td>43%</td>
</tr>
<tr>
<td>Median APACHE score (IQR)*</td>
<td>92 (73–112)</td>
<td>18 (14–24)</td>
</tr>
<tr>
<td>APACHE III</td>
<td></td>
<td></td>
</tr>
<tr>
<td>APACHE II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P/F &lt; 200</td>
<td>469 (69%)</td>
<td>413 (81%)</td>
</tr>
<tr>
<td>Vasopressors use</td>
<td>309 (45%)</td>
<td>332 (65%)</td>
</tr>
<tr>
<td>60-day mortality</td>
<td>184 (27%)</td>
<td>146 (29%)</td>
</tr>
</tbody>
</table>

*APACHE III was used for SAILS, APACHE II Was used for HARP-2

The median value of IL-18 in the SAILS cohort was 554pg/mL (Inter-quartile Range (IQR) 383–763 pg/mL). HARP-2 had higher IL-18 levels with a median value of 845 pg/mL (IQR 485–1538 pg/mL). Clinical characteristics and outcomes by LCA class and IL-18 level are outlined in Table 2. Of the patients in the SAILS cohort, 151 (22%) had elevated IL-18 levels (≥ 800 pg/mL), compared to 265 patients (52%) in the HARP-2 cohort. In SAILS, 255 patients (37%) were classified as hyper-inflammatory by LCA compared to 177 patients (35%) in the HARP-2 cohort. As was previously shown [10, 13], mortality was higher in the hyper-inflammatory LCA subgroup (36% in SAILS and 45% in HARP-2) and in patients with IL-18 levels ≥ 800 (44% in SAILS and 35% in HARP-2).
Table 2
Outcomes by LCA and IL-18 subgroups

<table>
<thead>
<tr>
<th></th>
<th>SAILS</th>
<th>HARP-2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Patients</td>
<td>LCA 1/</td>
</tr>
<tr>
<td></td>
<td>Hypo-inflammatory LCA /</td>
<td>Low IL-18</td>
</tr>
<tr>
<td>N (%)</td>
<td>683</td>
<td>189 (37%)</td>
</tr>
<tr>
<td>Median Age (IQR)</td>
<td>55 (42–65)</td>
<td>49 (40–61)</td>
</tr>
<tr>
<td>% Female</td>
<td>51%</td>
<td>41%</td>
</tr>
<tr>
<td>Median APACHE II Score (IQR)</td>
<td>92 (73–112)</td>
<td>18 (14–24)</td>
</tr>
<tr>
<td>P/F &lt; 200</td>
<td>469 (69%)</td>
<td>413 (81%)</td>
</tr>
<tr>
<td>Vasopressor use</td>
<td>309 (45%)</td>
<td>332 (65%)</td>
</tr>
<tr>
<td>60-day mortality</td>
<td>184 (27%)</td>
<td>146 (29%)</td>
</tr>
</tbody>
</table>

Elevated Plasma IL-18 identifies a high-risk group within hypo-inflammatory LCA patients in both cohorts
As has been previously described, in both SAILS and HARP-2, IL-18 level ≥ 800pg/mL was associated with mortality [17, 19]. Patients with IL-18 ≥ 800 in SAILS had a 60-day mortality of 44% compared to 22% in patients with IL-18 < 800 (Odds ratio (OR) 2.7, 95% confidence interval (CI) 1.8–4.1, Fisher’s p < 0.001). In HARP-2, patients with IL-18 ≥ 800 experienced a 60-day mortality of 35%, compared to 22% in patients with lower IL-18 levels (OR 1.9, 95% CI 1.3–2.9, Fisher’s p = 0.002). Kaplan-Meier survival analysis also showed decreased survival in patients with IL-18 ≥ 800 in both SAILS and HARP-2 (log-rank test p < 0.001 and p = 0.001 respectively, Fig. 1a/b).

There was significant overlap between IL-18 and LCA classifications. IL-18 and LCA class were concordant (i.e., IL-18 < 800 and LCA class 1 or IL-18 ≥ 800 and LCA class 2) in 66% of patients in SAILS (McNemar’s p < 0.001) and 60% of patients in HARP-2 (McNemar’s p < 0.001). Despite this overlap, IL-18 was ≥ 800 in the “lower-risk” LCA class 1 in 14% and 43% of cases in SAILS and HARP-2, respectively.

Among those patients classified as hypo-inflammatory by LCA, those who had IL-18 levels ≥ 800 had a higher 60-day mortality compared to those with lower IL-18 in both SAILS (42% vs 18% mortality, OR 3.3, 95% CI 1.8–6.1, p < 0.001) and HARP-2 (27% vs 15%, OR 2.1, 95% CI 1.2–3.8, p = 0.009), suggesting that IL-18 level identifies a high-risk sub-group of patients not captured by LCA. This finding is consistent using Kaplan-Meier Survival Analysis (log-rank p < 0.001 and p = 0.006 respectively, FIGURE 1c/d). In contrast, IL-18 ≥ 800 added prognostic value for hyper-inflammatory LCA subjects only in SAILS, with higher 60-day mortality (OR 1.8, 95% CI 1.0-3.1, p = 0.04) in hyper-inflammatory LCA subjects, but not in HARP-2 hyper-inflammatory LCA subjects (OR 0.9, 95% CI 0.48–1.88, p = 0.88). Kaplan-Meier survival analysis was consistent with these findings, showing decreased survival in hyper-inflammatory LCA patients with IL-18 ≥ 800 in SAILS (log-rank p = 0.03, Fig. 1e) but not in HARP-2 (log-rank p = 0.94, Fig. 1f).

Results were consistent in a sensitivity analysis using a pre-defined top-quintile cutoff to define high IL-18.

A higher proportion of patients in HARP-2 had IL-18 levels ≥ 800pg/mL, therefore, we performed a sensitivity analysis where elevated IL-18 was defined by highest quintile within the cohort (IL-18 ≥ 838 pg/mL in SAILS, and ≥ 1,807 pg/mL in HARP2). Using the quintile cut-offs, IL-18 remained highly associated with 60-day mortality and identified a high-risk subset of patients identified as hypo-inflammatory by LCA in both SAILS (OR 3.5, 95% CI 1.8–6.7, p < 0.001) and HARP-2 (OR 2.2, 95% CI 1.1–4.5, p = 0.02). Survival analysis revealed similar results (Supplemental Fig. 1).

**Plasma IL-18 is weakly to moderately correlated with inflammatory markers used in latent class analysis**

Finally, to assess the plausibility that IL-18 categorization could provide biologically distinct information about prognosis, we tested the association between log-transformed IL-18 and the plasma biomarkers used in latent class analysis class assignment in SAILS and HARP-2. In all cases, IL-18 was weakly to moderately correlated with biomarkers used in latent class analysis, with a correlation coefficient < 0.5 across all biomarkers (Fig. 2). The strongest correlation was seen with sTNFr-1 in SAILS, with a
correlation coefficient of 0.47 ($p < 0.001$). The lowest correlation was seen with IL-6 in SAILS and IL-8 in HARP-2 ($r = 0.17, p < 0.001$).

**Discussion**

Interleukin-18 is mediated by inflammasome activation, a pathway that is not measured by the biomarkers currently used in latent class analysis, and that is a potential targetable for therapeutic interventions [15, 18, 22]. Using the HARP-2 and SAILS statin trials (in which elevated plasma IL-18 level had been previously shown to be associated with adverse outcomes and with treatment response to simvastatin [17, 19]), this analysis reveals that IL-18 provides additive information to latent class analysis sub-phenotypes in ARDS. We found that 14% of patients in SAILS and 43% of patients in HARP-2 who were classified as hypo-inflammatory by LCA had IL-18 levels $\geq 800$. These patients, who otherwise would have been classified as “lower-risk” by LCA alone, experienced a significantly higher mortality in both SAILS and HARP-2, suggesting that IL-18 adds prognostic information to current LCA sub-phenotyping. Correspondingly, we found that plasma IL-18 level has only modest correlation with the biomarkers used in LCA classification, suggesting that IL-18 may reflect a complementary but distinct biologic pathway in ARDS.

Prior studies have shown that IL-18, along with other members of the IL-1 cytokine family, plays an important role in propagating the immune response in both overlapping and distinct pathways from those related to “traditional” pro-inflammatory cytokines included in prior LCA analyses [23]. Additionally, murine models have shown that IL-18 blocking antibodies as well as genetic deletion of IL-18 reduces lung injury [18]. However, it is important to recognize that though this study suggests that though this study suggests that IL-18 levels may serve as a predictive and prognostic marker in ARDS patients, this association does not necessarily equate to a causative role for IL-18 in inflammation in ARDS in humans. Our analysis suggests that there may be clinically valuable subclassifications in addition to the current well-accepted two LCA classes. Importantly, while a number of biomarker-based high-risk groups have been identified using various ‘omics’ methods, we focused on LCA in this study because it has been reproduced across several cohorts and has shown potential predictive enrichment for multiple therapies [10–14]. Further study is required to delineate the role that IL-18 plays in the inflammatory pathway in ARDS in humans and how this relates to other inflammatory biomarkers.

There are several important limitations to this study. Our study classified patients based on LCA as well as IL-18 levels. Although classification was performed without respect to outcomes, analysis of potential therapeutic effect of simvastatin in biomarker-defined subsets is post-hoc and requires prospective validation. Additionally, HARP-2 was a pragmatic trial with fewer variables available for LCA assignment relative to SAILS; how LCA categorization would have varied with more complete LCA biomarker and clinical data and whether this affects the interaction between LCA and IL-18 elevation in mortality prognostication is unknown. Finally, IL-18 was quantified using different assays in SAILS and HARP-2. The percentage of patients with elevated IL-18 differed substantially between the 2 cohorts, which could reflect either higher patient acuity in HARP-2 (with more shock), differences in cohort composition (i.e.,
SAILS included only sepsis-associated ARDS, whereas HARP-2 included ARDS of all etiologies), or the differences in IL-18 assays used between the two studies. Importantly, our IL-18 cut-off of 800pg/mL adds to the prognostic value of LCA in both studies despite the different assays, suggesting that these findings are robust to differences in assay. We additionally demonstrated similar prognostic value in a sensitivity analysis based on the highest quintile of IL-18 instead of an absolute cutoff in patients identified as hypo-inflammatory by LCA in HARP-2, indicating that observed difference in the relationship between IL-18 and LCA in SAILS and HARP-2 are not explained by differences in the median IL-18 levels alone. Interestingly, we found that IL-18 levels added prognostic information within patients identified as hyper-inflammatory by LCA in SAILS, but not in HARP-2, which again may reflect differences in assay or patient population as outlined above. Further study to determine the ideal IL-18 assay and other potential differences between the SAILS and HARP-2 cohorts may inform design of future clinical trials.

**Conclusions**

This study reports that IL-18 independently predicts mortality when combined with latent class analysis sub-phenotypes and identified a high-risk inflammatory group in patient defined as hypo-inflammatory by LCA in both cohorts. Further, we showed that elevated IL-18 level is only moderately correlated with biomarkers used in latent class analysis for ARDS, consistent with the fact that it is measuring a biologically distinct pathway. In summary, these findings provide further evidence of the importance of incorporating markers of inflammasome activation into methods for phenotyping ARDS patients.

**Abbreviations**

ARDS
Acute respiratory distress syndrome
CRP
C-reactive protein
ELISA
Enzyme-linked immunosorbent assay
HARP-2
Hydroxymethylglutaryl-CoA reductase inhibition with simvastatin in Acute lung injury to Reduce Pulmonary dysfunction trial
ICAM-1
intercellular adhesion molecule-1
IL-6
Interleukin-6
IL-8
Interleukin-8
IL-18
Interleukin-18
Declarations

Ethics approval and consent to participate: The Institutional Review Boards at each of the participating institutions in HARP-2 and SAILS approved the studies. During the consent process for SAILS and HARP-2, written informed consent was obtained for storage and future analysis of samples.

Consent for Publication: Not applicable

Availability of data and materials: The datasets used to generate this manuscript may be made available from the corresponding author on reasonable request.

Competing Interests: RMB has sat on advisory boards for Merck and Genentech.

Funding: SAILS was funded by the NHLBI as part of the ARDS Network and AstraZeneca (ClinicalTrials.gov number NCT00979121). HARP-2 was supported by the UK EME Programme, an MRC and NIHR partnership (08/99/08 and 16/33/01). The EME Programme is funded by the MRC and NIHR, with contributions from the Chief Scientist Office in Scotland, the National Institute for Social Care and Health Research in Wales, and the Health and Social Care (HSC) Research and Development Division, Public Health Agency for Northern Ireland. MS-H was supported by the NIHR Clinician Scientist Award (CS-2016-16-011). CSC was supported by R35 HL140026. RMB was supported by R01 HL112747-01 for the original IL18 analyses.

Author contributions: ARM, SMP, JEL, JGW, and AJR contributed to the study design, analysis, and the writing of the manuscript. JG and RMB performed IL-18 testing in SAILS. CO and DFM performed IL-18 measurements in HARP-2. PS, MAM, and CSC provided latent class analysis sub-phenotypes for the SAILS and HARP-2 trials. All authors critically reviewed the manuscript.

Author Information: (1) Division of Pulmonary, Allergy and Critical Care Medicine, Stanford University, Stanford, CA, USA. (2) Division of Critical Care, Department of Anesthesia, Washington University, Saint
Louis, MO, USA. (3) Division of Rheumatology, Brigham and Women's Hospital, and Harvard Medical School, Boston, MA, USA. (4) Centre for Infection and Immunity, Queen's University of Belfast, Belfast, UK. (5) Department of Emergency Medicine, Stanford University, Stanford, CA, USA. (6) The Centre for Inflammation Research, The University of Edinburgh, The Queen's Medical Research Institute, Edinburgh, UK (7) Department of Medicine, Cardiovascular Research Institute, University of California, San Francisco, CA, USA. (8) Department of Anesthesia, Cardiovascular Research Institute, University of California, San Francisco, CA, USA. (9) Division of Pulmonary and Critical Care Medicine, Brigham and Women's Hospital, and Harvard Medical School, Boston, MA, USA.

References


Figures
Figure 1

Mortality by IL-18 level in 2 cohorts; all patients and stratified by latent class analysis (LCA) sub-phenotype. Survival analysis shows that elevated IL-18 adds prognostic information in (a) all-comers, (c) hypo-inflammatory LCA patients, and (e) hyper-inflammatory LCA patients in SAILS. In HARP-2, elevated IL-18 adds prognostic information in (b) all-comers and (d) hypo-inflammatory LCA patients, but not in (f) hyper-inflammatory LCA patients.
HARP-2 = Hydroxymethylglutaryl-CoA reductase inhibition with simvastatin in Acute lung injury to Reduce Pulmonary dysfunction trial; SAILS = Statins for Acutely Injured Lungs from Sepsis trial

Figure 2

Pearson correlation coefficients between IL-18 and biomarkers used in latent class analysis. Log(2) transformed values for Interleukin-18 (IL-18) and the biomarkers used in latent class analysis assignment were mildly to moderately correlated. The weakest correlation was seen with IL-8 in HARP-2 (r
= 0.17) and IL-6 in SAILS (r = 0.017). The strongest correlation was seen with soluble tumor necrosis factor receptor-1 (sTNFR-1) in both SAILS (r = 0.47) and HARP-2 (r = 0.37).

HARP-2 = Hydroxymethylglutaryl-CoA reductase inhibition with simvastatin in Acute lung injury to Reduce Pulmonary dysfunction trial; SAILS = Statins for Acutely Injured Lungs from Sepsis trial; IL = Interleukin; CRP = C-reactive protein; ICAM-1 = intercellular adhesion molecule-1; PAI-1 = Plasminogen activator inhibitor-1; sTNF-1 = Soluble tumor necrosis factor receptor-1

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementalFigure1.pdf
- SupplementalMaterials.docx