APPENDIX

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Supplemental Methods

Data sources

Patients with suspected inhalation injury were identified using the burn registry maintained by HMC, and the inclusion and exclusion criteria in the main manuscript were applied to restrict to the study cohort. Demographic and standard clinical data were automatically extracted from the registry (e.g., age, sex, injury characteristics, mechanical ventilator days, death). Manual review of the electronic medical record was subsequently performed to extract additional clinical data including medical comorbidities, bronchoscopy findings including injury grade, microbiological data including admission bronchoalveolar lavage (BAL) bacterial growth, and diagnosis of VAP using criteria in Table E1.

Outcome measures

The main outcome was the first occurrence of ventilator-associated pneumonia (VAP). Secondary outcomes included hospital mortality, ventilator-free days (VFDs), and hospital length of stay (LOS).

HMC has adopted an invasive sampling approach to diagnose VAP, most commonly using bronchoscopy in mechanically ventilated patients with clinical features suggestive of respiratory infection. The diagnosis of VAP after at least 48 hours of mechanical ventilation for this study was adapted from the Center for Disease Control PNU2 criteria (Table E1).[1]

For secondary outcomes, mortality was defined as death prior to hospital discharge or transfer from HMC (e.g., to a skilled nursing facility). Hospital LOS was defined as the number of days

between admission and hospital discharge among survivors to discharge. VFDs were defined as VFDs = 0 if the patient died within 28 days of mechanical ventilation, VFDs = 28 − *d* if successfully liberated from ventilation *d* days after initiation and remained free from mechanical ventilation on day 28, and VFDs = 0 if the patient remained mechanically ventilated on day 28, regardless of prior extubation and intubation events.[2] For patients discharged from the hospital after extubation prior to day 28, the patient was assumed to remain ventilator-free to day 28 and these days added to their score.

Missing data

There was no missing outcome data. For covariables, 10/231 (2%) patients were missing data for TBSA and the median TBSA value for the cohort was imputed. No patients had missing data for comorbidities, though many patients may have been too ill to report their comorbidities, which were thus not recorded in the electronic health record. Comorbidities were assumed to be absent if not indicated as present during chart review. There was no missing data for age.

Effect modification of inhalation injury on hospital mortality by burn size

Because cutaneous burns and inhalation injury likely influence mortality through different mechanisms but with unclear interactions, we tested the hypothesis that burn size measured by percent total body surface area burned (TBSA) would exhibit effect modification on the relationship of inhalation injury severity and hospital mortality. We hypothesized that at lower levels of TBSA, inhalation injury would be a strong driver of mortality, but at higher levels of TBSA the consequences of cutaneous burns would drive mortality and the effect of inhalation injury on mortality would be attenuated. To assess an interaction between TBSA and inhalation

injury severity, TBSA was first dichotomized to <20% and $\geq$ 20%, an arbitrary cutoff often used to distinguish severe burns from mild and moderate burns.[3] The number of subjects that did and did not experience in-hospital mortality are provided in table 4 in the main manuscript. Relative risks (RR) and confidence intervals (CI) were calculated for each stratum of inhalation injury severity and TBSA compared with a single reference category of low-grade (grade 1-2) inhalation injury and TBSA <20% (Table 4). These RRs were calculated using Poisson regression adjusting for age, sex, and comorbid obstructive lung disease and assuming robust standard errors. Next, RR of mortality with CIs were calculated for inhalation injury within strata of TBSA (final column of Table 4). Finally, the relative excess risk due to interaction (RERI), a measure of effect modification on the additive scale, was calculated.[4]

Supplemental Tables

Table E1. Ventilator-associated pneumonia diagnostic criteria adapted from Center for Disease Control PNU2[1]

Patient has **one of the following** found in two or more serial chest imaging test results*
• Infiltrate • Consolidation • Cavitation
AND patient has at least ***one*** of the following
• Body temperature > 38.3 °C • Leukocytes < 4000/mm^3 or > 12,000/mm^3
AND patient has at least ***one*** of the following
• New onset of purulent sputum or change in character of sputum (color, odor, quantity, consistency), or increased respiratory secretions, or increased suctioning requirements • Worsening gas exchange (e.g., O2 desaturation or increased oxygen requirement) • New onset or worsening tachypnea
AND patient has at least ***one*** of the following
• Isolation of a pathogen on bronchoalveolar lavage >10,000 colony-forming units per ml • Isolation of a pathogen on protected specimen brush >1,000 colony-forming units per ml[†]
* In a patient in whom only one imaging test is available, if the imaging finding is an eligible finding, the imaging test evidence requirement can be met. [†] In this study, no protected specimen brush was performed

References

1. CDC VAP diagnostic criteria. Published online January 2021.

2. Yehya N, Harhay MO, Curley MAQ, Schoenfeld DA, Reeder RW. Reappraisal of Ventilator-Free Days in Critical Care Research. *Am J Respir Crit Care Med*. 2019;200(7):828-836. doi:10.1164/rccm.201810-2050CP

3. Pham TN, Cancio LC, Gibran NS. American Burn Association Practice Guidelines Burn Shock Resuscitation. *Journal of Burn Care & Research*. 2008;29(1):257-266. doi:10.1097/BCR.0b013e31815f3876

4. Knol MJ, VanderWeele TJ. Recommendations for presenting analyses of effect modification and interaction. *International Journal of Epidemiology*. 2012;41(2):514-520. doi:10.1093/ije/dyr218