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Outcomes Associated with Corticosteroid Dosage in Critically Ill Patients with Acute Exacerbations of Chronic Obstructive Pulmonary Disease

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■ Abstract

- **Rationale:** Studies evaluating corticosteroid (CS) dosing for patients hospitalized with an acute exacerbation of chronic obstructive pulmonary disease (AECOPD) have largely excluded patients admitted directly to the intensive care unit (ICU), and none have evaluated the effect of CS dosing regimens on mortality.
- **Objectives:** To examine the effectiveness and safety of **lower- versus high-dose CS** in patients admitted to the ICU with an AECOPD.
- **Methods:** This pharmacoepidemiologic cohort study evaluated ICU patients with AECOPD admitted to one of 473 hospitals and treated with CS within the first 2 days between January 1, 2003 and December 31, 2008. Patients were grouped into lower-dose (methylprednisolone, **≤240 mg/d**) or high-dose (methylprednisolone, >240 mg/d) groups based on CS dosage on hospital Day 1 or 2. The primary outcome was hospital mortality.

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- **Measurements and Main Results:** A total of 17,239 patients were included; 6,156 (36%) were in the lower-dose and 11,083 (64%) in the high-dose CS group. After propensity score matching and adjustment for unbalanced covariates, **lower-dose CS was not associated with a significant reduction in mortality** (odds ratio, 0.85; 95% confidence interval [CI], 0.71–1.01; $P = 0.06$), but it was associated with **reduced hospital** (–0.44 d; 95% CI, –0.67 to –0.21; $P < 0.01$) **and ICU** (–0.31 d; 95% CI, –0.46 to –0.16; $P < 0.01$) **length-of-stay, hospital costs** (–\$2,559; 95% CI, –\$4,508 to –\$609; $P = 0.01$), **length of invasive ventilation** (–0.29 d; 95% CI, –0.52 to –0.06; $P = 0.01$), **need for insulin therapy** (22.7% vs. 25.1%; $P < 0.01$), **and fungal infections** (3.3% vs. 4.4%; $P < 0.01$).

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- **Conclusions:** Two-thirds of patients admitted to the ICU with an AECOPD are treated with high doses of CS that are associated with worse outcomes and more frequent adverse effects. **Lower dosage strategies should be encouraged for patients admitted to the ICU and the optimum dose should be determined through clinical trials.**

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Risk of Cardiovascular Events in Survivors of Severe Sepsis

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- **Abstract**
- **Rationale:** The risk of **cardiovascular events** after severe sepsis is not known, and these events may explain **increased long-term mortality** in survivors of severe sepsis.
- **Objectives:** To determine whether survivors of severe sepsis hospitalization have high long-term risk of cardiovascular events. We examined whether higher risk is due to severe sepsis hospitalization or poor prehospitalization health status, and if the higher risk is also observed in patients hospitalized for infectious and noninfectious reasons, and in other critically ill patients.

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- **Methods:** Unmatched and matched-cohort analyses of Medicare beneficiaries. For unmatched analysis, we compared patients with severe sepsis admitted to the intensive care unit (ICU) and survived hospitalization ($n = 4,179$) to unmatched population control subjects ($n = 819,283$). For matched analysis, we propensity-score-matched each patient with severe sepsis to four control subjects (population, hospitalized, non-severe sepsis ICU control subjects, and infection hospitalization). Primary outcome was 1-year incidence rate of hospitalization for cardiovascular events.

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- **Measurements and Main Results:** Cardiovascular events were common among patients discharged alive after severe sepsis hospitalization (29.5%; 498.2 events/1,000 person-years). Survivors of severe sepsis had a 13-fold higher risk of cardiovascular events compared with unmatched control subjects (498.2 vs. 36 events/1,000 person-years; $P < 0.0001$), and a 1.9-fold higher risk compared with matched-population control subjects ($P < 0.0001$). Survivors of severe sepsis had 1.1-fold higher risk compared with matched hospitalized patients and infection hospitalizations ($P = 0.002$ and 0.001) and similar risk compared with matched-ICU control subjects.

Conclusions: Survivors of severe sepsis **have high risk of cardiovascular events.** The higher risk is mainly due to poor prehospitalization health status, and is also seen in a broader population of acutely ill patients.

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Small Acute Increases in Serum Creatinine Are Associated with Decreased Long-Term Survival in the Critically Ill

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- **Abstract**
- **Rationale:** Long-term outcomes after acute kidney injury (AKI) are poorly described.
- **Objectives:** We hypothesized that one single episode of minimal (stage 1) AKI is associated with reduced long-term survival compared with no AKI after recovery from critical illness.
- **Methods:** A prospective cohort of 2,010 intensive care unit (ICU) patients admitted to the ICU between years 2000 and 2009 at a provincial tertiary care hospital. Development of AKI was determined according to the KDIGO classification and mortality up to 10 years after ICU admission was recorded.

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- **Measurements and Main Results:** Of the 1,844 eligible patients, 18.4% had AKI stage 1, 12.1% had stage 2, 26.5% had stage 3, and 43.0% had no AKI. The 28-day, 1-year, 5-year, and 10-year survival rates were 67.1%, 51.8%, 44.1%, and 36.3% in patients with mild AKI, which was significantly worse compared with the critically ill patients with no AKI at any time ($P < 0.01$). The unadjusted 10-year mortality hazard ratio was 1.53 (95% confidence interval, 1.2–2.0) for 28-day survivors with stage 1 AKI compared with critically ill patients with no AKI. Adjusted 10-year mortality risk was 1.26 (1.0–1.6). After propensity matching stage 1 AKI with no AKI patients, mild AKI was still significantly associated with decreased 10-year survival ($P = 0.036$).

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- **Conclusions:** Patients with one episode of mild AKI have significantly **lower long-term survival rates** than critically ill patients with no AKI. Close medical follow-up of these patients may be warranted and mechanistic research is required to understand how AKI influences long-term events.

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Association between Source of Infection and Hospital Mortality in Patients Who Have Septic Shock

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■ Abstract

- **Rationale:** Mortality caused by septic shock may be determined by a systemic inflammatory response, independent of the inciting infection, but it may also be influenced by the **anatomic source of infection**.
- **Objectives:** To determine the association between the anatomic source of infection and hospital mortality in critically ill patients who have septic shock.
- **Methods:** This was a retrospective, multicenter cohort study of 7,974 patients who had septic shock in 29 academic and community intensive care units in Canada, the United States, and Saudi Arabia from January 1989 to May 2008.

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- **Measurements and Main Results:** Subjects were assigned 1 of 20 anatomic sources of infection based on clinical diagnosis and/or isolation of pathogens. The primary outcome was hospital mortality. Overall crude hospital mortality was 52% (21–85% across sources of infection). Variation in mortality remained after adjusting for year of admission, geographic source of admission, age, sex, comorbidities, community- versus hospital-acquired infection, and organism type. The source of infection with the highest standardized hospital mortality was **ischemic bowel** (75%); the lowest was **obstructive uropathy–associated urinary tract infection** (26%). Residual variation in adjusted hospital mortality was not explained by Acute Physiology and Chronic Health Evaluation II score, number of Day 1 organ failures, bacteremia, appropriateness of empiric antimicrobials, or adjunct therapies. In patients who received appropriate antimicrobials after onset of hypotension, source of infection was associated with death after adjustment for both predisposing and downstream factors.

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Risk Factors for Physical Impairment after Acute Lung Injury in a National, Multicenter Study

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Conclusions: Patients had substantial impairments, from predicted values, for 6-minute-walk distance and SF-36 Physical Function outcome measures. **Minimizing corticosteroid** dose and implementing existing evidence-based methods to **reduce duration of intensive care unit stay** and associated patient immobilization may be important interventions for **improving ALI survivors' physical outcomes**.

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Reduction of Bacterial Resistance with Inhaled Antibiotics in the Intensive Care Unit

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■ Abstract

- **Rationale:** Multidrug-resistant organisms (MDRO) are the dominant airway pathogens in the intensive care unit (ICU) and present a major treatment challenge to intensivists. **Aerosolized antibiotics** (AA) result in airway concentrations of drug 100-fold greater than the minimal inhibitory concentration of most bacteria including MDRO. These levels, without systemic toxicity, may eradicate MDRO and reduce the pressure for selection of new resistant organisms.
- **Objectives:** To determine if AA effectively eradicate MDRO in the intubated patient without promoting new resistance.
- **Methods:** In a double-blind placebo-controlled study, critically ill **intubated** patients were randomized if they exhibited signs of **respiratory infection** (purulent secretions and Clinical Pulmonary Infection Score ≥ 6). Using a well-characterized aerosol delivery system, AA or saline placebo was given for 14 days or until extubation. The responsible clinician determined administration of systemic antibiotics for ventilator-associated pneumonia and any other infection.

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- **Measurements and Main Results:** AA eradicated 26 of 27 organisms present at randomization compared with 2 of 23 organisms with placebo ($P < 0.0001$). AA eradicated the original resistant organism on culture and Gram stain at end of treatment in 14 out of 16 patients compared with 1 of 11 for placebo ($P < 0.001$). New drug resistance to AA was not seen. Compared with AA, resistance to systemic antibiotics significantly increased in placebo patients ($P = 0.03$). Compared with placebo, AA significantly reduced Clinical Pulmonary Infection Score (mean \pm SEM, 9.3 ± 2.7 to 5.3 ± 2.6 vs. 8.0 ± 2.3 to 8.6 ± 2.10 ; $P = 0.0008$).
- **Conclusions:** In chronically intubated critically ill patients, AA successfully **eradicated existing MDRO** organisms and **reduced** the pressure from systemic agents for **new respiratory resistance**.

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Predicting Survival after Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Failure. The Respiratory Extracorporeal Membrane Oxygenation Survival Prediction (RESP) Score

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Conclusions: The **RESP score** is a relevant and validated tool to predict survival for patients receiving ECMO for respiratory failure.

Propofol Is Associated with Favorable Outcomes Compared with Benzodiazepines in Ventilated Intensive Care Unit Patients

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- **Rationale:** Mechanically ventilated intensive care unit (ICU) patients are frequently managed using a continuous-infusion sedative. Although recent guidelines suggest avoiding benzodiazepines for sedation, this class of drugs is still widely used. There are limited data comparing sedative agents in terms of **clinical outcomes** in an ICU setting.
- **Objectives:** Comparison of **propofol** to **midazolam** and **lorazepam** in adult ICU patients.
- **Methods:** Data were obtained from a multicenter ICU database (2003–2009). Patient selection criteria included age greater than or equal to 18 years, single ICU admission with single ventilation event (>48 h), and treatment with continuously infused sedation (propofol, midazolam, or lorazepam). Propensity score analysis (1:1) was used and mortality measured. Cumulative incidence and competing risk methodology were used to examine time to ICU discharge and ventilator removal.

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- **Measurements and Main Results:** There were 2,250 propofol-midazolam and 1,054 propofol-lorazepam matched patients. **Hospital mortality** was statistically **lower in propofol-treated patients** as compared with midazolam- or lorazepam-treated patients (risk ratio, 0.76; 95% confidence interval [CI], 0.69–0.82 and risk ratio, 0.78; 95% CI, 0.68–0.89, respectively). Competing risk analysis for 28-day ICU time period showed that **propofol-treated patients had a statistically higher probability for ICU discharge** (78.9% vs. 69.5%; 79.2% vs. 71.9%; $P < 0.001$) and **earlier removal from the ventilator** (84.4% vs. 75.1%; 84.3% vs. 78.8%; $P < 0.001$) when compared with midazolam- and lorazepam-treated patients, respectively.
- **Conclusions:** In this large, propensity-matched ICU population, patients treated with **propofol had a reduced risk of mortality and had both an increased likelihood of earlier ICU discharge and earlier discontinuation of mechanical ventilation.**

Endothelial Progenitor Cells and a Stromal Cell-derived Factor-1 α Analogue Synergistically Improve Survival in Sepsis

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Conclusions: EPCs and CTCE represent important potential therapeutic strategies in sepsis.

Keratinocyte Growth Factor Promotes Epithelial Survival and Resolution in a Human Model of Lung Injury

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Conclusions: KGF treatment **increases BAL surfactant protein D**, a marker of type II alveolar epithelial cell proliferation in a human model of acute lung injury. Additionally, KGF **increases** alveolar concentrations of the **antiinflammatory cytokine IL-1Ra**, and mediators that **drive epithelial repair** (MMP-9) and **enhance macrophage clearance of dead cells and bacteria** (GM-CSF).

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Increased 1-Year Healthcare Use in Survivors of Severe Sepsis

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- **Rationale:** Hospitalizations for severe sepsis are common, and a growing number of patients survive to hospital discharge. Nonetheless, **little is known** about survivors' **post-discharge healthcare use**.
- **Objectives:** To measure **inpatient healthcare** use of severe sepsis survivors compared with patients' **own presepsis resource** use and the resource use of survivors of **otherwise similar nonsepsis hospitalizations**.
- **Methods:** This is an observational cohort study of survivors of severe sepsis and nonsepsis hospitalizations identified from participants in the Health and Retirement Study with linked Medicare claims, 1998–2005. We matched severe sepsis and nonsepsis hospitalizations by demographics, comorbidity burden, premorbid disability, hospitalization length, and intensive care use.

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- **Measurements and Main Results:** Using Medicare claims, we measured patients' use of inpatient facilities (hospitals, long-term acute care hospitals, and skilled nursing facilities) in the 2 years surrounding hospitalization. **Severe sepsis survivors spent more days** (median, 16 [interquartile range, 3–45] vs. 7 [0–29]; $P < 0.001$) **and a higher proportion of days alive** (median, 9.6% [interquartile range, 1.4–33.8%] vs. 1.9% [0.0–7.9%]; $P < 0.001$) **admitted to facilities in the year after hospitalization**, compared with the year prior. The increase in facility-days was similar for nonsepsis hospitalizations. However, **the severe sepsis cohort experienced greater post-discharge mortality** (44.2% [95% confidence interval, 41.3–47.2%] vs. 31.4% [95% confidence interval, 28.6–34.2%] at 1 year), a steeper **decline in days spent at home** (difference-in-differences, -38.6 d [95% confidence interval, -50.9 to 26.3]; $P < 0.001$), and a greater **increase in the proportion of days alive spent in a facility** (difference-in-differences, 5.4% [95% confidence interval, 2.8–8.1%]; $P < 0.001$).

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- **Conclusions:** Healthcare use is **markedly elevated** after severe sepsis, and **post-discharge management** may be **an opportunity** to **reduce resource use**.

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Oxygenation Response to Positive End-Expiratory Pressure Predicts Mortality in Acute Respiratory Distress Syndrome. A Secondary Analysis of the LOVS and ExPress Trials

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- **Rationale:** Previous trials of higher positive end-expiratory pressure (PEEP) for acute respiratory distress syndrome (ARDS) failed to demonstrate mortality benefit, possibly because of differences in lung recruitability among patients with ARDS.
- **Objectives:** To determine whether the physiological response to **increased PEEP** is associated with **mortality**.
- **Methods:** In a secondary analysis of the Lung Open Ventilation Study (LOVS, n = 983), we examined the relationship between the initial **response to changes in PEEP** after randomization and **mortality**. We sought to corroborate our findings using data from a different trial of higher PEEP (ExPress, n = 749).

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- **Measurements and Main Results:** The oxygenation response (change in ratio of arterial partial pressure of oxygen to fraction of inspired oxygen: P/F) after the initial change in PEEP after randomization varied widely (median, 9.5 mm Hg; interquartile range, -16 to 47) and was **only weakly related to baseline P/F or the magnitude of PEEP change**. Among patients in whom PEEP was increased after randomization, **an increase in P/F was associated with reduced mortality** (multivariable logistic regression; adjusted odds ratio, 0.80 [95% confidence interval, 0.72–0.89] per 25-mm Hg increase in P/F), particularly in patients with severe disease (baseline P/F [less-than-or-equal-to] 150 mm Hg). Changes in compliance and dead space were **not** associated with mortality. These findings were confirmed by a similar analysis of data from the ExPress trial.

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- **Conclusions:** Patients with ARDS who respond to **increased PEEP by improved oxygenation** have **a lower risk of death**. The oxygenation response to PEEP might be used to **predict** whether patients will benefit from higher versus lower PEEP.

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Respiratory Syncytial Virus Increases the Virulence of *Streptococcus pneumoniae* by Binding to Penicillin Binding Protein 1a. A New Paradigm in Respiratory Infection

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- **Conclusions:** The direct interaction between a **respiratory virus protein** and the **pneumococcus** resulting in **increased bacterial virulence** and **worsening disease outcome** is a **new paradigm** in respiratory infection.

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Nasal High-Flow versus Venturi Mask Oxygen Therapy after Extubation. Effects on Oxygenation, Comfort, and Clinical Outcome

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VOLUME 190, ISSUE 3 (AUGUST 1, 2014)

■ Abstract

- **Rationale:** Oxygen is commonly administered after extubation. Although **several devices** are available, data about their **clinical efficacy** are **scarce**.
- **Objectives:** To compare the effects of the **Venturi mask** and the **nasal high-flow (NHF)** therapy on **Pa_{O_2}/FI_{O_2SET} ratio** after extubation. Secondary endpoints were to assess effects on **patient discomfort, adverse events, and clinical outcomes**.
- **Methods:** Randomized, controlled, open-label trial on 105 patients with a **Pa_{O_2}/FI_{O_2} ratio less than or equal to 300** immediately before extubation. The Venturi mask (n = 52) or NHF (n = 53) were applied for 48 hours postextubation.

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- **Measurements and Main Results:** Pa_{O_2}/FI_{O_2SET} , patient discomfort caused by the interface and by symptoms of airways dryness (on a 10-point numerical rating scale), interface displacements, oxygen desaturations, need for ventilator support, and reintubation were assessed up to 48 hours after extubation. From the **24th hour**, Pa_{O_2}/FI_{O_2SET} was higher with the NHF (287 ± 74 vs. 247 ± 81 at 24 h; $P = 0.03$). Discomfort related both to the interface and to airways dryness was better with NHF (respectively, 2.6 ± 2.2 vs. 5.1 ± 3.3 at 24 h, $P = 0.006$; 2.2 ± 1.8 vs. 3.7 ± 2.4 at 24 h, $P = 0.002$). **Fewer patients** had interface displacements (32% vs. 56%; $P = 0.01$), oxygen desaturations (40% vs. 75%; $P < 0.001$), required reintubation (4% vs. 21%; $P = 0.01$), or any form of ventilator support (7% vs. 35%; $P < 0.001$) **in the NHF group**.

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- **Conclusions:** Compared with the Venturi mask, **NHF** results in **better** oxygenation for the same set FI_{O_2} after extubation. Use of NHF is associated with better comfort, fewer desaturations and interface displacements, and a lower reintubation rate.

Acute Outcomes and 1-Year Mortality of Intensive Care Unit-acquired Weakness. A Cohort Study and Propensity-matched Analysis

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- **Abstract**
- **Rationale:** Intensive care unit (ICU)-acquired **weakness** is a frequent complication of critical illness. It is unclear **whether it is a marker or mediator of poor outcomes**.
- **Objectives:** To determine **acute outcomes, 1-year mortality,** and **costs** of ICU-acquired weakness among long-stay (≥ 8 d) ICU patients and to assess the impact of recovery of weakness at ICU discharge.
- **Methods:** Data were prospectively collected during a randomized controlled trial. Impact of weakness on outcomes and costs was analyzed with a **one-to-one propensity-score-matching for baseline characteristics, illness severity, and risk factor exposure before assessment.** Among weak patients, impact of persistent weakness at ICU discharge on risk of death after 1 year was examined with multivariable Cox proportional hazards analysis.

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- **Measurements and Main Results:** A total of 78.6% were admitted to the surgical ICU; 227 of 415 (55%) long-stay assessable ICU patients were weak; 122 weak patients were matched to 122 not-weak patients. As compared with matched not-weak patients, weak patients had a lower likelihood for live weaning from mechanical ventilation (hazard ratio [HR], 0.709 [0.549–0.888]; $P = 0.009$), live ICU (HR, 0.698 [0.553–0.861]; $P = 0.008$) and hospital discharge (HR, 0.680 [0.514–0.871]; $P = 0.007$). In-hospital costs per patient (+30.5%, +5,443 Euro per patient; $P = 0.04$) and 1-year mortality (30.6% vs. 17.2%; $P = 0.015$) were also higher. The 105 of 227 (46%) weak patients not matchable to not-weak patients had even worse prognosis and higher costs. The 1-year risk of death was further increased if weakness persisted and was more severe as compared with recovery of weakness at ICU discharge ($P < 0.001$).

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- **Conclusions:** After careful matching the data suggest that ICU-acquired weakness **worsens acute morbidity** and **increases healthcare-related costs** and **1-year mortality**. Persistence and severity of weakness at ICU discharge further increased 1-year mortality.

Thank You!

