Original Article

J Trauma Inj 2022;35(2):76-83
https://doi.org/10.20408/jti.2021.0064

Journal of Trauma and Injury JTI

pISSN 2799-4317 • eISSN 2287-1683

Clinical implications of the newly defined concept of ventilator-associated events in trauma patients

Tae Yeon Lee, MD[1], Jeong Woo Oh, MD[1], Min Koo Lee, MD, PhD[1], Joong Suck Kim, MD[1], Jeong Eun Sohn, MD[2], Jeong Hwan Wi, MD[2]

[1]Trauma Center, Cheju Halla General Hospital, Jeju, Korea
[2]Department of Anesthesiology, Cheju Halla General Hospital, Jeju, Korea

Purpose: Ventilator-associated pneumonia is the most common nosocomial infection in patients with mechanical ventilation. In 2013, the new concept of ventilator-associated events (VAEs) replaced the traditional concept of ventilator-associated pneumonia. We analyzed risk factors for VAE occurrence and in-hospital mortality in trauma patients who received mechanical ventilatory support.

Methods: In this retrospective review, the study population comprised patients admitted to the Jeju Regional Trauma Center from January 2020 to January 2021. Data on demographics, injury characteristics, and clinical findings were collected from medical records. The subjects were categorized into VAE and no-VAE groups according to the Centers for Disease Control and Prevention/National Healthcare Safety Network VAE criteria. We identified risk factors for VAE occurrence and in-hospital mortality.

Results: Among 491 trauma patients admitted to the trauma center, 73 patients who received ventilator care were analyzed. Patients with a chest Abbreviated Injury Scale (AIS) score ≥3 had a 4.7-fold higher VAE rate (odds ratio [OR], 4.73; 95% confidence interval [CI], 1.46–17.9), and those with a glomerular filtration rate (GFR) <75 mL/min/1.73 m^2 had 4.1-fold higher odds of VAE occurrence (OR, 4.15; 95% CI, 1.32–14.1) and a nearly 4.2-fold higher risk for in-hospital mortality (OR, 4.19; 95% CI, 1.30–14.3). The median VAE-free duration of patients with chest AIS ≥3 was significantly shorter than that of patients with chest AIS <3 (P=0.013).

Conclusions: Trauma patients with chest AIS ≥3 or GFR <75 mL/min/1.73 m^2 on admission should be intensively monitored to detect at-risk patients for VAEs and modify the care plan accordingly. VAEs should be closely monitored to identify infections early and to achieve desirable results. We should also actively consider modalities to shorten mechanical ventilation in patients with chest AIS ≥3 to reduce VAE occurrence.

Keywords: Trauma centers; Pneumonia; Hospital mortality; Ventilator-associated pneumonia

Received: August 12, 2021
Revised: November 29, 2021
Accepted: December 7, 2021

Correspondence to
Tae Yeon Lee, MD
Trauma Center, Cheju Halla General Hospital, 65 Doryeong-ro, Jeju 63127, Korea
Tel: +82-64-740-5760
E-mail: arahant79@gmail.com

INTRODUCTION

Ventilator-associated pneumonia (VAP) is the most common nosocomial infection in patients requiring endotracheal tubes with mechanical ventilation [1]. The reported prevalence of VAP in trauma patients is about 4-fold higher than that in non-trauma patients [2]. Before 2013, the Centers for Disease Control and Prevention (CDC), the American Thoracic Society, and the Infectious Diseases Society of America collaborated to provide the surveillance definition of VAP [3–6]. However, over time, many concerns were raised about the effectiveness, reproducibility, and interpretation of VAP rates [7]. In 2013, the National Healthcare Safety Network (NHSN) replaced the previous definition of pneumonia with a classification of ventilator-associated events (VAEs). The concept of VAEs was defined to overcome many of the limitations of traditional VAP definitions, with the aim of establishing definitions that are objective, reproducible, automated, and a powerful predictor of poor outcomes [8]. VAEs are common complications in patients undergoing mechanical ventilation in the intensive care unit (ICU) [9,10]. These can lead to further complications that can extend the duration of mechanical ventilation, the length of stay (LOS) in the ICU, as well as costs, morbidity, and mortality [11,12]. Therefore, we analyzed the patients who received mechanical ventilator support at Jeju Regional Trauma Center.

METHODS

Ethical statements

The study was approved by the Institutional Review Board of the Cheju Halla General Hospital (No. 2021-L06-01). Informed consent was waived due to the retrospective nature of the study.

Design and sample

In this retrospective review, the study population comprised patients admitted to Jeju Regional Trauma Center between January 2020 and January 2021. For each patient, information regarding demographics (e.g., age and sex), injury characteristics, and clinical data were collected. Injury characteristics included injury mechanism (e.g., traffic accident, fall from height, slip down), Glasgow Coma Scale (GCS) score, Abbreviated Injury Scale (AIS), and Injury Severity Score (ISS). The GCS was calculated at the time of first contact with medical services before intubation and sedation. Clinical data were obtained from patients' electronic medical records. The data included hospital LOS in days, ICU LOS in days, and ventilator support days and other clinical and laboratory values such as positive end-expiratory pressure (PEEP), fraction of inspired oxygen (FiO_2), white blood cell count, hematocrit, hemoglobin, platelet count, serum creatinine, blood urea nitrogen, glomerular filtration rate (GFR), temperature, antimicrobial agents administered, and culture results.

Ventilator-associated events

VAEs, as defined by the NHSN [4], were categorized as ventilator-associated conditions (VACs), infection-related ventilator-associated complications (IVACs), and possible VAP (PVAP). Patients classified as having VACs had a baseline period of 2 days of stable or improved FiO_2 or PEEP followed by deterioration of oxygenation. Those categorized as having IVACs met the criteria for VACs, had a core temperature $>38°C$ or $<36°C$ or had a white blood cell $>12,000$ or $<4,000$ cells/mm^3, and were administered eligible antimicrobial agents that were continued for more than 4 days. For PVAP, in addition to meeting the criteria for IVAC, patients had $>10^5$ colony-forming units in their tracheal aspirates and $>10^4$ colony-forming units of microorganisms in cultures of bronchoalveolar lavage specimens (Table 1) [13].

Statistics

Demographics, injury characteristics, clinical data, comorbidities, and nosocomial complications were compared between the two groups. The independent t-test and Fisher exact test were used for continuous and categorical variables, respectively. A logistic regression model adjusted for age, sex, GCS score, GFR, chest and head AIS, and ISS was used to estimate odds ratios (ORs) and associated 95% confidence intervals (CIs) for VAE occurrence and in-hospital mortality. A Cox proportional hazard model was used for investigating the association between VAE occurrence and several variables over time. The Kaplan-Meier method and the log-rank test were used for estimating the VAE-free rate curve and for statistical comparisons between the two groups. All tests of significance were two-tailed, and a P-value of <0.05 was considered statistically significant. Statistical analyses were performed using R statistics ver. 4.0.2. (The R Foundation for Statistical Computing, Vienna, Austria; https://www.r-project.org/).

RESULTS

From January 2020 to January 2021, 492 patients were admitted to Jeju Regional Trauma Center, of whom 210 patients received ventilator support. Among them, 84 patients had at least 4 calendar days of ventilator support. In accordant with 2013 CDC/

Table 1. NHSN VAE criteria

NHSN surveillance guidelines for diagnosis of VAE		
Name: description	Dependent qualification	Definition
VAC: new respiratory deterioration	≥2 calendar days of stable or decreasing daily minimum PEEP or daily minimum FIO_2	Followed by a daily Minimum PEEP of ≥3 cm H_2O OR Minimum FIO_2 by >20 points sustained for ≥2 calendar days
IVAC: VAC+clinical signs of infection	Within 2 calendar days before or after onset of a VAC Excludes the first 2 days of mechanical ventilation	Temperature: <36°C or >38°C OR Leukocyte count: ≤4,000 or ≥12,000 cells/mm^3 AND One or more new antibiotics continued for ≥4 days
Possible VAP: IVAC+qualitative evidence of pulmonary infection	Within 2 calendar days before or after onset of a VAC Excludes the first 2 days of mechanical ventilation	Gram staining of endotracheal aspirate or BAL showing ≥25 neutrophils and ≤10 epithelial cells per low-power field OR Positive culture from sputum, endotracheal aspirate, BAL, lung tissue
Probable VAP: IVAC+qualitative evidence of pulmonary infection	Within 2 calendar days before or after onset of a VAC Excludes the first 2 days of mechanical ventilation	Positive culture of endotracheal aspirate ≥10^5 CFU/mL, positive BAL culture with ≥10^4 CFU/mL, or positive culture of protected specimen brush ≥10^3 CFU/mL OR One of the following (without requirement for purulent secretions): Positive pleural fluid culture (where specimen was obtained during thoracentesis or initial placement of chest tube and NOT from indewelling chest tube) Positive lung histopathology Positive diagnostic test for legionella Positive diagnostic test on respiratory secretions for influenza virus, respiratory syncytial virus, adenovirus, parainfluenza virus, rhinovirus, human metapneumovirus, coronavirus

Highlights the stepwise respiratory deterioration associated with VAC, IVAC, possible pneumonia, and probable pneumonia with specific, objective criteria that define each category. Sputum cultures excludes the following: normal respiratory/oral flora, mixed respiratory/oral flora or equivalent; *Candida* species or yeast not otherwise specified; coagulase-negative *Staphylococcus* species; and *Enterococcus species*.
NHSN, National Healthcare Safety Network; VAE, ventilator-associated event; VAC, ventilator-associated condition; IVAC, infection-related ventilator-associated complication; PEEP, positive end-expiratory pressure; FIO_2, fraction of inspired oxygen; VAP, ventilator-associated pneumonia; BAL, bronchoalveolar lavage; CFU, colony-forming unit.
Adapted from Spalding et al. [13] with permission from Elsevier.

NHSN VAE surveillance criteria, those who were under 18 years old (n = 4), received extracorporeal membrane oxygenation therapy (n = 6), and had incomplete data (n = 1) were excluded from this study (n = 11). Finally, the study population comprised 73 patients, of whom 48 had no VAEs (65.8%), 16 met the definition for VACs (21.9%), three met the criteria for IVACs (4.1%), and six met the criteria for PVAP (8.2%). The subjects categorized as belonging to the no-VAE group had no VAEs during mechanical ventilatory support. The subjects in the VAE group had at least one VAE criterion (including VACs, IVACs, and PVAP). There were no significant differences in demographics, comorbidities, injury characteristics, clinical data, and laboratory values between the two groups (Table 2). Additionally, there were no significant differences in ICU LOS (P = 0.200), ventilator support days (P = 0.164), the incidence of nosocomial complications, and in-hospital mortality (P = 0.111) between the two groups (Tables 3, 4). However, the VAE subjects were more likely to have higher GCS scores (P = 0.012) and chest AIS (P = 0.024) (Tables 2, 5) and less likely to have normal kidney function as measured by the GFR (P = 0.001) (Table 3) than the no-VAE subjects. The VAE

https://doi.org/10.20408/jti.2021.0064

Table 2. Comparison of demographics, comorbidities, and injury characteristics by VAE status

Variable	No VAE (n=48)	VAE (n=25)	P-value
Age (yr)	57.6±19.1	64.4±16.5	0.138
Sex			
Male	62.5	80.0	0.207
Female	37.5	20.0	
Comorbidity			
Hypertension	37.5	40.0	>0.999
Diabetes mellitus	8.3	20.0	0.287
Chronic kidney disease	0	8.0	0.218
Cerebrovascular attack	10.4	12.0	>0.999
Tumor	0	8.0	0.218
Liver disease	6.2	0	0.512
Mechanism of injury			
Traffic accident	43.8	56.0	0.455
Fall from height	20.8	12.0	0.539
Slip down	14.6	16.0	>0.999
Struck by object	6.2	12.0	0.689
Glasgow Coma Scale score	9.2±4.1	11.8±4.1	0.012*
Injury Severity Score	25.8±10.2	23.2±11.2	0.813
Abbreviated Injury Scale			
Head	3.35±1.92	2.86±2.00	0.327
Face	0.41±0.90	0.45±1.01	0.858
Chest	1.43±1.60	2.36±1.53	0.024*
Abdomen	0.92±1.34	0.68±1.17	0.469
Extremity	0.86±1.34	1.27±1.12	0.214
External	0.67±0.89	0.59±0.59	0.715

Values are presented as mean±standard deviation or percentage. P-value obtained using chi-square test and Student t-tests for categorical and continuous variables, respectively.
VAE, ventilator-associated event.
*P<0.05.

Table 3. Comparison of clinical characteristics and laboratory values by VAE status

Variable	No VAE (n=48)	VAE (n=25)	P-value
Clinical values			
SBP (mmHg)	130±51	134±47	0.760
DBP (mmHg)	77±29	79±27	0.843
Pulse rate (/min)	86±29	89±31	0.631
Respiratory rate (/min)	22±7	22±4	0.947
Body temperature (°C)	36.3±0.8	36.4±0.5	0.291
Blood cell count			
WBC (×1,000 cells/mm^3)	13.4±5.4	12.2±6.2	0.421
Hemoglobin (g/dL)	12.5±2.3	12.6±1.9	0.845
Hematocrit (%)	36.3±6.7	37.1±5.3	0.606
Platelet (×1,000/μL)	228±91	214±73	0.512
Chemistry			
BUN (mg/dL)	19±15	22±15	0.422
Creatinine (mg/dL)	0.9±0.5	1.7±2.4	0.125
GFR (mL/min/1.73 m^2)	98.5±46.5	68.4±27.8	0.001**
CRP (mg/dL)	1.9±7.3	0.6±2.1	0.264
CPK (U/L)	366±331	441±482	0.508
ABGA			
pH	7.3±0.1	7.4±0.1	0.512
$PaCO_2$ (mmHg)	35.8±8.1	33.9±6.5	0.334
PaO_2 (mmHg)	165.7±69.9	137.6±58.1	0.094
Saturation (%)	97.6±4.3	97.4±3.3	0.836
Lactate (mg/dL)	35.5±22.0	49.5±33.7	0.508

Values are presented as mean±standard deviation. P-value obtained using Student t-tests for continuous variables.
VAE, ventilator-associated event; SBP, systolic blood pressure; DBP, diastolic blood pressure; WBC, white blood cell; BUN, blood urea nitrogen; GFR, glomerular filtration rate; CRP, C-reactive protein; CPK, creatine phosphokinase; ABGA, arterial blood gas analysis.
**P<0.01.

subjects had a higher number of bronchoscopies (P=0.004) and were more likely to have acute respiratory distress syndrome (P=0.021) than the no-VAE subjects (Table 4). Continuous values were converted to categorical values for logistic regression analysis. The cutoff values were set as 65 years for age, 3 points for AIS, 15 points for ISS, 7 points for GCS, and 75 mL/min/1.73 m^2 for GFR. In the multivariate analysis, the risk for VAE occurrence was 4.7-fold higher in patients with chest AIS ≥3 (OR, 4.73; 95% CI, 1.46–17.9) and 4.1-fold higher in those with a GFR <75 mL/min/1.73 m^2 (OR, 4.15; 95% CI, 1.32–14.1). The in-hospital mortality risk was more than 4-fold higher in patients with a GFR <75 mL/min/1.73 m^2 (OR, 4.19; 95% CI, 1.30–14.3) (Table 6). In addition, VAEs occurred in 50.0% of patients with a chest AIS ≥3 within 15 days of mechanical ventilatory support (Fig. 1). The median VAE-free duration of patients with a chest AIS ≥3 was significantly shorter than that of patients with a chest AIS <3 (P=0.013).

DISCUSSION

To our best knowledge, this study is the first surveillance study of the incidence, risk factors, and outcomes with the newly defined concept of VAEs in trauma patients. The present study revealed that several factors were associated with VAE occurrence and in-hospital mortality in polytrauma patients.

The VAE group was more likely to have higher GCS scores, which were used to define the severity of traumatic brain injuries (TBIs) in several studies. Patients with TBIs often suffer from profound suppression of cellular immunity and impaired con-

sciousness [14], and they usually require endotracheal intubation and mechanical ventilatory care, both of which increased the incidence of VAP. Therefore, severe TBI patients were more vulnerable to VAP [15]. However, chest injury and the combination of chest injury and TBI were found to be independent predictors for the development of pneumonia in polytrauma patients [15]. This suggests that TBI itself was not associated with the development of pneumonia. Our results showed that patients in the VAE group had relatively higher GCS scores, although the GCS scores were not related to in-hospital mortality.

Second, blunt chest trauma may cause intra-thoracic organ injuries, which may lead to serious complication and mortality in polytrauma patients [16]. The risk of respiratory failure and subsequent pneumonia development depends on the severity of the chest injury [17]. Hofman et al. [18] reported that although chest trauma was not an independent risk factor for mortality, it was an independent risk factor for pneumonia. Their results showed that a chest AIS ≥3 in poly-traumatized patients was associated with an increased risk of pneumonia (OR, 4.193; P=0.004) in multivariate regression analysis. The present study showed similar results, in that the patient with a chest AIS ≥3 were likely to have a higher risk of VAE.

Table 4. Comparison of clinical outcomes by VAE status

Variable	No VAE (n=48)	VAE (n=25)	P-value
MV day	17.7±15.4	25.2±23.9	0.164
Length of stay			
ICU in day	26.3±22.0	33.7±25.7	0.200
Hospital in day	86.8±69.9	61.0±33.9	0.037*
Bronchoscopy	3.9± 4.7	14.1±15.9	0.004**
Complication			
AKI	4 (8.3)	3 (12.0)	0.931
ARDS	0	4 (16.0)	0.021*
CPR	4 (8.3)	4 (16.0)	0.548
VTE	7 (14.6)	4 (16.0)	1.000
PTE	8 (16.7)	5 (20.0)	0.975
UTI	3 (6.2)	1 (4.0)	1.000
CRBSI	1 (2.1)	1 (4.0)	1.000
Unplanned intubation	6 (12.5)	7 (28.0)	0.187
Unplanned operation	6 (12.5)	4 (16.0)	0.957
Unplanned ICU transfer	5 (10.4)	6 (24.0)	0.232
In-hospital mortality	11 (22.9)	11 (44.0)	0.111

Values are presented as mean±standard deviation or number (%). P-value obtained using chi square test and student t-tests for categorical and continuous variables, respectively.
VAE, ventilator-associated event; MV, mechanical ventilator; ICU, intensive care unit; AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; CPR, cardiopulmonary resuscitation; VTE, venous thromboembolism; PTE, pulmonary thromboembolism; UTI, urinary tract infection; CRBSI, catheter-related blood stream infection.
*P<0.05; **P<0.01.

Table 5. Chest Abbreviated Injury Scale (AIS)

AIS 2008	Skeletal	Lung
1	Contusion	-
	1 Rib fracture	-
2	2 Rib fractures	Unilateral contusion with minor <1 lobe
	Sternal fracture	Pneumothorax, pneumomedisatinum
3	≥3 Ribs	Unilateral contusion with major ≥1 lobe
	3–5 Flail chest	Hemopneumothorax
4	≥5 Flail chest	Bilateral contusion with major ≥1 lobe
		Pneumothorax >50% collapse
		Hemothorax >1,000 mL in unilateral cavity
5	Bilateral flail chest	Tension pneumothorax

Table 6. Multivariate analysis of factors associated with VAE occurrence and in-hospital mortalit

Variable	VAE occurrence		In-hospital mortality	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Male sex	2.25 (0.66–8.81)	0.2102	0.54 (0.15–1.90)	0.3357
Age ≥65 years	0.95 (0.25–3.32)	0.9365	2.14 (0.67–7.33)	0.2167
Injury Severity Score ≥15	0.30 (0.05–1.73)	0.1841	1.96 (0.34–12.4)	0.4554
Abbreviated Injury Scale				
Chest ≥3	4.73 (1.46–17.9)	0.0135*	0.48 (0.12–1.70)	0.2662
Head ≥3	1.24 (0.31–5.61)	0.7615	0.49 (0.12–2.04)	0.3151
GFR <75 mL/min/1.73 m^2	4.15 (1.32–14.1)	0.0170*	4.19 (1.30–14.3)	0.0181*
VAE (+)			2.53 (0.67–10.1)	0.1733

P-value obtained from logistic regression model.
VAE, ventilator-associated event; OR, odds ratio; CI, confidence interval; GFR, glomerular filtration rate.
*P<0.05.

https://doi.org/10.20408/jti.2021.0064

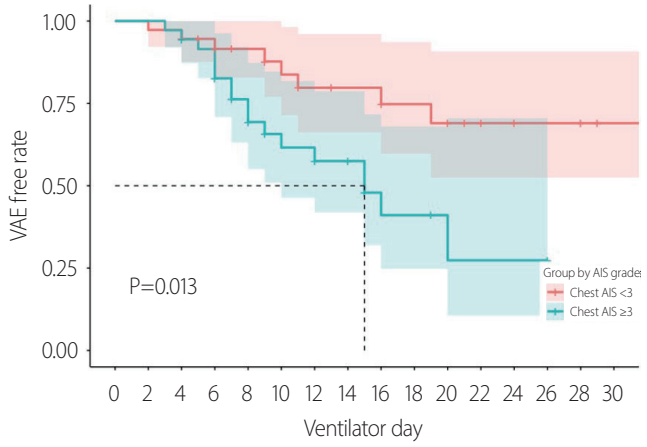

Fig. 1. Ventilator-associated event (VAE) free rate curves between low-grade and high-grade chest Abbreviated Injury Scale (AIS) group (estimated by the Kaplan-Meier log-rank test).

Table 7. Risk factor associated with posttraumatic acute kidney injury

	GFR <75 mL/min/1.73 m^2	GFR ≥75 mL/min/1.73 m^2	P-value
Categorical values			
Male sex	20 (27.4)	30 (41.1)	0.5993
Hypertension	15 (20.5)	13 (17.8)	0.0388*
Diabetes mellitus	5 (6.8)	4 (5.4)	0.2765
Continuous values			
Age (yr)	66.5±16.3	56.0±18.7	0.0153*
ISS	22.6±10.7	26.2±10.3	0.1648
ICU stay (day)	35.1±29.0	25.2±18.9	0.1179
MVD	26.7±25.4	16.5±12.8	0.0595†

Values are presented as number (%) or mean±standard deviation. P-value obtained from t-test.
GFR, glomerular filtration rate; ISS, Injury Severity Score; ICU, intensive care unit; MVD, mechanical ventilator days.
*P<0.05; †P<0.1.

Lastly, several recent studies showed that reduced renal function was associated with an increased risk of pneumonia [19]. An explanation for this is that decreased renal function may increase the risk of infection due to immune impairment, which is supported by reports of abnormalities in neutrophil and lymphocyte function [20]. The observed association between kidney function and infection may be due to an increased susceptibility to infection and/or a greater severity of infection in older patients with chronic kidney disease [21]. Our study also showed similar results, as decreased renal function was associated with VAE occurrence and in-hospital mortality. VAEs themselves did not affect the risk of in-hospital mortality. However, patients with a low GFR showed a statistically significant increase in mortality. In other words, posttraumatic acute kidney injury (AKI) can be a direct risk factor for mortality in trauma patients. Harrois et al. [22] performed a systematic review and meta-analysis of AKIs in trauma patients that included 24 studies with 25,182 patients. In their analysis, they observed that posttraumatic AKI was associated with a 3.4-fold increased risk of mortality (95% CI, 2.1–5.7) and they observed that the risk factors for posttraumatic AKI were specific race, old age, hypertension, and diabetes mellitus. In our study, we performed a subgroup analysis based on GFR that showed statistically significant differences in patients' age (P=0.0153) and hypertension (P=0.0388) between the two groups (Table 7).

This study had several limitations. First, the study period was short, and the sample size was small. Although we were able to derive several risk factors associated with VAE occurrence and in-hospital mortality, it is necessary to estimate more significant risk factors using a largescale study in the future. Second, although the number of bronchoscopies was significantly higher (P=0.004) in the VAE group, we were not able to establish a significant effect of bronchoscopy on VAE occurrence and in-hospital mortality. However, there is some evidence that diagnostic bronchoscopy may improve VAP-related outcomes [23,24]. Bronchoscopic sputum aspiration has also shown promising results and significant benefits in various indicators, including shorter mechanical ventilation, reduced hospital LOS, and improved weaning success rates [25]. Considering these points, it will also be necessary to study whether bronchoscopy may affect the occurrence and mortality rate of VAE in trauma patients. Third, in this study, the effect of tracheostomy was not considered in patients with a mechanical ventilator. However, tracheostomy may have several advantages, such as improved airway suctioning, less direct laryngeal injury, decreased airway resistance for promoting weaning from mechanical ventilation, and decreased risk for nosocomial pneumonia [26]. Thus, research on the association between tracheostomy and VAE occurrence is needed in the future.

In conclusion, based on our study results, traumatized patients with chest AIS ≥3 or GFR <75 mL/min/1.73 m^2 on admission should be intensively monitored to detect patients at risk for VAEs and modify their care plans to reduce the risk of VAEs during mechanical ventilator support. VAEs should be closely monitored to identify infections in the target subjects early and to achieve desirable results. We should also actively consider modalities that can minimize the duration of mechanical ventilators (less than 15 days) in patients with a chest AIS ≥3 to reduce VAE occurrence.

NOTES

Ethical statements

The study was approved by the Institutional Review Board of the Cheju Halla General Hospital (No. 2021-L06-01). Informed consent was waived due to the retrospective nature of the study.

Conflicts of interest

The authors have no conflicts of interest to declare.

Funding

None.

Author contributions

Conceptualization: TYL, JWO, MKL, JSK, JES; Data curation: TYL, JWO, JES, JHW; Formal analysis: MKL, JSK, JHW; Methodology: TYL, JWO, MKL, JES; Project administration: TYL, JWO; Visualization: JSK, JHW; Writing–original draft: all authors; Writing–review & editing: all authors.
All authors read and approved the final manuscript.

Additional information

This study was posted at the 2021 Pan Pacific Trauma Congress (PPTC).

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