Severity of smoke inhalation injury and risk of ventilator-associated pneumonia: a retrospective cohort study

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Abstract

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Introduction: Inhalation injury is present in up to one-third of severe burn injuries and is a major contributor to burn-related mortality. Bronchoscopy is commonly performed within 48 hours of presentation to grade inhalation injury severity. Whether higher grade inhalation injury is associated with increased risk of ventilator-associated pneumonia (VAP), an important complication in patients with burn injury, is unknown.

Methods: We performed a retrospective cohort study of patients with suspected inhalation injury at a large American Burn Association-verified burn center from 2011-2022 who underwent diagnostic bronchoscopy within 48 hours of admission. Abbreviated injury severity score (AIS) was used to grade inhalation injury. VAP was defined using CDC PNU2 clinical criteria and isolation of a pathogenic organism from bronchoalveolar lavage fluid $\geq$10,000 CFU/ml after $\geq$48

hours of mechanical ventilation. Competing risk analysis was performed to estimate the association of high-grade (grades 3-4) inhalation injury versus low-grade (grades 1-2) inhalation injury with VAP. Death and extubation were considered competing risks. Poisson regression was performed to test for associations between inhalation injury severity and mortality.

Results: 231 patients were analyzed. Fifty-one (21%) had high-grade injury and 181 (74%) had low-grade injury, and 14 (6%) had no inhalation injury. VAP occurred in 10/51 (18%) patients with high-grade injury and 21/181 (11%) with low-grade injury. After excluding patients who received <48 hours of mechanical ventilation, high-grade injury was not associated with increased incidence of VAP in competing risk analysis (subdistribution hazard ratio: 1.59, 95% CI 0.66-3.87, p = 0.30; cause-specific hazard ratio: 1.03, 95% CI 0.43-2.48, p =0.94) after adjusting for age, burn size, and pre-injury lung disease, High-grade injury compared with low-grade injury was associated with fewer ventilator-free days (RR 0.72, 95%CI 0.57-0.9, p=0.01). Burn size modified the association of inhalation injury severity and hospital mortality (interaction term p value 0.01). At burn size <20% TBSA, higher inhalation injury severity exhibited a strong association with mortality (RR 3.83; 95%CI 1.71–8.58; p = 0.001), but at burn size ≥20% TBSA the association was attenuated (RR 0.75; 95% CI 0.35–1.62); p = 0.47).

Conclusion: Among patients with inhalation injury, higher grade of inhalation injury was not associated with increased incidence of VAP in competing risk analysis, though low-grade patients were more likely to be extubated within 48 hours which may explain the null findings. High-grade injury was associated with fewer ventilator-free days, higher hospital mortality, and higher hospital length of stay. Additional research is needed to disentangle the relationship of inhalation injury and VAP.

INTRODUCTION

Inhalation injury is an acute respiratory tract insult caused by toxic inhalants in smoke that complicates approximately one third of large burn injuries and 8% of all burn admissions.[1,2] Inhalation injury is a major contributor to burn-related mortality accounting for up to 80-90% of burn-related deaths.[3–6] Smoke causes neuropeptide-mediated injury to respiratory epithelium, changes in regional blood flow via upregulation of nitric oxide synthase, pro-inflammatory cytokine release, and impairment of alveolar macrophage function.[3,7] Such insults likely predispose patients to bacterial lung infections, particularly ventilator-associated pneumonia (VAP), defined as pneumonia following at least 48 hours of mechanical ventilation.[5,8] Among general critically-ill populations, VAP is associated with comorbid conditions (e.g., comorbid lung disease, diabetes), duration of mechanical ventilation, and severity of critical illness and immune dysregulation.[9] Intubated patients with injured airways, with or without concurrent burn injuries, may be at particular risk of VAP due to disrupted immune defenses and prolonged mechanical ventilation.[10,11] Moreover, despite widespread improvements in care, patients with inhalation injury remain at high risk of VAP; incidence following inhalation injury ranges from 24% to as high as 87%.[12–15] Though inhalation injury is a graded phenomenon, the relationship of inhalation injury severity to VAP risk remains unclear.[16]

Flexible bronchoscopy performed early after inhalation injury (<24-48 hours) is recommended to grade severity of inhalation injury.[17,18] The Abbreviated Injury Score (AIS), the most commonly used grading system, ranges from 0 (no injury) to 4 (massive injury) based on bronchoscopy findings (Figure 1).[19] AIS is variably associated with specific outcomes (e.g., ARDS, resuscitation volumes, respiratory failure and pulmonary complications, mortality) and has not

been clearly associated with risk of pneumonia.[1,16] Further, the few studies that investigated an association of AIS and VAP did not account for differences in duration of mechanical ventilation.[1,19] This distinction is crucial to determine if increased VAP risk is directly related to pathophysiologic changes caused by inhalation injury, or instead is a result of prolonged mechanical ventilation – the key risk factor for VAP.[9,20]

Disentangling the complex relationship of the inhalation injury with VAP over the range of injury severity can enhance our understanding of the driving forces underpinning high VAP incidence in this population, an important step toward development of targeted interventions, including prophylactic strategies. Therefore, we conducted a retrospective cohort study of patients with inhalation injury who required mechanical ventilation to investigate the association between inhalation injury severity determined on admission bronchoscopy (i.e., <48 hours from admission) and incidence of VAP, considering death or extubation as competing risks. We also investigated the association of inhalation injury severity with other patient-centered clinical outcomes.

METHODS

Study design

We employed a single-center retrospective cohort design to determine the association of severity of inhalation injury measured by AIS grade on admission bronchoscopy with 1) incidence of first VAP episode, and 2) other clinical outcomes: mortality, ventilator-free days (VFDs), and hospital length of stay (LOS).

Study setting and population

All adult patients age ≥18 years admitted to the burn intensive care unit at UW Medicine Regional Burn Center at Harborview Medical Center (HMC) between January 1, 2011, and June 30, 2022 who underwent bronchoscopy within 48 hours of admission and required mechanical ventilation were included in the study cohort. Per burn center protocol, flexible bronchoscopy was performed by a surgical intensivist or pulmonologist within 48 hours of admission on all intubated patients at risk of inhalation injury to quantify the extent of airway injury using the AIS grading scale. Patients were excluded from this analysis if they did not have evidence of inhalation injury (grade 0) on admission bronchoscopy, if they suffered non-smoke-related upper airway injury such as chemical burns or steam injury, or if they experienced systemic toxicity alone (e.g., carbon monoxide or cyanide poisoning).

Exposure measures

The exposure of interest was inhalation injury severity, defined by AIS grade. AIS grade was determined by the bronchoscopist based on the appearance of the visualized airways on bronchoscopy performed within 48 hours of admission (Figure 1). AIS was grouped as high-grade injury (grades 3-4) or low-grade injury (grades 1-2). Such subgrouping has been utilized by previous studies to reduce misclassification given the moderate subjectivity of AIS grading.[1,16]

Outcomes

The primary outcome was the first occurrence of ventilator-associated pneumonia (VAP), defined as pneumonia after at least 48 hours of mechanical ventilation. The diagnosis of VAP for

this study was adapted from the Center for Disease Control PNU2 criteria (Table E1 in the Appendix) and required isolation of a pathogen on bronchoalveolar lavage at a concentration >10,000 colony-forming units (CFU) per ml.[21] When considering the outcome of VAP, patients were excluded if they were mechanically ventilated <48 hours, as they did not contribute any time at risk for VAP by definition. These patients were included in analysis of secondary outcomes: hospital mortality, ventilator-free days (VFDs), and hospital length of stay (LOS) among survivors to discharge. VFDs were defined as the number of days from successfully weaning to day 28; patients who died before weaning were deemed to have no ventilator-free days.[22]

Covariables

Patient and burn injury factors that might confound the relationship between inhalation injury severity and VAP incidence were determined a priori. These included age, burn size, and comorbid lung disease (e.g., chronic obstructive pulmonary disease, asthma). Burn size, measured as percent total body surface area (TBSA) burned, was recorded for all patients using a computerized Lund-Browder diagram. Details of missing data for the covariables are provided in the Appendix.

Competing Risk

Patients are no longer at risk for VAP after death or liberation from mechanical ventilation. In this context, standard survival methods are inappropriate because they assume that censoring, (e.g., upon death or extubation in this analysis) is non-informative.[23] Instead, death and extubation are competing risks for VAP occurrence.[24,25] Ignoring these competing risks—by, for

example, treating individuals who die or are extubated as censored—would produce biased estimates.[26,27] Thus, in analyzing these data it is important to use statistical methods designed for the competing risk setting. Two established regression models for time-to-event outcomes subject to competing risks are the cause-specific hazards model and the Fine-Gray subdistribution hazards model. These two models estimate different parameters with different interpretations: cause-specific hazard ratio (CSHR) and subdistribution hazard ratio (SHR), respectively. The primary scientific question of interest – is more severe inhalation injury associated with a higher risk of VAP independent of duration of mechanical ventilation? – is more etiological in nature than prognostic, suggesting the use of the cause-specific hazards model. However, understanding the association between inhalation injury severity and the cumulative incidence of VAP via the Fine-Gray subdistribution hazards model is also of interest, as this provides insight into the overall effect of inhalation injury grade on the risk of VAP. Thus, we used both the proportional cause-specific hazards model and the Fine-Gray subdistribution hazards model in this analysis. This approach of using both models is commonly recommended for competing risks data, allowing for more complete understanding of the association between an explanatory variable and the risk of the event.[26–28] As VAP diagnosis cannot occur in those intubated < 48 hours, patients intubated <48 hours were excluded from this analysis. Chi-square test of proportions was performed to compare the proportion of patients extubated within 48 hours between high-grade and low-grade groups.

Mortality, VFDs, and hospital LOS

Because cutaneous burns and inhalation injury likely influence mortality through different mechanisms but with unclear interactions, we tested the hypothesis that burn size would exhibit

effect modification on the relationship of inhalation injury severity and hospital mortality using Poisson regression with an interaction term TBSA x AIS in addition to the covariables above. Finally, Poisson regression was performed to test for associations between inhalation injury severity and ventilator-free days (VFDs) and hospital length-of-stay (LOS) adjusted for the same covariables and assuming robust standard errors. Additional methodologic details are provided in the Appendix.

Ethics Approval

This study was approved the University of Washington Human Subjects Division Institutional Review Board (STUDY00009179).

RESULTS

Study population

Between May 1, 2011 and June 30, 2022, 246 mechanically ventilated adult patients admitted with suspected inhalation injury underwent bronchoscopy within 48 hours of admission. Of these, 14/246 (6%) had no evidence of inhalation injury on bronchoscopy and were excluded from analysis, and one patient had non-smoke related inhalation injury (chemical injury from inhaled anhydrous ammonia) and was excluded from analysis (Figure 2). Therefore, 231 patients were analyzed. Of these individuals, 180/231 (78%) patients had low-grade inhalation injury and 51/231 (22%) had high-grade inhalation injury. Baseline characteristics are shown in Table 1. Median age was 47 years (IQR 35-60 years) and the majority were male (71%). BMI was 26

(IQR 23-30). Median burn size was 10% TBSA (IQR 1–30%), 23/231 (10%) had diabetes, and 29/23 (13%) had comorbid lung disease. Measured baseline characteristics were similar between patients with high-grade injury and those with low-grade injury.

Ventilator-associated pneumonia

Among the entire cohort, VAP occurred in 10/51 (20%) patients with high-grade injury and 21/180 (12%) patients with low-grade injury (Table 2). After excluding 88 patients with <48 hours of ventilator time, VAP occurred in 8/40 (20%) of the high-grade group and 17/103 (17%) of the low-grade group who received at least 48 hours of mechanical ventilation. Notably, the proportion of patients extubated within 48 hours was lower in the high-grade group compared with the low-grade group: 10/51 (20%) vs 75/180 (42%), p = 0.004. Death within the first 48 hours occurred in one patient in the high-grade group and two patients in the low-grade group. Median time to first VAP episode in patients ventilated ≥48 hours was 10.5 days (IQR 7-16) in the high-grade group and 9 days (IQR 7-17) in the low-grade group. The most common pathogen recovered during a first VAP episode was *Staphylococcus aureus* (n=12) followed by *Haemophilus influenzae* (n=8). Figure 3 shows the cumulative incidence functions (CIF) for VAP, death, and extubation for patients with high-grade and low-grade inhalation injury who were mechanically ventilated for ≥48 hours. While the estimated cumulative incidence of VAP is slightly higher for patients with high-grade inhalation injury compared to patients with low-grade injury, overall, the CIF curves are similar.

Table 4 provides estimates and 95% CIs for the cause-specific hazards ratios (CSHR) for VAP and the subdistribution hazard ratios (SHR) for VAP. When adjusting for age, TBSA, and pre-injury lung disease, there was no statistically significant association between injury grade and

cause-specific hazard of VAP (CHSR for VAP, 1.03; 95% CI, 0.43-2.48; p =0.94). There was also no significant association between injury grade and subdistribution hazard of VAP (SHR for VAP, 1.59; 95% CI, 0.66-3.87; p = 0.30).

Hospital mortality

Among patients with high-grade inhalation injury, 13/51 (25%) died in-hospital compared with 28/180 (15%) patients with low-grade injury (Table 2). Burn size (dichotomized to <20% and ≥20% TBSA) modified the effect of inhalation injury severity on hospital mortality (Table 4) as evidenced by a statistically significant interaction term (p = 0.01) and relative excess risk due to interaction (RERI) of -4.5 (95% CI -10.2 – 1.33, p = 0.13). At burn size <20% TBSA, higher inhalation injury severity exhibited a strong association with mortality (RR 3.83; 95%CI 1.71–8.58; p = 0.001), but at burn size ≥20% TBSA the association was attenuated (RR 0.75; 95% CI 0.35–1.62); p = 0.47).

Ventilator-free days and hospital length of stay

Median VFDs were 23 days (5-26 days), and among survivors to hospital discharge, median hospital LOS was 20 days (6-44 days). High-grade injury compared with low-grade injury was associated with fewer VFDs (RR 0.72; 95%CI 0.57-0.91; p=0.01) and, among survivors to discharge, longer hospital LOS (RR 1.58; 95% CI 1.16-2.16; p=0.004).

DISCUSSION

In this single-center retrospective cohort study of adults with inhalation injury receiving mechanical ventilation, we found that higher inhalation injury severity was not associated with

increased VAP risk among patients ventilated for 48 hours or longer. This was consistent in both cause-specific and cumulative incidence analyses.

Several possible explanations exist for these findings that differ from prior studies assessing an association of inhalation injury severity and pneumonia.[1,19] Importantly, 88/231 (38%) of the cohort received mechanical ventilation for less than 48 hours and were never at risk for VAP. Only three of these excluded patients died within 48 hours, and the remaining were extubated. Low-grade injury patients were significantly more likely to be extubated within 48 hours of mechanical ventilation compared with high-grade patients. Thus, low-grade injury may confer a lower VAP risk through expeditious ventilator weaning and lower duration of mechanical ventilation. Another explanation is the low VAP event rate in this cohort compared to other studies of inhalation injury, limiting power to detect a difference between the groups.[11,12,15] Early de-resuscitation and extubation practices at Harborview Medical Center may minimize time on the ventilator, thus reducing VAP risk. Finally, because VAP required a microbiologic diagnosis in this study, cases of VAP clinically diagnosed may be missed. However, due to the challenge of clinical pneumonia diagnosis in patients with major burn injury, microbiologic diagnosis is the agreed-upon method.[29] Further studies are needed to clarify the relationship of inhalation injury severity and VAP, with particular attention to the interplay of pathophysiology changes that may directly influence pneumonia risk and factors that prolong duration of mechanical ventilation. Protocols to minimize duration of mechanical ventilation and reduce VAP risk for those who are intubated are critical in this high-risk population.

Burn size was found to modify the relationship between inhalation injury severity and hospital mortality. Among patients with TBSA <20%, higher inhalation injury severity was associated with increased hospital mortality, but this relationship was attenuated among patients with TBSA ≥20%. Burn size and inhalation injury likely represent two distinct but interacting biological pathways that potentiate systematic immunoinflammatory activation and disproportionately increase the risk of death.[11] One explanation for the null finding in higher TBSA patients is that immune suppression and critical illness due to large cutaneous burns drive mortality in this group. In contrast, in the setting of milder cutaneous burns, airway injuries are likely the dominant driver of complications and subsequent mortality. Interventions targeting inhalation injury may be the most beneficial for patients with smaller burn sizes, and clinical trials could be enriched for these patients. An alternative explanation for these findings is collider bias.[30] Because patients in this study were selected based on receipt of mechanical ventilation after burn injury, and burn size and inhalation injury are each independently associated with intubation, this could alter the relationship of TBSA and inhalation injury severity.[31] However, because patients who are not mechanically ventilated do not routinely undergo bronchoscopy, a study assessing inhalation injury severity among spontaneously breathing patients would be challenging.

Higher inhalation injury severity was independently associated with fewer ventilator-free days and, among survivors, longer hospital length of stay. These findings are consistent with previous studies, confirming the heavy burden to patients and hospital resources attributable to severe inhalation injury.[1,19] A confluence of patient- and injury-related factors likely drive these adverse outcomes; the precise mechanisms underpinning them and the direct contribution from inhalation injury remain unclear.

Strengths of this study include the large sample size in comparison with other studies of inhalation injury, protocolized bronchoscopy diagnosis and grading of inhalation injury, objective VAP criteria including microbiological diagnosis, and the novel use of competing risk analysis in this population. This study does have limitations. The single center observational study design reduces generalizability and limits causal inference. While bronchoscopy grading of inhalation injury severity using AIS has been validated, it is inherently subjective between operators and there remains equipoise in its utility to accurately grade inhalation injury. Finally, empiric antibiotics given for admission BAL organisms or for non-pulmonary reasons (e.g., wound infection) may influence the results of subsequent BAL for VAP diagnosis.

In conclusion, among patients with inhalation injury who required mechanical ventilation, higher severity inhalation injury was associated with fewer ventilator-free days, longer hospital length of stay, and higher hospital mortality modified by burn size. Higher severity inhalation injury was not associated with increased VAP risk in competing risk analysis among patients ventilated for $\geq$48 hours. Additional research is needed to clarify the relationship of inhalation injury and pulmonary complications, including pneumonia, to facilitate development of targeted interventions in this important population.

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Table 1. Demographic and clinical characteristics of patients with inhalation injury

Patient characteristics	All patients n = 231	Low-grade injury n = 180	High-grade injury n = 51	p-value
Demographics				
Age in years - median (IQR)	47 (35-60)	46 (34-59)	52 (39-64)	0.24
Sex, female - no (%)	67 (29)	50 (28)	17 (33)	0.44
BMI - median (IQR)	26 (23-30)	27 (24-30)	25 (22-28)	0.18
BMI, grouped - no (%)				0.38
<18.5	6 (3)	4 (2)	2 (4)	
18.5 - 24.9	81 (35)	59 (33)	22 (43)	
25 - 29.9	87 (38)	69 (38)	18 (35)	
≥ 30	57 (25)	48 (27)	9 (18)	
Comorbidities - no (%)				
COPD or asthma	29 (13)	26 (14)	3 (6)	0.10
Home Oxygen	8 (5)	6 (4)	2 (6)	0.68
Smoking	20 (9)	15 (8)	5 (10)	0.52
Diabetes	23 (10)	17 (9)	6 (12)	0.63
Mental disorder	41 (17)	36 (20)	7 (13)	0.71
Substance use disorder	26 (11)	22 (12)	4 (8)	0.56
Clinical				
TBSA - median (IQR)	11.8 (1-30)	11.7 (0.5-31)	11.8 (2-27)	0.11
AIS grade, grouped - no (%)				
1	105 (45)	105 (58)	-	
2	75 (32)	75 (42)	-	
3	46 (20)	-	46 (90)	
4	5 (2)	-	5 (10)	
Initial CO level - median (IQR)	2.6 (1-9)	2.2 (1-7)	6.9 (3-19)	0.004

Abbreviations: IQR = interquartile range, BMI = body mass index, COPD = chronic obstructive pulmonary disease, TBSA = total body surface area burned, AIS = abbreviated injury score, CO = carbon monoxide.

Table 2. Outcomes and associations with inhalation injury severity

Outcomes	All patients n = 231	Low-grade injury* n = 180	High-grade injury n = 51	RR† (95% CI)	p value
Ventilator-associated pneumonia - no (%) ‡	31 (13)	21 (12)	10 (20)	-	-
Among patients with ≥ 48 hours MV	25/143 (17)	17/103 (17)	8/40 (20)	-	-
Hospital mortality - no (%)‡	41 (18)	28 (15)	13 (25)	-	-
Ventilator-free days - median (IQR)	23 (3-26)	25 (11-26)	16 (0-24)	0.72 (0.57-0.91)	0.01
Hospital length of stay - median (IQR)	20 (6-44)	19 (5-40)	32 (10-59)	1.58 (1.16-2.2)	0.004

Abbreviations :RR = relative risk, IQR = interquartile range, MV = mechanical ventilation

* Low-grade injury is defined by abbreviated injury score 1-2, high-grade injury is defined by abbreviated injury score 3-4.

† RR is reported for associations of inhalation injury severity and ventilator-free days and hospital length of stay in Poisson regression with robust standard errors adjusted for age, sex, total body surface area burned, and obstructive lung disease.

‡ Results of analyses for ventilator-associated pneumonia are provided in Table 3, and results for hospital mortality provided in Table 4.

Table 3. Cause-specific hazard ratios and subdistribution hazard ratios for VAP

Variables	Cause-specific hazard ratio (95% CI)	p-value	Subdistribution hazard ratio (95% CI)	p-value
Injury grade (high-grade)	1.03 (0.43-2.48)	0.94	1.59 (0.66-3.87)	0.30
Age (years)	0.99 (0.98-1.02)	0.97	1.004 (0.98-1.03)	0.66
TBSA (%)	1.01 (0.99-1.02)	0.30	1.03 (1.01-1.04)	0.01
Pre-injury lung disease	0.28 (0.04-1.90)	0.19	0.68 (0.17-2.65)	0.58

Abbreviations: VAP = ventilator-associated pneumonia; TBSA = total body surface area burned.

Table 4. Modification of the effect of inhalation injury severity on mortality by TBSA

	Low-grade inhalation injury		High grade inhalation injury		
	n died in-hospital (%)	RR (95% CI)	n died in-hospital (%)	RR (95% CI)	RRs (95% CI) for inhalation injury severity within strata of TBSA
TBSA < 20%	8/111 (7)	1.0	9/36 (25)	3.67 (1.69–7.96); p = 0.001	3.83 (1.71–8.58); p = 0.001
TBSA ≥ 20%	20/69 (29)	6.63 (3.35–13.1); p < 0.001	4/14 (29)	5.00 (2.17–11.5); p <0.001	0.75 (0.35–1.62); p = 0.47

Abbreviations : RR = relative risk, CI = confidence interval, TBSA = total body surface area burned

Measure of effect modification on additive scale: RERI (95% CI) = -4.5 (-10.2 - 1.33); p = 0.13

RRs are adjusted for age, sex and obstructive lung disease

Figure legends

Figure 1: Abbreviated Injury Score (AIS) for inhalation injury

Figure 2: Study flow diagram

Figure 3: Aalen-Johansen cumulative incidence curves for VAP, death, and extubation among patients requiring mechanical ventilation for ≥48 hours, stratified by inhalation injury grade: high-grade (grades 3 & 4) compared with low grade (grades 1 & 2)

Figure 1.[1,32,33]

Injury Grade	Findings
0 (None)	• Absence of carbonaceous deposits, erythema, edema, bronchorrhea, or obstruction
1 (Mild)	• Minor or patchy areas of erythema • Carbonaceous deposits in either proximal or distal bronchi
2 (Moderate)	• Moderate degree of erythema, carbonaceous deposits, bronchorrhea • With or without bronchi compromise
3 (Severe)	• Severe inflammation with friability • Copious carbonaceous deposits, bronchorrhea • Bronchial obstruction
4 (Massive)	• Evidence of mucosal sloughing, necrosis, endoluminal obliteration

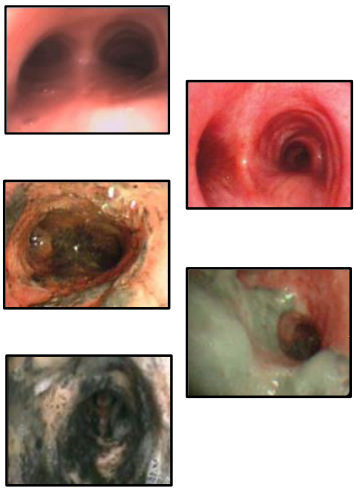


Figure 2.

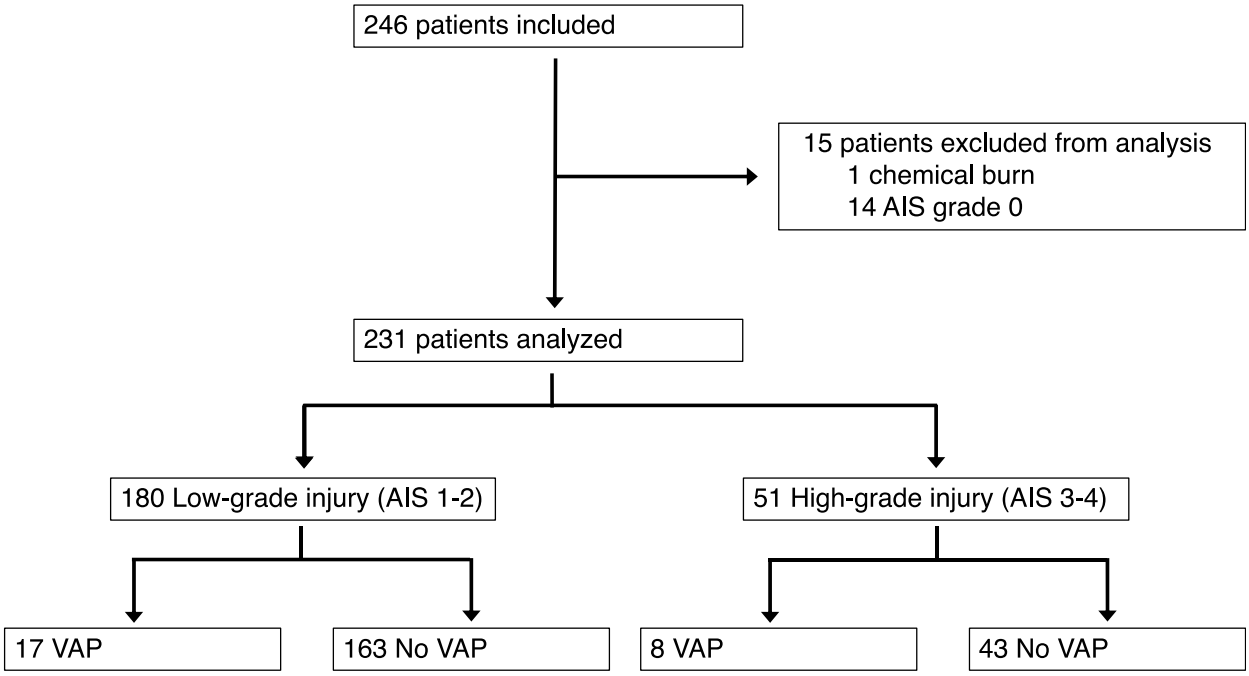
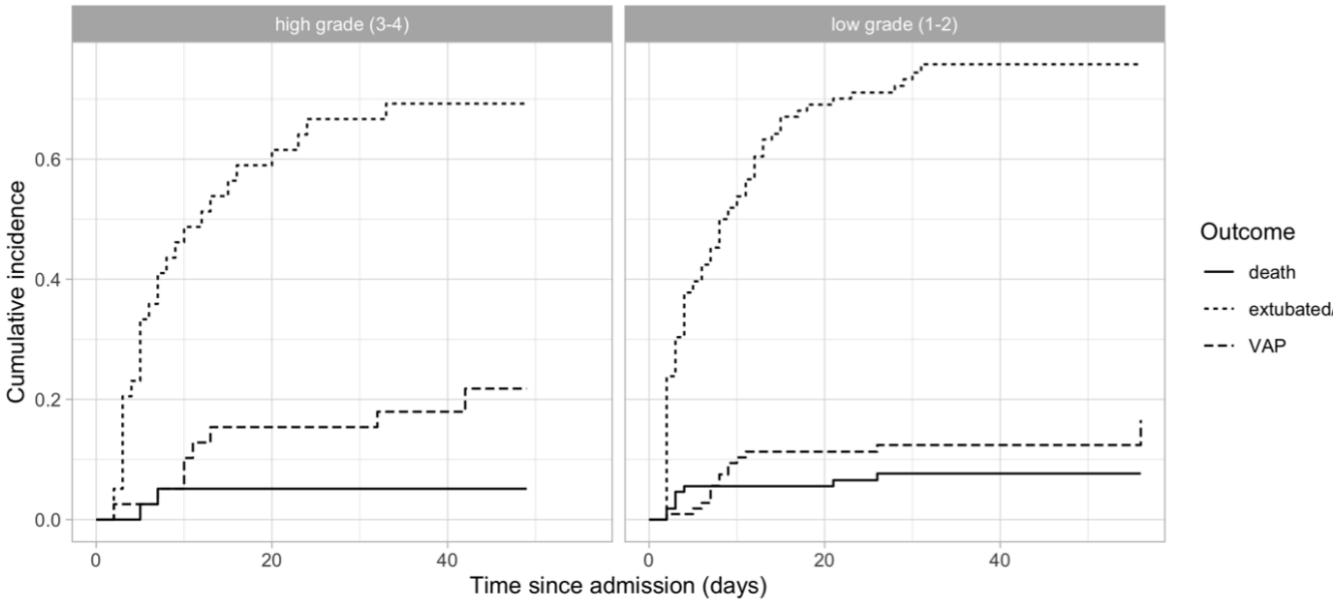

246 patients included
15 patients excluded from analysis
1 chemical burn
14 AIS grade 0
231 patients analyzed
180 Low-grade injury (AIS 1-2)
51 High-grade injury (AIS 3-4)
17 VAP
163 No VAP
8 VAP
43 No VAP

Figure 3


high grade (3-4)
low grade (1-2)
Cumulative incidence
0.0
0.2
0.4
0.6
0
20
40
Time since admission (days)
Outcome
death
extubated
VAP