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Plasma concentrations of soluble ST2 and IL-6 are predictive of successful liberation from mechanical ventilation in patients with the acute respiratory distress syndrome

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Abstract

Objective—Soluble ST2 (sST2) and IL-6 concentrations have been associated with the inflammatory cascade of acute respiratory distress syndrome (ARDS). We determined whether sST2 and IL-6 levels can be used as prognostic biomarkers to guide weaning from mechanical ventilation and predict the need for reintubation.

Design, Setting, and Patients—We assayed plasma sST2 (N=826) concentrations and IL-6 (N=755) concentrations in the Fluid and Catheter Treatment Trial (FACTT), a multi-center randomized controlled trial of conservative fluid management in ARDS. We tested whether sST2 and IL-6 levels were associated with duration of mechanical ventilation, the probability of passing a weaning assessment, and the need for reintubation.

Measurements and Main Results—In models adjusted for APACHE score and other relevant variables, patients with higher day 0 and day 3 median sST2 and IL-6 concentrations had decreased probability of extubation over time (day 0 sST2 HR 0.85, 95% CI 0.72–1.00, *P*=.05; day 0 IL-6 HR 0.64, 95% CI 0.54–0.75, *P*<.0001; day 3 sST2 HR 0.64, 95% CI 0.54–0.75; *P*<.0001; day 3 IL-6 HR 0.73, 95% CI 0.62–0.85, *P*=.0001). Higher biomarker concentrations were also predictive of decreased odds of passing day 3 weaning assessments (sST2 OR 0.62, 95% CI 0.44–0.87, *P*=.006; IL-6 OR 0.61, 95% CI 0.43–0.85, *P*=.004) and decreased odds of passing a spontaneous breathing trial (sST2 OR 0.45, 95% CI 0.28–0.71, *P*=.0007; IL-6 univariate analysis only OR 0.55, 95% CI 0.36–0.83, *P*=.005). Finally, higher biomarker levels were significant

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predictors of need for reintubation with OR 3.23, 95% CI 1.04–10.07, *P*=.04 for sST2 and OR 2.58, 95% CI 1.14–5.84, *P*=.02 for IL-6.

Conclusions—Higher sST2 and IL-6 concentrations are each associated with worse outcomes during weaning of mechanical ventilation and increased need for reintubation in patients with ARDS. Biomarker-directed ventilator management may lead to improved outcomes in weaning of mechanical ventilation in patients with ARDS.

INTRODUCTION

Mechanical ventilation is a life-saving therapy in patients with acute respiratory distress syndrome (ARDS), but one that carries the potential for serious complications. Prolonged mechanical ventilation has been shown in numerous studies to increase mortality and has predictable effects on hospital and intensive care unit (ICU) length of stay (1). The process of liberation from mechanical ventilation comprises close to 40% of the total time on the ventilator in mechanically ventilated patients, suggesting an opportunity for improving care (2). Current practices incorporate a number of recent advances in weaning from mechanical ventilation including daily spontaneous breathing trials (SBT) and minimization of sedation (3). However, 10–20% of all patients extubated after passing an SBT require reintubation within 48 hours (4, 5). These patients have increased mortality, length of stay, and a decreased likelihood of returning home as compared to patients who are successfully liberated from mechanical ventilation (6). Thus, it is essential that physicians attempt to minimize the amount of time that patients undergo mechanical ventilation and identify risk factors for failure of extubation despite successful SBT. Since ARDS is a syndrome that combines elements of lung inflammation and cardiac dysfunction (7), we investigated whether circulating biomarkers of cardiovascular stress and inflammation can provide objective measures of time to resolution of ARDS and whether these biomarkers could therefore predict the likelihood of liberation from mechanical ventilation and the need for reintubation.

We selected soluble suppression of tumorigenicity-2 (sST2) and interleukin 6 (IL-6) for study. sST2 is a member of the interleukin-1 receptor family which, along with its functional ligand interleukin-33, has been implicated in signaling pathways of cardiac and vascular stress as well as inflammation (8). It has been well studied as a marker of myocardial strain including acute myocardial infarction and heart failure (9–11), but is also upregulated under conditions of lung inflammation such as in asthma and idiopathic pulmonary fibrosis (12). We previously showed higher sST2 levels are associated with worse outcomes in ARDS including longer duration of mechanical ventilation, longer ICU stay, and increased mortality (13). Interleukin 6 (IL-6) is a complex cytokine that has also been implicated in many infectious and inflammatory disease states (14) and has been found both in the plasma and bronchoalveolar lavage samples of patients with ARDS; IL-6 has been associated with both a proinflammatory state and a paradoxical protective role against vascular leakage (15–17). Like sST2, elevated IL-6 levels are also associated with worse outcomes in ARDS (18). Due to their well-described associations with the inflammatory cascade of ARDS, we hypothesized that plasma sST2 and IL-6 concentrations can be used as prognostic

biomarkers to guide weaning from mechanical ventilation in ARDS and predict the need for reintubation.

MATERIALS & METHODS

Study Design

Patients with ARDS enrolled in a randomized controlled trial of conservative vs. liberal fluid management (the Fluid and Catheter Treatment Trial or FACTT), were analyzed (18). This study demonstrated increased ventilator-free days (VFD) and ICU-free days (IFD) with conservative fluid management. All FACTT patients with available blood samples were included in our study. FACTT exclusion criteria included presence of ARDS for more than 48 hours, inability to obtain consent, or presence of chronic or irreversible conditions influencing survival (such as advanced cancer), impairing weaning, or compromising protocol compliance (e.g., dialysis dependence) (17). We utilized blood samples taken from FACTT patients on day 0 (the day of study enrollment) and day 3 (72 hours later). FACTT was approved by institutional review boards (IRB) of participating institutions and the present study was approved by our local IRB.

Data Collection

FACTT baseline data included demographic characteristics, coexisting conditions, cause of ARDS, and Acute Physiology and Chronic Health Evaluation (APACHE) III score (18). Physiologic variables were collected according to study protocol. Clinical outcomes included 60-day mortality, VFD, and IFD from hospital day 1–28. According to study protocol, patients were assessed for commencement of ventilator weaning each study day between 0600h and 1000h beginning on the day following enrollment, with a minimum period of 12 hours since initial settings. Weaning assessment was passed when FiO_2 was ≤ 0.5 and PEEP was ≤ 5 cm H_2O, along with other clinical criteria. Patients who passed weaning assessment were placed on a 2 hour spontaneous breathing trial (SBT). SBT was passed if patients tolerated the 2 hour period without worsening respiratory failure, tachypnea, acidosis, respiratory distress, or other subjective distress. The full weaning protocol, including detailed criteria and definitions, can be found in the original publication (18). Specific SBT results such as rapid shallow breathing index were not recorded in the original trial data.

Blood sample analysis

Samples were stored in EDTA plasma at −80 degrees C and assayed using a highly sensitive sST2 assay (Presage™, Critical Diagnostics, San Diego, CA, USA) and IL-6 assay (IMMULITE, Siemens Healthcare, Erlangen, Germany).

Statistical Analysis

Data were analyzed using SAS v9.3 software (SAS Institute, Cary, NC, USA). Categorical variables were compared using chi-squared tests. Continuous variables were compared using Wilcoxon rank-sum tests. Patients were stratified into groups according to low or high sST2 and IL-6 concentrations, using the median value for each as the cut point. In order to

demonstrate the robustness of the cut point, we also evaluated statistical associations using an ROC-determined cut point for each marker and obtained similar results (data not shown).

Cox proportional hazards models were used to test associations between biomarker levels and probability of successful extubation (liberation from mechanical ventilation) over 60 days. We decided a priori to include age and APACHE III severity of illness score in the model. Remaining covariates for the model were selected from clinically relevant variables using stepwise selection. Separate models were constructed for use with day 0 and with day 3 biomarker levels. Patients were excluded from day 3 analysis if they were extubated prior to day 3.

Multivariate logistic regression was used to study the association between biomarkers and odds of successful ventilator weaning (both weaning assessments and SBT). As with the Cox models, the decision was made *a priori* to adjust for age and APACHE III score, and additional covariates were selected using stepwise selection. Net reclassification index (NRI) for multivariable models was calculated according to the method of Kerr (19).

RESULTS

Characteristics of the Study Population

Demographic and baseline physiologic data for the study population are shown in Table 1. In all, 826 patients from the study population had plasma available for sST2 biomarker testing. Because IL-6 assays required a higher sample volume, only 755 patients had sufficient plasma available for concurrent IL-6 testing. Patients with available samples were clinically similar to those who did not have samples.

On day 0, the median sST2 concentration was 534.3 ng/mL, with 25–75% interquartile range (IQR) 325.0 – 724.9 ng/mL, while the median IL-6 concentration was 186.0 pg/mL (IQR 63.6 – 605.0 pg/mL). On day 3, the median sST2 concentration was 297.6 (IQR 161.6 – 515.9), while IL-6 median was 67.4 pg/mL (IQR 27.9 – 163.0 pg/mL).

Patients were categorized into groups according to median day 0 sST2 and IL-6 levels. Across groups, patients with higher biomarker levels also had higher APACHE III severity of illness scores (Table 1). Patients with higher sST2 levels were less likely to have trauma as an etiologic factor for ARDS. Patients with higher IL-6 levels were more likely to have pneumonia as an etiologic factor, and were less likely to have human immunodeficiency virus (HIV) infection or acquired immune deficiency syndrome (AIDS), or be immunosuppressed for other reasons.

Biomarker level and ventilator outcomes

Patients with higher day 0 sST2 and IL-6 levels (defined as the median value for each) had significantly fewer days free of mechanical ventilation, with median VFD 16 (IQR 0–22) vs. 21 days (IQR 11–24) $P<.0001$ for sST2 and median VFD 16 (IQR 0–22) vs. 20 days (IQR 9–24), $P<.0001$ for IL-6. In a Cox proportional hazards model, higher sST2 concentrations were associated with decreased probability of extubation over time, with hazard ratio (HR) 0.81, 95% confidence interval (CI) 0.69–0.94, $P=.006$. This association remained significant

when pre-specified adjustments for age and APACHE III score were included (HR 0.85, 95% CI 0.72–1.00; *P*=.05). Similar associations were seen with higher day 0 IL-6 level, with HR 0.60, 95% CI 0.51–0.71, *P*<.0001 for IL-6 alone, and HR 0.64, 95% CI 0.54–0.75, *P*<.0001 when adjusted for age and APACHE III. A final Cox model was created that included both biomarkers. Given the differences between groups demonstrated in Table 2, pneumonia, trauma, HIV/AIDS, and immunosuppression were considered as covariates using backward stepwise selection with cutoff for inclusion $P < 0.2$. Pneumonia and trauma survived selection and were included in the model. Full results are shown in Table 2, Model 1, demonstrating that the strongest biomarker association was between higher day 0 IL-6 level and extubation.

Patients with higher day 3 sST2 and IL-6 levels also had significantly fewer days free of mechanical ventilation, with median 10 (IQR 0–20) vs. 21 days (IQR 14–25), *P*<.0001 for sST2 and median 13 (IQR 0–21) vs. 21 days (IQR 11–25), *P*<.0001. In a Cox model, higher sST2 level was associated with decreased probability of extubation over 60 days, (HR 0.48, 95% CI 0.41–0.56, *P*=<.0001), and remained significant when age and day 3 Brussels organ dysfunction score were included (HR 0.64, 95% CI 0.54–0.75; *P*<.0001). Higher IL-6 was also associated with probability of extubation in both univariate (HR 0.61, 95% CI 0.52–0.72, *P*<.0001) and adjusted analyses (HR 0.73, 95% CI 0.62–0.85, *P*=.0001). As above, a full model was created including both biomarkers and using stepwise selection for other covariates. This model demonstrated strong relationships between biomarker levels and extubation, in an inverse relationship (Table 2, Model 2). Although the power to study subgroups was limited, the effects remained when the analysis was restricted to patients without sepsis or pneumonia. Similarly, interaction terms for etiology of ARDS including sepsis, pneumonia, trauma, etc. were not significant when included in the models (data not shown).

Biomarker level and weaning tests

Biomarker levels from day 3 were analyzed for association with weaning assessments and spontaneous breathing trials. Biomarkers from day 0 were not analyzed because by protocol no weaning assessments or spontaneous breathing trials occurred on study day 0.

Higher day 3 sST2 level decreased the odds of passing the day 3 weaning assessment by approximately two-thirds (OR 0.35, 95% CI 0.25–0.48, *P*<.0001), and this remained significant after adjusting for age and day 3 Brussels score (OR 0.62, 95% CI 0.44–0.87, *P*=.006).Likewise, higher day 3 IL-6 level was associated with lower odds of passing weaning assessment in both univariate (OR 0.47, 95% CI 0.34–0.65, *P*<.0001) and adjusted analyses (OR 0.61, 95% CI 0.43–0.85, *P*=.004). A full logistic regression model was created that included both biomarkers. Stepwise selection was used as above to select additional covariates for inclusion. This model demonstrated both higher IL-6 and sST2 levels predicted failure of passing weaning assessment (Table 3).

Higher day 3 sST2 level was associated with decreased odds of passing the day 3 SBT in both univariate (OR 0.31, 95% CI 0.20–0.48, *P*<.0001) and adjusted analyses (OR 0.45, 95% CI 0.28–0.71, *P*=.0007). IL-6 level was significantly associated with decreased odds in the univariate (OR 0.55, 95% CI 0.36–0.83, *P*=.005) but not in the adjusted analysis (OR

0.69, 95% CI 0.45–1.08, *P*=.10 for the adjusted analysis). A logistic regression model was created as above, which included passing of SBT as the outcome, and both biomarkers and covariates as independent variables. This model showed that higher levels of day 3 ST2, but not IL-6 were associated with decreased odds of passing SBT (Table 4).

Both day 3 sST2 and IL-6 levels were then separated into quartiles and the rate of success of weaning assessments and SBT were examined. These data are presented in Figures 1 and 2. Monotonic trends were seen, with each biomarker showing decreasing likelihood of successful weaning assessment or SBT as biomarker quartile increased. As shown, each trend was statistically significant (chi-squared test of trend).

Net Reclassification Index

To determine the additive value of biomarkers to the multivariable models, NRI was calculated for each of the main multivariable models. Results are shown in Table 5, including the percent of events (extubations, passed weaning assessments, passed SBT) and non-events that were reclassified by addition of biomarkers to the relevant model. The NRI P-value was not significant for the day 0 Cox model of 60-day probability of extubation, but was significant for the other three main models.

Requirement for re-intubation

We next studied the relationship between biomarkers and liberation from mechanical ventilation. On day 3, 66 patients were successfully liberated. Of these, 10 patients (15%) required resumption of mechanical ventilation. Patients who required reintubation had significantly higher day 3 sST2 levels (median 361.5 ng/mL, IQR 263.4–471.1 ng/mL vs. median 192.8, IQR 99.7–314.9, *P*=.02) and higher IL-6 levels (median 133.0, IQR 24.9–141.0 vs. median 33.6, IQR 12.6–66.8, *P*=.02) than patients who did not require resumption of mechanical ventilation. Biomarker levels were then log-transformed to normalize them for use in logistic regression. Increasing biomarker levels were significant predictors of resumption of mechanical ventilation, with OR 2.58, 95% CI 1.14–5.84, *P*=.02 for IL-6 and OR 3.23, 95% CI 1.04–10.07, *P*=.04 for sST2. By contrast, day 3 PaO2/FiO2 ratio was not associated with return to mechanical ventilation (OR 0.99, 95% CI 0.97 – 1.02; *P*=.52). Adjusted analyses were not performed because of the smaller sample size.

DISCUSSION

In this post hoc observational analysis of a large multi-center randomized controlled trial of patients with ARDS, biomarkers sST2 and IL-6 were significantly associated with successful liberation from mechanical ventilation and need for reintubation. Our study is the first to date to investigate the plausibility of biomarker-tailored weaning specifically in patients with ARDS. This study demonstrates potential utility for biomarkers in predicting the likelihood of weaning readiness, presumably related to decrease in biomarker levels concentrations during resolution of ARDS. Clinically, these biomarkers might be useful for establishing a threshold level for beginning the weaning process and making decisions regarding extubation.

McConville and Kress grouped efforts to liberate patients from mechanical ventilation into two categories – earlier recognition of readiness for SBTs and a shorter process of discontinuing mechanical ventilation (21). SBTs are initiated when patients meet readiness criteria, which generally consist of assessment of improvement of the cause of respiratory failure, hemodynamic stability, P/F ratio, and PEEP (22). There have been attempts to predict readiness for SBT such as the rapid shallow breathing index (RSBI) or ratio of the respiratory rate to tidal volume; however, weaning predictors have been shown to prolong weaning time and expert opinion suggests that a daily trial of SBT once readiness criteria are met is the best method to determine whether patients are ready to breathe on their own (22–24). Interestingly, in the same review article, McConville and Kress report that they "routinely break" the rules regarding readiness for initiating SBT if they believe the underlying disease process is starting to improve (21). Moreover, studies on predictive variables of duration of mechanical ventilation have been inconsistent and have not substantially changed clinical practice (25–28). Clinicians are thus often left with assessing multiple variables to make their predictions, however we know that the accuracy of intensive care physicians' early clinical predictions of duration of mechanical ventilation is limited (29). While the standard of care has moved towards more aggressive and earlier attempts at initiation of SBT and liberation from mechanical ventilation, there remains a fair amount of clinical judgment and provider variability regarding determination of readiness and prediction of duration of mechanical ventilation (30). More objective measures are needed to help guide assessment both of readiness – particularly with regards to determining whether the underlying cause of respiratory failure has improved – as well as prognostication and prediction of duration of ventilator support.

sST2 has gained recent attention as a biomarker in cardiovascular disease states, where it strongly predicts adverse outcome across a wide spectrum of disease, most notably in heart failure (31, 32). However, concentrations of sST2 are also prognostic in generic acute dyspnea as well as in those with pulmonary diseases (31, 33, 34). Biologically, sST2 is thought to play a role in immunologic tolerance but also plays a role in mitigating strain in the vasculature as well as in the myocardium. Thus, sST2 concentrations reflect two pivotal processes in patients with ARDS, namely inflammation and cardiovascular disarray. Similarly IL-6 plays numerous roles in the body; hardly simply an inflammatory marker, IL-6 may be viewed as a Janus hormone, stimulating inflammation in certain organs, while down-regulating inflammation in others (14, 35). Concentrations of IL-6 are considered prognostic in inflammatory states such as ARDS, and yet may be also thought of as protective as well. Despite the complexity of the underlying biology for both sST2 and IL-6, we found clear potential utility in our patients.

Lower concentrations of both biomarkers were associated with better outcomes with regard to duration of mechanical ventilation and overall probability of being liberated from mechanical ventilation, one could hypothesize because both biomarkers are indicative of more intense early inflammation and therefore more severe disease. While sST2 and IL-6 plasma levels have potential prognostic implications, the primary question remains whether weaning ventilation based on biomarker levels adds value to the standard of care. The use of a biomarker to assist in determining weaning readiness would be tremendously useful to clinicians. It is well accepted that patients with ARDS should be managed using lung-

protective ventilation strategies. However, the timing for cessation of such strategies has not been rigorously tested and is largely based on consensus (21). Current standard of practice for ventilator weaning assessment is delineated by ARDSnet protocol: patients with FiO2 0.5 and PEEP 5 who meet hemodynamic criteria are considered ready for initiation of weaning attempts. However, it is well known that patients with ARDS are particularly predisposed to ventilator-induced lung injury due to the vulnerable state of the lungs and heterogeneous pattern of lung damage (36, 37). Due to this heterogeneous pattern of injury, it follows that simply tracking global FiO2 requirement and changes in PEEP may not accurately represent improvement in lung injury. Additional objective data are needed to assess progression of ARDS and successful extubation. Illustrative of this point, we found that biomarker levels were significantly associated with the need for reintubation but that PaO2/FiO2 ratio showed no association with such a failure. All patients underwent an SBT after oxygenation and PEEP reached specified thresholds; and, even with this similar starting point, biomarkers appear to add information to clinical assessment for weaning readiness. Thus, it is possible that for many patients, weaning is being initiated either too early, thereby exposing them to non-protective ventilator settings, or too late, thereby exposing them to risk for complications of prolonged mechanical ventilation.

Of the 66 patients who were successfully extubated in our study, 15% required reintubation. This number is consistent with previously reported reintubation rates of patients requiring mechanical ventilation, and it is well described that the need for reintubation confers significantly increased risk of death and prolonged ICU stay (4–6). Given the heterogeneous nature of lung injury in ARDS, one could reason that biomarker levels may be better indicators of the need for reintubation than a clinical assessment following a 2 hour SBT or PaO2/FiO2 ratio. The clinical utility of a more sensitive marker of ARDS progression is certainly applicable to our daily practice of weaning assessment. For instance, an obese patient with atelectasis may not meet the FiO2 or PEEP criteria for weaning, however if they had biomarker values suggestive of improvement in their underlying lung damage they could benefit from early weaning despite not meeting the criteria currently in use. Moreover, high biomarker levels in a patient with difficulty weaning from the ventilator could help confirm that the driving etiology is persistent underlying lung damage as opposed to other myriad variables including sedation effects, hemodynamic status, or fluid overload.

Higher day 3 plasma biomarker concentrations were associated with decreased odds of passing both weaning assessment and SBT. Indeed, there was a decreasing likelihood of successful weaning assessment or SBT as biomarker quartile increased. This suggests a stepwise relationship between increasing biomarker levels and decreased odds of passing a weaning assessment and SBT. These findings suggest that threshold levels of a biomarker might be usefully applied for clinical prediction of weaning readiness.

We acknowledge important limitations to our findings. First, our analysis is performed primarily on the day 3 timepoint of the study, approximately 72–96 hours after enrollment. While this is an important period in the time course of ARDS, the ability to fully evaluate the relationship of biomarkers with the capacity to wean ventilation would require analysis at multiple time points. In addition, as this study is purely observational, the decisions to proceed with weaning were made according to the clinical protocol and limit the ability to

determine what the results would have been if biomarkers levels were combined with clinical assessment during an SBT. Given the retrospective design of this study, further prospective trials are required to determine the clinical implications of biomarker-tailored liberation from mechanical ventilation. Evaluations of the relationship between biomarker levels and ventilator weaning on serial days at multiple time points are needed. If these relationships are confirmed and threshold levels for these biomarkers can be established, efforts could be focused on development of readily available point-of-care assays, and clinical trials could be planned which compare biomarker-guided weaning to weaning based on conventional/physiologic parameters. The commercial availability of immunoassays for these biomarkers will facilitate the conduct of confirmatory trials.

CONCLUSION

Higher sST2 and IL-6 concentrations are significantly associated with fewer VFD and decreased odds of passing a weaning assessment and SBT. Higher concentrations are associated with failed extubation and this need for reintubation was not predicted by PaO2/FiO2 ratio, which is part of the current standard of weaning assessment. Therefore, biomarker guided weaning in ARDS could better inform clinicians about the status of underlying lung injury and cardiovascular reserve and offer a threshold for readiness of extubation.

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REFERENCES

1. Mancebo J. Weaning from mechanical ventilation. Eur Respir J. 1996; 9:1923–1931. [PubMed: 8880113]
2. Esteban A, Alía I, Ibañez J, et al. Modes of mechanical ventilation and weaning. A national survey of Spanish hospitals. The Spanish Lung Failure Collaborative Group. Chest. 1994; 106:1188–1193. [PubMed: 7924494]
3. Kress JP, Pohlman AS, O'Connor MF, et al. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. N Engl J Med. 2000; 342:1471–1477. [PubMed: 10816184]
4. Esteban A, Alía I, Tobin MJ, et al. Effect of spontaneous breathing trial duration on outcome of attempts to discontinue mechanical ventilation. Spanish Lung Failure Collaborative Group. Am J Respir Crit Care Med. 1999; 159:512–518. [PubMed: 9927366]
5. Esteban A, Alía I, Gordo F, et al. Extubation outcome after spontaneous breathing trials with T-tube or pressure support ventilation. The Spanish Lung Failure Collaborative Group. Am J Respir Crit Care Med. 1997; 156:459–465. [PubMed: 9279224]
6. Epstein SK, Ciubotaru RL, Wong JB. Effect of failed extubation on the outcome of mechanical ventilation. Chest. 1997; 112:186–192. [PubMed: 9228375]

7. Bajwa EK, Boyce PD, Januzzi JL, et al. Biomarker evidence of myocardial cell injury is associated with mortality in acute respiratory distress syndrome. Crit Care Med. 2007; 35:2484–2490. [PubMed: 18084839]
8. Schmitz J, Owyang A, Oldham E, et al. IL-33, an interleukin-1-like cytokine that signals via the IL-1 receptor-related protein ST2 and induces T helper type 2-associated cytokines. Immunity. 2005; 23:479–490. [PubMed: 16286016]
9. Weinberg EO, Shimpo M, De Keulenaer GW, et al. Expression and regulation of ST2, an interleukin-1 receptor family member, in cardiomyocytes and myocardial infarction. Circulation. 2002; 106:2961–2966. [PubMed: 12460879]
10. Sabatine MS, Morrow DA, Higgins LJ, et al. Complementary roles for biomarkers of biomechanical strain ST2 and N-terminal prohormone B-type natriuretic peptide in patients with ST-elevation myocardial infarction. Circulation. 2008; 117:1936–1944. [PubMed: 18378613]
11. Pascual-Figal DA, Manzano-Fernández S, Boronat M, et al. Soluble ST2, high-sensitivity troponin T- and N-terminal pro-B-type natriuretic peptide: complementary role for risk stratification in acutely decompensated heart failure. Eur J Heart Fail. 2011; 13:718–725. [PubMed: 21551163]
12. Tajima S, Oshikawa K, Tominaga S, et al. The increase in serum soluble ST2 protein upon acute exacerbation of idiopathic pulmonary fibrosis. Chest. 2003; 124:1206–1214. [PubMed: 14555548]
13. Bajwa EK, Volk JA, Christiani DC, et al. Prognostic and diagnostic value of plasma soluble suppression of tumorigenicity-2 concentrations in acute respiratory distress syndrome. Crit Care Med. 2013; 41:2521–2531. [PubMed: 23939353]
14. Jawa RS, Anillo S, Huntoon K, et al. Analytic review: Interleukin-6 in surgery, trauma, and critical care: part I: basic science. J Intensive Care Med. 2011; 26:3–12. [PubMed: 21262749]
15. Takala A, Jousela I, Takkunen O, et al. A prospective study of inflammation markers in patients at risk of indirect acute lung injury. Shock Augusta Ga. 2002; 17:252–257.
16. Meduri GU, Headley S, Kohler G, et al. Persistent elevation of inflammatory cytokines predicts a poor outcome in ARDS. Plasma IL-1 beta and IL-6 levels are consistent and efficient predictors of outcome over time. Chest. 1995; 107:1062–1073. [PubMed: 7705118]
17. Goldman JL, Sammani S, Kempf C, et al. Pleiotropic effects of interleukin-6 in a “two-hit” murine model of acute respiratory distress syndrome. Pulm Circ. 2014; 4:280–288. [PubMed: 25006447]
18. Wiedemann HP, Wheeler AP, et al. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Comparison of two fluid-management strategies in acute lung injury. N Engl J Med. 2006; 354:2564–2575. [PubMed: 16714767]
19. Kerr KF, Wang Z, Janes H, et al. Net Reclassification Indices for Evaluating Risk-Prediction Instruments: A Critical Review. Epidemiol Camb Mass. 2014; 25:114–121.
20. Armand D, et al. Natriuretic Peptide–driven Fluid Management during Ventilator Weaning. AJRCCM. 2012; 186:1256–1263.
21. McConville JF, Kress JP. Weaning patients from the ventilator. N Engl J Med. 2012; 367:2233–2239. [PubMed: 23215559]
22. MacIntyre NR, Cook DJ, Ely EW, et al. Evidence-based guidelines for weaning and discontinuing ventilatory support: a collective task force facilitated by the American College of Chest Physicians; the American Association for Respiratory Care; and the American College of Critical Care Medicine. Chest. 2001; 120:375S–395S. [PubMed: 11742959]
23. Yang KL, Tobin MJ. A prospective study of indexes predicting the outcome of trials of weaning from mechanical ventilation. N Engl J Med. 1991; 324:1445–1450. [PubMed: 2023603]
24. Tanios MA, Nevins ML, Hendra KP, et al. A randomized, controlled trial of the role of weaning predictors in clinical decision making. Crit Care Med. 2006; 34:2530–2535. [PubMed: 16878032]
25. Seneff MG, Zimmerman JE, Knaus WA, et al. Predicting the duration of mechanical ventilation. The importance of disease and patient characteristics. Chest. 1996; 110:469–479. [PubMed: 8697853]
26. Estenssoro E, González F, Laffaire E, et al. Shock on admission day is the best predictor of prolonged mechanical ventilation in the ICU. Chest. 2005; 127:598–603. [PubMed: 15706002]
27. Sapijaszko MJ, Brant R, Sandham D, et al. Nonrespiratory predictor of mechanical ventilation dependency in intensive care unit patients. Crit Care Med. 1996; 24:601–607. [PubMed: 8612410]

28. Meade M, Guyatt G, Cook D, et al. Predicting success in weaning from mechanical ventilation. Chest. 2001; 120:400S–424S. [PubMed: 11742961]
29. Figueroa-Casas JB, Connery SM, Montoya R, et al. Accuracy of early prediction of duration of mechanical ventilation by intensivists. Ann Am Thorac Soc. 2014; 11:182–185. [PubMed: 24069941]
30. Girard TD, Kress JP, Fuchs BD, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. Lancet Lond Engl. 2008; 371:126–134.
31. Januzzi JL, Peacock WF, Maisel AS, et al. Measurement of the interleukin family member ST2 in patients with acute dyspnea: results from the PRIDE (Pro-Brain Natriuretic Peptide Investigation of Dyspnea in the Emergency Department) study. J Am Coll Cardiol. 2007; 50:607–613. [PubMed: 17692745]
32. Rehman SU, Mueller T, Januzzi JL. Characteristics of the novel interleukin family biomarker ST2 in patients with acute heart failure. J Am Coll Cardiol. 2008; 52:1458–1465. [PubMed: 19017513]
33. Martinez-Rumayor A, Camargo CA, Green SM, et al. Soluble ST2 plasma concentrations predict 1-year mortality in acutely dyspneic emergency department patients with pulmonary disease. Am J Clin Pathol. 2008; 130:578–584. [PubMed: 18794051]
34. Bajwa EK, Mebazaa A, Januzzi JL. ST2 in Pulmonary Disease. Am J Cardiol. 2015; 115:44B–47B.
35. Jawa RS, Anillo S, Huntoon K, et al. Interleukin-6 in surgery, trauma, and critical care part II: clinical implications. J Intensive Care Med. 2011; 26:73–87. [PubMed: 21464062]
36. Slutsky AS, Ranieri VM. Ventilator-induced lung injury. N Engl J Med. 2013; 369:2126–2136. [PubMed: 24283226]
37. Gattinoni L, Caironi P, Pelosi P, et al. What has computed tomography taught us about the acute respiratory distress syndrome? Am J Respir Crit Care Med. 2001; 164:1701–1711. [PubMed: 11719313]

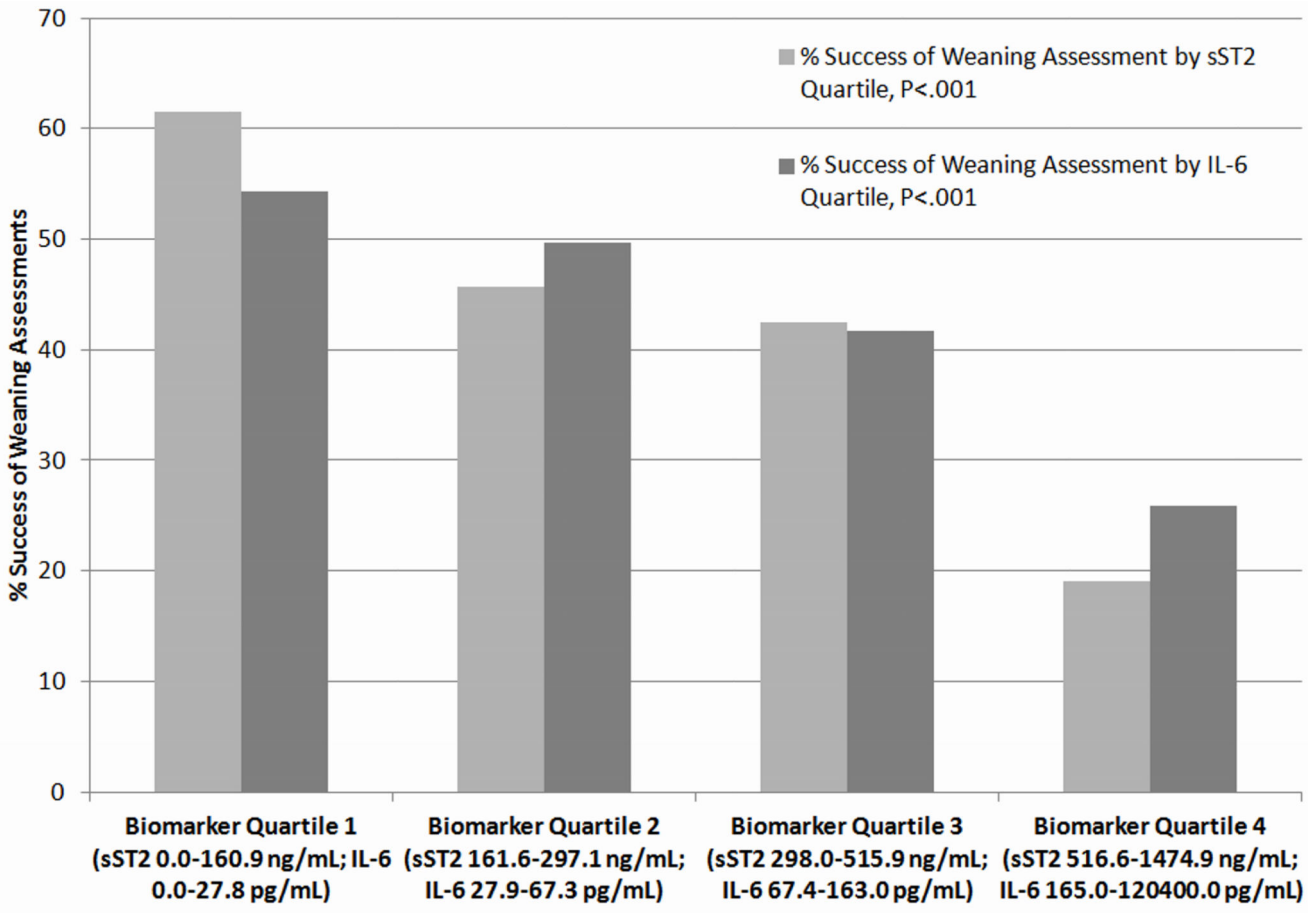

Figure 1.
Success of day 3 weaning assessments according to day 3 biomarker quartiles (N=605)

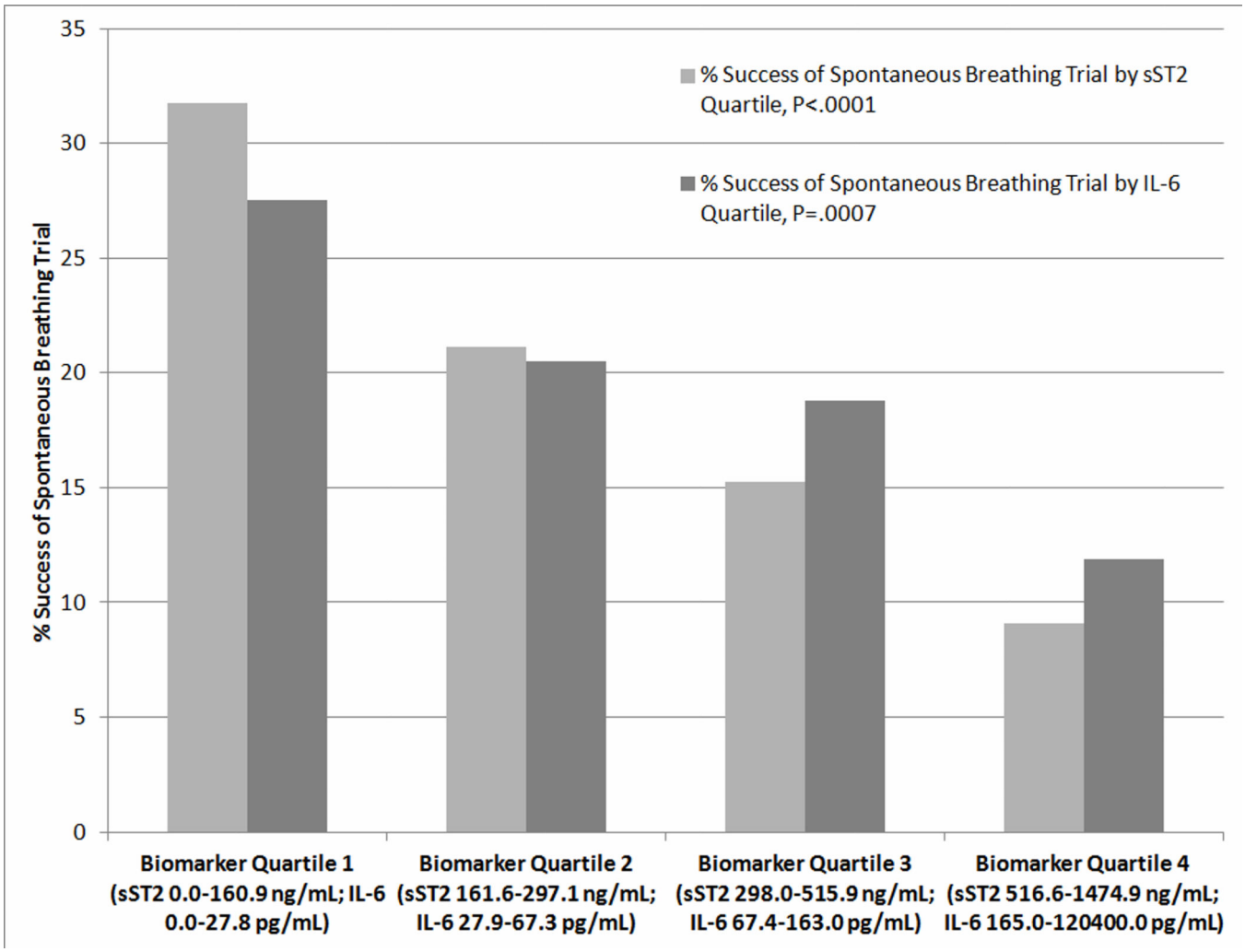

Figure 2.
Success of day 3 spontaneous breathing trials by day 3 biomarker quartiles (N=333)

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Table 1

Demographics and baseline characteristics of the study population, grouped by sST2 and IL-6 values

Variable*	Day 0 sST2 below median (n=413)	Day 0 sST2 above median (n=413)	*P*	Day 0 IL-6 below median (n=378)	Day 0 IL-6 above median (n=377)	*P*
Age (yr)	49 (38–59)	49 (39–60)	.62	49 (39–59)	49 (38–61)	.90
Female Gender (%)	45%	47%	.53	47%	47%	.52
Caucasian race (%)	68%	63%	.19	65%	67%	.56
APACHE III score	80 (63–100)	99 (80–123)	<.0001	83 (64–106)	95 (74–118)	<.0001
ARDS risk factor (%) **						
-Sepsis	67%	72%	.10	68%	70%	.49
-Pneumonia	48%	44%	.21	42%	51%	.02
-Trauma	10%	6%	.01	8%	8%	.89
-Multiple Transfusions	1%	1%	.48	1%	0%	.18
-Aspiration	16%	14%	.50	18%	14%	.11
Coexisting conditions (%)						
-Diabetes	19%	18%	.74	19%	19%	.99
-HIV infection/AIDS	7%	7%	.09	10%	5%	.006
-Cirrhosis	4%	3%	.84	3%	4%	.45
-Solid tumors	2%	2%	1.00	1%	2%	.38
-Leukemia	1%	3%	.11	2%	2%	.98
-Lymphoma	1%	2%	.76	1%	1%	.98
-Immunosuppression	8%	8%	.80	10%	6%	.03

*Continuous variables are presented as median (25%–75% interquartile range)

**Percentages do not add up to 100% because it was possible for patients to have multiple ARDS risk factors.

Table 2

Cox Proportional Hazards Models with probability of extubation as outcome

Model 1: Day 0 Biomarkers (N=725)				
Variable	**Hazard Ratio**	**95% Confidence Intervals**		***P***
Day 0 IL-6 level above median	0.65	0.55	0.77	<.0001
Day 0 sST2 level above median	1.00	0.85	1.20	.97
Age (per year)	1.00	0.99	1.01	.62
APACHE III (per point)	0.99	0.99	1.00	.001
Pneumonia	0.83	0.70	0.99	.04
Trauma	0.66	0.48	0.90	.008
Model 2: Day 3 Biomarkers (N=724)				
Variable	**Hazard Ratio**	**95% Confidence Intervals**		***P***
Day 3 IL-6 level above median	0.55	0.46	0.65	<.0001
Day 3 sST2 level above median	0.80	0.68	0.95	<.0001
Age (per year)	1.00	0.99	1.00	.07
Brussels score (per point)	0.86	0.82	0.89	<.0001
Pneumonia	0.81	0.68	0.96	.02
Trauma	0.86	0.63	1.17	.33
Immunosuppression	0.88	0.62	1.25	0.49

Table 3

Logistic Regression Model with odds of passing day 3 weaning assessment as outcome (N=625)

Variable	Odds Ratio	95% Confidence Intervals		Coefficient	*P*
Day 3 IL-6 level above median	0.59	0.41	0.83	−0.53	.003
Day 3 sST2 level above median	0.63	0.44	0.90	−0.47	.01
Age (per year)	1.01	1.00	1.02	0.01	.14
Brussels score (per point)	0.75	0.68	0.81	−0.29	<.0001
Pneumonia	0.59	0.41	0.83	−0.53	.002

Table 4

Association of biomarker levels with subsequent successful 2-hour spontaneous breathing trial (N=333)

Variable	Odds Ratio	95% Confidence Intervals		Coefficient	*P*
Day 3 IL-6 level above median	0.74	0.47	1.15	−0.31	0.17
Day 3 sST2 level above median	0.46	0.29	0.75	−0.77	0.002
Age (per year)	1.00	0.99	1.02	0.003	0.65
Brussels score (per point)	0.78	0.70	0.87	−0.25	<.0001

Table 5

Net reclassification indices for multivariable models

Model	% of events correctly reclassified	% of non-events correctly reclassified	Net Reclassification Improvement (95% CI)	NRI P-value
Day 0 Probability of Extubation (Table 2, Model 1)	55%	−59%	−0.04 (−0.19–0.11)	.69
Day 3 Probability of Extubation (Table 2, Model 2)	34%	31%	0.61 (0.44–0.79)	<.0001
Day 3 Weaning Assessment (Table 3)	14%	2%	0.16 (0.01–0.31)	.04
Day 3 Spontaneous Breathing Trial (Table 4)	20%	18%	0.38 (0.17–0.58)	.0004