Driving Pressure and Lung Injury in Mechanically Ventilated Patients without Acute Respiratory Distress Syndrome

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Abstract

Background: Driving pressure is associated with mortality in patients with acute respiratory distress syndrome (ARDS). However, whether driving pressure is associated with outcomes in mechanically ventilated patients without ARDS is unknown.

Objective: This study primarily aimed to determine the association between driving pressure and severe lung injury (lung injury score ≥ 2.5). The secondary outcomes were to determine the cutoff point of driving pressure associated with severe lung injury and compare patient mortality between severe and non-severe lung injury score in mechanically ventilated patients without ARDS.

Methods: Mechanically ventilated patients without ARDS admitted in the intensive care unit (ICU) of Faculty of Medicine Vajira Hospital, Navamindradhiraj University, Bangkok, Thailand, between 2018 and 2020 were enrolled. Baseline characteristics including sex, age, diagnosis, sedative drug, and lung mechanic from the ventilator were recorded. Moreover, the patients' driving pressure [plateau pressure–positive end expiratory pressure (PEEP)] and lung injury score were obtained. Multivariable logistic regression analysis was performed to determine associations between driving pressure and patient lung severity with lung injury score. The mechanically ventilated patients without ARDS were categorized according to lung injury score ≥ 2.5; then, a severe form of the area under the receiver operating characteristic (AuROC), as a dependent outcome, was observed to determine the association between driving pressure and severe lung injury. The optimal cutoff point of driving pressure that determined severe lung injury was calculated by Youden's index.

Result: In total, 155 mechanically ventilated patients without ARDS were enrolled. Overall mortality was 28.3%. Driving pressure was associated with severe lung injury (OR, 1.28; 95% CI, 1.15–1.42; p-value <0.001). A good discriminative ability of driving pressure to determine severe lung injury was noted (AuROC = 0.859; 95%CI, 0.768–0.950). The optimal cutoff point of driving pressure indicating severe lung injury was 16 cmH_2O with, 89.5% sensitivity (95% CI, 66.9–98.7), 75% specificity (95% CI, 66.9–82.0), 33.3% positive predictive value (95% CI, 20.8–47.9), and 98.1% negative predictive value (95% CI, 93.2–99.8).

Conclusion: In mechanically ventilated patients without ARDS, increased driving pressure was associated with severe lung injury. A driving pressure >16 cmH_2O was associated with severe lung injury.

Keywords: driving pressure, severe lung injury, lung injury score, acute respiratory distress syndrome

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การศึกษาความสัมพันธ์ของค่าความดันต้นทางและปลายทางเดินหายใจกับการบาดเจ็บเนื้อปอดในผู้ป่วยวิกฤตที่ไม่มีภาวะหายใจลำบากเฉียบพลัน

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บทคัดย่อ

บทนำ: ความดันต้นทางและปลายทางเดินหายใจ (driving pressure) มีความสัมพันธ์กับอัตราการตายในผู้ป่วยที่มีภาวะหายใจลำบาก แต่ในกลุ่มผู้ป่วยที่ใส่เครื่องช่วยหายใจที่ไม่มีภาวะหายใจลำบากเฉียบพลัน [without acute respiratory distress syndrome (ARDS)] ยังไม่มีข้อมูลว่าค่าความดันต้นทางและปลายทางเดินหายใจจะส่งผลต่อผู้ป่วยอย่างไร

วัตถุประสงค์:

วัตถุประสงค์หลัก

1. เพื่อศึกษาความสัมพันธ์ของค่าความดันต้นทางและปลายทางเดินหายใจ (driving pressure) กับ lung injury score ในกลุ่มผู้ป่วยที่ไม่มีภาวะหายใจลำบากเฉียบพลัน (without-ARDS)
2. หาค่าความดันต้นทางและปลายทางเดินหายใจ (driving pressure) ที่มีผลต่ออัตราการเสียชีวิตในผู้ป่วยที่ไม่มีภาวะหายใจลำบากเฉียบพลัน (without-ARDS)

วัตถุประสงค์รอง

1. เปรียบเทียบอัตราการเสียชีวิตของกลุ่มที่ lung injury score < 2.5 และ ≥ 2.5

วิธีดำเนินการวิจัย: รวบรวมผู้ป่วยคนที่ใส่เครื่องช่วยหายใจที่ไม่มีภาวะหายใจลำบากเฉียบพลันในหอผู้ป่วยวิกฤตและหอผู้ป่วยกึ่งวิกฤตในคณะแพทยศาสตร์วชิรพยาบาลระหว่างปีพุทธศักราช 2561-2563 เพื่อเก็บข้อมูลค่าความดันต้นทางและปลายทางเดินหายใจ (driving pressure) ค่าการบาดเจ็บเนื้อปอด (lung injury score) และข้อมูลพื้นฐานของผู้ป่วยได้แก่ เพศ อายุ การวินิจฉัย ยาระงับอาการกระวนกระวาย วิเคราะห์ข้อมูลโดยใช้วิธี Multivariable logistic regression analysis, Receiver operating characteristic (ROC) และ Area under curve (AUC) เพื่อวิเคราะห์ความสัมพันธ์ของข้อมูล ใช้วิธี Youden’s index เพื่อหาค่าจุดตัดที่เหมาะสมของค่าความดันต้นทางและปลายทางเดินหายใจในผู้ป่วยที่ไม่มีภาวะหายใจลำบากเฉียบพลัน

วันที่รับบทความ: 16 มิถุนายน 2563 **วันแก้ไขบทความ:** 26 พฤศจิกายน 2563 **วันตอบรับบทความ:** 10 ธันวาคม 2563

ผลการวิจัย: กลุ่มตัวอย่างเป็นผู้ป่วยวิกฤตที่ใส่เครื่องช่วยหายใจและไม่มีภาวะหายใจลำบากเฉียบพลัน (non-ARDS) ที่ได้รับการรักษาในหออภิบาลผู้ป่วยวิกฤตและหออภิบาลผู้ป่วยกึ่งวิกฤตจำนวน 155 คน ผลการศึกษาพบว่า ค่าความดันต้นทางเดินและปลายทางหายใจ (driving pressure) มีความสัมพันธ์กับการบาดเจ็บเนื้อปอดในระดับ severe lung injury (lung injury score ≥2.5) ในผู้ป่วยวิกฤตที่ไม่ใช่กลุ่มที่มีภาวะหายใจลำบากเฉียบพลันอย่างมีนัยสำคัญทางสถิติ (OR = 1.28, 95%CI: 1.15-1.42, p-value < 0.001) และพบว่า ค่าความดันต้นทางและปลายทางเดินหายใจ (driving pressure))ที่มีค่ามากกว่าหรือเท่ากับ 16 สามารถพยากรณ์การบาดเจ็บเนื้อปอดรุนแรง (lung injury score ≥2.5) ได้ โดยมีค่าความไว (sensitivity) ร้อยละ 89.5 (95%CI: 66.9-98.7) ความจำเพาะ (specificity) ร้อยละ 75 (95%CI: 66.9-82.0) ค่าคาดทำนายของผลบวก (positive predictive value, PPV) ร้อยละ 33.3 (95%CI: 20.8-47.9) และค่าคาดทำนายของผลลบ (negative predictive value, NPV) ร้อยละ 98.1 (95%CI: 93.2-99.8)

สรุป: ในกลุ่มผู้ป่วยที่ใส่เครื่องช่วยหายใจและไม่มีภาวะหายใจลำบากเฉียบพลัน ความดันต้นทางเดินและปลายทางหายใจ (driving pressure) มีความสัมพันธ์กับการบาดเจ็บเนื้อปอดในระดับ severe lung injury อย่างมีนัยสำคัญทางสถิติ และพบว่า driving pressure ที่มากกว่าหรือเท่ากับ 16 สามารถพยากรณ์การเกิดการบาดเจ็บเนื้อปอดที่รุนแรง (lung injury score ≥2.5) ในผู้ป่วยวิกฤตที่ไม่มีภาวะหายใจลำบากเฉียบพลัน (without-ARDS)

คำสำคัญ: ความดันต้นทางและปลายทางเดินหายใจ, ค่าการบาดเจ็บเนื้อปอด, ARDS

วันที่รับบทความ: 16 มิถุนายน 2563 **วันแก้ไขบทความ:** 26 พฤศจิกายน 2563 **วันตอบรับบทความ:** 10 ธันวาคม 2563

Introduction

Acute lung injury resulting from mechanical ventilation is common in critically ill patients and associated with poor outcomes including increased patient disability and mortality[1]. Lung injury is caused by lung stress and strain. Lung stress is due to an increase in lung pressure from an external force applied to the lung's cross-sectional area (measured in N/mm² or pascal units). Lung strain occurs subsequently due to shape and length changes of the lung in response to an applied stress[1-3]. Stress and strain are important mechanisms to determine lung injury.

Katira et al. investigated a mouse's lungs by abruptly weaning from mechanical ventilation and reducing positive end expiratory pressure (PEEP) from 3–11 to 0 mmHg. Electron microscopy was performed, and microvascular leak was measured by Evans blue dye. Measuring the left ventricular end diastolic pressure (LVEDP) showed that LVEDP increases when deflation increased left ventricular preload and afterload that elevates pulmonary microvascular pressure and wet/dry lung ratio from the leak of water substance with abrupt deflation and supported the theory that lung injury occurs in mechanically ventilated patients[4].

In some recent studies, lung injury score was used as a follow-up parameter along the treatment course; for example, a study by Tongyoo et al.[5] investigated the use of corticosteroid in early sepsis patients. Their study showed that the patient group who received corticosteroid had better responses (better PaO2-FiO2 ratio). The lung injury score (cutoff point at 2.5) was lesser in the group who received corticosteroids than in the group who did not. Lung injury score is the basic parameter to determine lung injury severity a score ≥ 2.5 indicated severe lung injury[6-7]. Soto et al.[8] studied lung injury prediction scores of hospital patients and showed that increased injury prediction score was associated with ARDS, with a cutoff point ≥ 4. Amato et al. collated all studies about driving pressure and its related clinical results and revealed that the patient group who had increased driving pressure had the highest mortality, and the patient group who had lower driving pressure had decreased mortality; after multivariate adjustment at patient level was applied according to the median values of driving pressure, plateau pressure, and tidal volume. The ventilator variables did not improve the association of tidal volume and plateau pressure with survival; however, it improved the association of driving pressure with survival. An explanation of the decreased mortality is decreasing ventilator support induced lung injury[9].

In a study by Talmor et al., mechanical ventilation of ARDS patients was adjusted, particularly the esophageal pressure, and the result was compared with that of the control group; the esophageal pressure guide group had higher PEEP level, and the difference was statistically significant. The esophageal pressure guide group had higher plateau pressure than the conventional group. The transpulmonary pressure in the esophageal pressure guide and control groups were similar, potentially affecting and decreasing lung injury and most likely reducing mortality even though there was no statistical significance[10]. Moreover, another study reported on the decrease of lung injury through other ways, such as the use of neuromuscular blocking agents in ARDS patients. Papazian et al. studied severe ARDS patients by evaluating clinical outcomes after neuromuscular blocker therapy. Their study showed improved 90-day survival without increased muscle weakness[11]. Several studies limited the breath quantity of the lungs to not more than 6-8 ml/kg compared to conventional tidal volumes. All of these results of reduced mortality, respiratory cytokines, or progression to ARDS due to decrease ventilator-induced lung injury[12-13].

There is still no study on whether the driving pressure in patients without ARDS affects or reduces lung injury and on the ideal driving pressure. Therefore, this study aimed to find the relevance of driving pressure and lung injury score in critically ill patients without ARDS and determine the cutoff point and whether there are differences from the ARDS patient group which has 15 cmH_2O.

The objective of this prospective study was to investigate the association between driving pressure and severe lung injury in mechanically ventilated patients without ARDS and in turn determine the optimal cutoff level of driving pressure that affects the severity of lung injury in mechanically ventilated patients without ARDS. Secondary outcome was to compare the mortality between severe and not severe lung injury, according to patient lung injury score.

Methods

We included 155 mechanically ventilated patients without ARDS admitted in the ICU of Faculty of Medicine, Vajira Hospital, Bangkok, Thailand, between October 2018 and January 2020. Patient baseline characteristics including sex, age, diagnosis, sedative drug, and mechanical ventilation parameters were recorded. Driving pressure was calculated from plateau pressure subtracted by PEEP[9] on hospitalization days 1 and 3. The average lung injury score[14] was calculated involving four components, including the number of consolidation quadrants on chest X-ray, PaO2/FiO2, PEEP level, and respiratory system compliance on days 1 and 3.

Study design

A prospective cohort study was applied. Patients who did not meet the Berlin definition of ARDS that were treated in the ICU of Faculty of Medicine, Vajira Hospital were included. Patients aged 18 years old or above, receiving sedative and analgesic drugs, with controlled breathing or breathing under mechanical ventilation without resistance, and using assisted ventilator for more than 48 hours were included. The exclusion was patients with unstable hemodynamics while on mechanical ventilation. Eligible participants whose condition progressed to ARDS or patients who were successfully extubated within 72 hours after enrollment were terminated from the study.

Sample Size

The sample size for diagnostic test study by using specificity was calculated as follows. $Z\alpha/2$ is the standard value under normal curve associated with level of significance. By level of significance, $\alpha = 0.05$ then $Z\alpha/2 = 1.96$, with absolute error at 5% (d = 0.05). As regards the probability of expected specificity (Sp), since there is no study on this topic, there was no specificity of reference; hence, the researchers set the specificity at 90% (Sp = 0.90). The study "The large observational study to understand the global impact of severe acute respiratory failure (LUNG SAFE)[14]," which included 50 ICUs worldwide, showed that prevalence of lung injury and ARDS are 10.4%. Thus, the formula to find the number of patients for this research is 155 patients.

Variable and Definition of Variable

Independent Variable

1. Driving pressure (Plateau pressure – PEEP)[9]

2. Lung injury score (lung X-ray, hypoxemic score (PaO2/FiO2), PEEP score, and respiratory compliance score)[14]

Confounding Variable and Partiality

Age more than 65 years old, obesity, positive fluid balance, and respiratory effort. (This research did not exclude patients who were above 65 years old and obese and had positive fluid balance.)

Definition of Variables

1. Lung injury score is the overall score from chest X-ray, PaO2/FiO2 score, positive and expiratory pressure scores, and respiratory system compliance score (tidal volume/plateau pressure–PEEP), using ml/cmH2O. Higher rates indicate inflammation in the lungs, particularly higher than 2.5.

2. Driving pressure is the driving force to breathe, which equals to pressure differences of plateau pressure and PEEP.

3. Sedative drugs include opioids and benzodiazepines.

4. Respiratory effort is the patients' breathing efforts, in which if these efforts are overly increased, breathing might not be associated with mechanical ventilation and the rates will be less or more than accurate.

5. ARDS (acute respiratory distress syndrome) is an acute respiratory condition which happens when the lung tissues are severely damaged and is identified with the Berlin definition: patients have acute onset within 7 days, patients' lung radiation show bilateral opacity, and patients have unexplained opacity by cardiac failure or fluid overload and exchange abnormal oxygenation, PaO2/FiO2 ≤ 300 mmHg with PEEP ≥ 5[15].

Methodology and the process of volunteer researcher agreement

After the volunteers were admitted in the hospital's ICU or semi-ICU, the researcher will consider inclusion/exclusion criteria for basic information, age, sex, sedative drug, congenital disease, and medical record assumption.

The driving pressure and lung injury score were collected at the same time as the volunteers put on mechanical ventilation.

Driving pressure: collected the data by measuring plateau pressure and PEEP before calculating driving pressure in days 1 and 3 for driving pressure average collection.

- Lung injury score (Table 1): collected the data by calculating from chest X-ray results, ABG, PaO2/FiO2, and lung compliance in days 1 and 3 after joining the research and using the highest lung injury score.

For volume control ventilation mode, inserts inspiratory hold for 5 seconds and measures the pressure before calculating the driving pressure, according to driving pressure = plateau pressure–PEEP.

For pressure control ventilation, plateau pressure is equal to inspired pressure.

Table 1:
Components of the Murray lung injury score[14]

Lung injury score					
Score	Consolidation on chest x-ray	PaO2/Fi02	PEEP	Compliance = TV/ plateau pressure-PEEP	Total
0	No consolidation	≥300	≤5	≥80	
0.25	1 quadrant	225-299	6-8	60-79	
0.50	2 quadrants	175-224	9-11	40-59	
0.75	3 quadrants	100-174	12-14	20-39	
1	4 quadrant	<100	≥15	≤19	
total score 0 = no lung injury, total score ≥ 2.5 = severe lung injury					

Measuring the driving pressure was done after the patients were admitted in the ICU and received primary treatment until hemodynamics were stable in days 1 and 3 after joining the research.

Since this study collected data from patients with breathing tubes and who were receiving sedative drugs according to medical indications, the dose of the sedative drug have been deemed as appropriate for the individual patient as stated by the primary doctor.

The Process of Volunteer Researcher Agreement

The primary doctor in the patients' ward asked for a verbal and written permission instantly after the patients meet the inclusion criteria. Moreover, the volunteers' representative were signed the consent agreement to let the researcher took a blood sample. Normally, the patients in the ICU ward would be analyzed for arterial blood gas frequently; in this study, the blood gas had to be obtained daily during the data collection period.

Variable Measuring Instruments

The variable parameter (driving pressure, compliance) were measured by GE Carescape R860^{TM} and Hamilton G5 model.

IRB

Research work has been approved by the research committee of Navamindradhiraj University.

Statistical Analysis

Analyzing and Presenting Data

Continuous variables were presented by mean and standard deviation (SD) or median and interquartile range 1–3 (IQR 1–3) and compared by categorical variable and were presented by number count and percentage; a comparison by multivariable logistic regression analysis was done to identify the association between driving pressure and lung injury score and survival. The area under the receiver operating characteristic (AuROC) was analyzed to identify how driving pressure causes severe lung injury using Youden's index.

Results

Overall, 155 mechanically ventilated patients without ARDS were enrolled. The basic information showed that 60% of them were male with mean aged 66 years old. The most common underlying disease was hypertension (36.8%), followed by diabetes mellitus (20.64%) and ischemic stroke (12.3%). Most of the participants group was diagnosed with sepsis (23.2%), pneumonia (31.0%), and acute coronary syndrome/congestive heart failure (9%) and other diagnoses (36.7%) while treating other conditions such as stroke, status epilepticus, bed ridden with aspiration, neuromuscular disease, volume overload in end-stage kidney disease, and diabetic ketoacidosis. Almost half of (43.9%) the participants received sedative drugs such as fentanyl (40.6%), midazolam (12.9%), and cisatracurium (3.9%). Radiography showed that the median of PEEP was 5 cmH2O, plateau pressure was 19.1 cmH2O (IQR, 16.5–24.6), driving pressure was 14 cmH2O (IQR, 11.3–17.8), consolidation score of chest X-ray was 0.5 (infiltration 2 quadrant, IQR 0.25–0.5), PaO2/FiO2 score was 0.25 (P/F ratio, 225–299;(IQR 0.0–0.5), PEEP score was 0 (PEEP ≤ 5 IQR, 0.0–0.25), compliance score was 0.75 (compliance, 20–39 ml/cmH2O; IQR, 0.50–0.75), and tidal volume was 8–10 ml/predicted bodyweight (Table 2).

The primary outcome was an analysis using logistic regression analysis; we found a significant association between driving pressure and severe lung injury in mechanically ventilated patients without ARDS (OR, 1.28; 95% CI, 1.15–1.42; p-value < 0.001) which remained statistically significant when adjusted by covariates (adjOR, 1.28; 95% CI, 1.14–1.43; p-value < 0.001) (Table 3).

Table 2:
Baseline characteristics of the without ARDS patients (n = 155)

Characteristics	n(%)
Gender	
Male	93 (60.0)
Female	62 (40.0)
Age (year), mean (SD)	66.26 ± 17.36
Underlying disease	128 (82.6)
HTN	57 (36.8)
DM	32 (20.6)
DLP	4 (2.6)
CKD	15 (9.7)
COPD	12 (7.7)
Ischemic stroke	19 (12.3)
Coronary disease	14 (10.9)
Diagnosis	
Sepsis	36 (23.2)
Pneumonia	48 (31.0)
ACS/CHF	14 (9.0)
Other	57 (36.7)
Sedative drug	68 (43.9)
Fentanyl	63 (40.6)
Midazolam	20 (12.9)
Cisatracurium	6 (3.9)
PEEP	5 (5–6)
Plateau pressure	19.1 (16.5–24.6)
Driving pressure	14 (11.3–17.8)
Consolidation chest X-ray (score)	0.5 (0.25–0.5)
PaO2/FiO2 (score)	0.25 (0.0–0.5)
PEEP (score)	0 (0.0–0.25)
Compliance(score)	0.75 (0.50–0.75)

Data are presented as number (%), mean ± SD, or median (interquartile range).
HTN, hypertension; DM, diabetes mellitus; DLP, dyslipidemia; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; ACS, acute coronary syndrome; CHF, congestive heart failure; PaO2, partial pressure of arterial oxygen; FiO2, inspired oxygen fraction

Table 3:
Multivariable logistic regression model for severe lung injury (lung injury score ≥2.5)

Factors	Univariable analysis			Multivariable analysis		
	OR[1]	95%CI	p-value	OR_{adj}[2]	95%CI	p-value
Driving pressure	1.28	(1.15–1.42)	<0.001	1.28	(1.14–1.43)	<0.001
Age	0.98	(0.95–1.00)	0.080	0.98	(0.94–1.02)	0.239
Underlying disease	0.40	(0.14–1.16)	0.090	0.36	(0.09–1.45)	0.150
Diagnosis						
Sepsis	0.59	(0.16–2.13)	0.417	0.42	(0.08–2.18)	0.303
Pneumonia	1.35	(0.50–3.68)	0.555	1.55	(0.41–5.89)	0.524
Sedative drug	4.25	(1.45–12.49)	0.008	4.02	(1.09–14.77)	0.036

Note: OR, odds ratio; OR_{adj}, adjusted odds ratio; CI, confident interval.
[1] Crude odds ratio estimated by binary logistic regression.
[2] Adjusted odds ratio estimated by multiple logistic regression adjusted for gender, age, underlying diseases, diagnosis, sedative drug, and driving pressure.

The secondary outcome was to determine the driving pressure to discriminate severe lung injury in mechanically ventilated patients without ARDS, which was excellent, AuROC = 0.859 (95% CI, 0.768–0.950) (Figure 1).

The optimal cutoff of driving pressure for discriminating severe lung injury using Youden's index was 16 cmH_2O with 89.5% sensitivity (95% CI, 66.9–98.7), 75% specificity (95% CI, 66.9–82.0), 33.3% positive predictive value (PPV) (95% CI, 20.8–47.9), and 98.9% negative predictive value (NPV) (95% CI, 94.2–100) (Table 4).

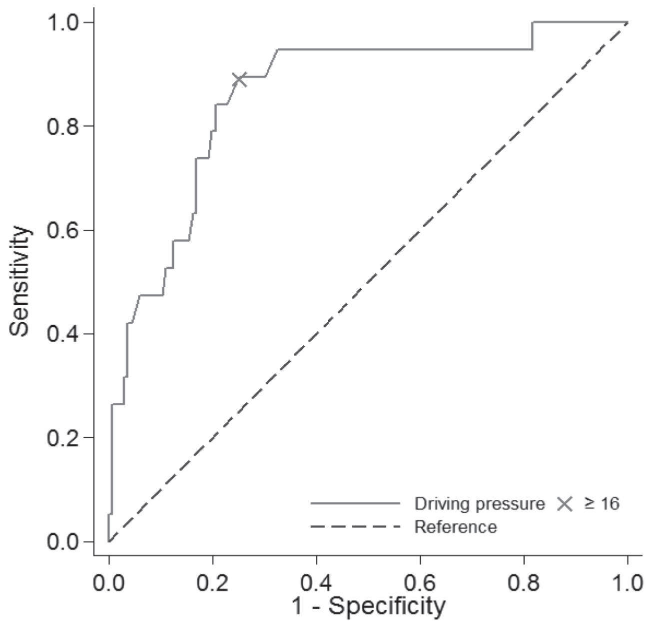

Figure 1: The discriminative ability of driving pressure for predicting severe lung injury. The area under the receiver operating characteristic curve value was 0.859 (95% CI, 0.768–0.950).

Table 4:
The diagnosis performance of driving pressure for discriminating severe lung injury

Parameter	Cutoff	Sensitivity	Specificity	PPV	NPV	LR+	LR-
Driving pressure	≥15	94.7 (74.0–99.9)	67.6 (59.1–75.4)	29.0 (18.2–41.9)	98.9 (94.2–100)	2.93 (2.25–3.82)	0.08 (0.01–0.53)
Driving pressure	≥16*	89.5 (66.9–98.7)	75.0 (66.9–82.0)	33.3 (20.8–47.9)	98.1 (93.2–99.8)	3.58 (2.57–4.98)	0.14 (0.04–0.52)

Note: PPV, positive predictive value; NPV, negative predictive value; LR, likelihood ratio
* Optimal diagnostic thresholds were determined by Youden's index.

In comparing survival between patients who had driving pressure ≥16 cmH2O and patients who had driving pressure <16 cmH2O, we found that the former had lesser survival; however, it was not statistically significant (p = 0.147) by log-rank test (Figure 2).

Additionally, Table 5 shows baseline characteristics between patients who survived and those who did not. The result demonstrated that less survival were found in patients with severe lung injury than those with non-severe injury (p-value = 0.007) (Figure 3). The hazard ratio for death with severe lung injury was 2.25; 95% CI, 1.22–4.14; p-value = 0.009 and remained significant HR adj = 2.11; 95% CI, 1.21–3.99; p-value = 0.021 when controlling influence of confounding variable (Table 6).

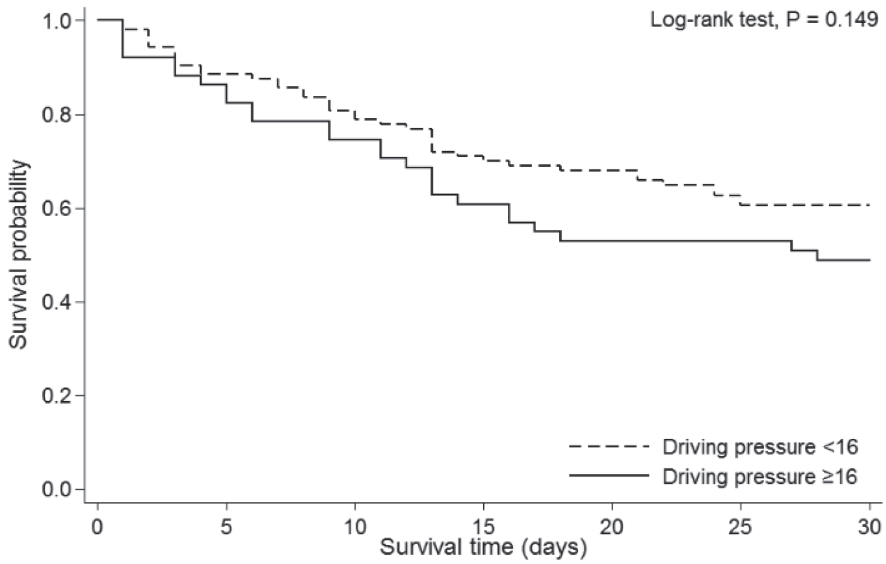

Figure 2: Kaplan–Meier curve of survival probability of driving pressure <16 cmH2O and driving pressure ≥16 cmH2O

Table 5:
Baseline characteristics of non-ARDS patients who died and lived

Variables	Died (n = 44)	Lived (n = 111)	P-value
Male gender	28 (63.6)	65 (58.5)	0.426
Age (years)	69.61 ± 16.11	63.78 ± 17.91	0.038
Underlying disease	54 (81.8)	74 (83.1)	0.829
Diagnosis			
Sepsis	6 (9.1)	30 (33.7)	<0.001
Pneumonia	20 (30.3)	28 (31.5)	0.878
Sedative drug	30 (45.5)	38 (42.7)	0.732
Lung injury score	1.55 ± 0.75	1.39 ± 0.62	0.153
Lung injury score ≥2.5	13 (19.7)	6 (6.7)	0.015
PEEP	5 (5–7.25)	5 (5–5)	0.069
Plateau pressure	20.2 (16.9–26.025)	19 (16.4–22.5)	0.122
Driving pressure	14 (11.4–18.5)	14 (11.2–16.6)	0.348
Consolidation CXR (score)	0.50 (0.25–0.75)	0.25 (0.12–0.50)	0.243
PaO2/FiO2 (score)	0.25 (0–0.5)	0.25 (0–0.5)	0.641
PEEP (score)	0 (0–0.25)	0 (0–0)	0.7
Compliance(score)	0.75 (0.5–0.75)	0.75 (0.5–0.75)	0.467

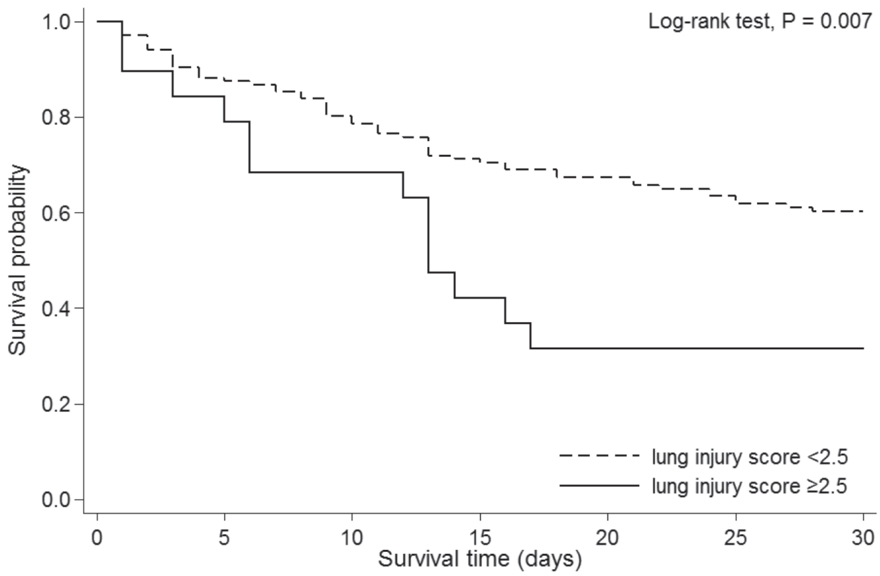

Figure 3: Kaplan–Meier curve of survival probability of lung injury score <2.5 and lung injury score ≥2.5

Table 6:
Cox proportional hazard model for mortality

Factors	Univariable analysis			Multivariable analysis		
	HR	95%CI	p-value	HR_{adj}	95%CI	p-value
Lung injury score ≥2.5	2.25	(1.22–4.14)	0.009	2.11	(1.12–3.99)	0.021
Age	1.02	(1.01–1.03)	0.031	1.02	(1.01–1.04)	0.010
Underlying disease	0.98	(0.53–1.84)	0.957	0.84	(0.42–1.68)	0.624
Diagnosis						
Sepsis	3.90	(1.68–9.04)	0.001	3.63	(1.56–8.47)	0.003
Pneumonia	1.01	(0.60–1.71)	0.974	0.82	(0.48–1.40)	0.475
Sedative drug	1.10	(0.68–1.79)	0.700	1.01	(0.61–1.67)	0.962

Discussion

In this study, we showed that driving pressure was associated with severe lung injury (≥ 2.5) in mechanically ventilated patients without ARDS, and we detected a trends toward significant mortality of a high driving pressure. It was also well known that driving pressure was an issue of concern in ARDS patients where driving pressure was significantly associated with mortality[16-17]. We found no relationship between compliance and plateau pressure on mortality in our patients, suggesting that volutrauma, which depends on the relationship of tidal volume and lung size or functional residual capacity[18], in our sample population might be different from that of ARDS patients. Our study noted that respiratory compliance, driving pressure, and plateau pressure between the survived and did-not-survive groups was not significantly different, which is consistent with prior studies[19]. Neto As et al. reported that patients were at risk for ARDS if their lung injury score was > 4 and if they used high PEEP (higher PEEP score). Moreover, they found an increase in mortality in this group[20]. In our study, the PEEP score between the groups was not significantly different. It may be due to the fact that the efficacy of PEEP to reduce lung stress and strain in patient without ARDS is still unknown. In our study, lung injury score was significantly associated with mortality, same with previous studies[20]. We postulated to use lung injury score in mechanically ventilated patients without ARDS to predict mortality and attempted to keep the lung injury score below 2.5.

Our study was the first to explore the association between driving pressure and lung injury score in mechanically ventilated patients without ARDS. There were several possible explanations why driving pressure influenced lung injury. First, high driving pressure can precede lung injury from many previous studies[8] especially in ARDS patients. The negative pleural pressure swing and patient-ventilator asynchrony contribute in the development of ventilator-induced lung injury as well as the use of sedative drugs.

Among patient included in our study, 53.5% showed no abnormality on chest radiography and 9% had rapid resolution during imaging (which indicate cardiogenic pulmonary edema). Patient-ventilator asynchrony or ventilator-induced lung injury was unexampled. Driving pressure in this group was lower than others. In the subgroup of this study's population, sepsis patients (23.2%) received fluid for resuscitation and restored hemodynamics, and if excessive fluid treatment occurred, it can lead to serious complications such as pulmonary edema that can worsen lung injury and frequently adjusted ventilator to maintain adequate oxygenation and ventilation. In subgroup of sepsis other than pulmonary caused was calculated lower lung injury score and driving pressure on admission after that developed higher driving pressure and higher lung injury score follow changed in the clinical setting and duration of admission. Our research suggested that driving pressure potentially help tailor ventilator and improved the management of patient without ARDS. Driving pressure ≥16 cmH2O in mechanically ventilated patients without ARDS is associated with severe lung injury.

Limitation of our study were not be informative for other mode of ventilation and breathing effort was not evaluated. In a patient with more breathing effort, the driving pressure was changed.

Conclusion

In mechanically ventilated patients without ARDS, driving pressure was associated with severe lung injury. Driving pressure ≥16 was highly associated with severe lung injury, and severe lung injury was associated with mortality. This study confirms that driving pressure is also an important parameter to consider in minimizing lung injury in mechanically ventilated patients without ARDS.

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