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Factors related to adjusting positive end-expiratory pressure guided by transpulmonary pressure in acute respiratory distress syndrome: a prospective analysis of Vietnamese patients

Tu Ngoc Nguyen[1,2,*], Ngan Hoang Kim Trieu[2], Thanh Chi Pham[2], Linh Thanh Tran[2], Xuan Thi Phan[3], Thao Thi Ngoc Pham[1,2]

[1]Department of Emergency and Critical Care Medicine, University of Medicine and Pharmacy at Ho Chi Minh City, Ho Chi Minh City, Vietnam
[2]Intensive Care Unit, Cho Ray Hospital, Ho Chi Minh City, Vietnam
[3]Intensive Care Unit, Tam Anh Hospital, Ho Chi Minh City, Vietnam

Abstract

Introduction: Critically ill patients often face elevated chest wall weight and increased pleural pressures. Positive transpulmonary end-expiratory pressure (P_L-exp) indicative of chest wall mechanical stiffness of the chest wall and has been evidenced to improve blood oxygenation and respiratory mechanics. Our study focuses on the incidence of positive P_L-exp in initial Positive End-Expiratory Pressure (PEEP) settings and to identify factors for adjustments of PEEP adjustments in Vietnamese patients with Acute Respiratory Distress Syndrome (ARDS).

Method: The study was conducted on 46 patients with moderate to severe ARDS from November 2021 to October 2023, in a tertiary hospital in Vietnam. Patients were divided into two groups based on PL-exp: the Constant PEEP group (P_L-exp > 0 cm H_2O) and the Adjusted PEEP group (P_L-exp > 10 or < 0 cm H_2O). The primary outcome measured was the incidence of positive P_L-exp. Secondary outcomes included the number of ventilator days, length of hospital stay, and in-hospital mortality.

Results: This study included 46 patients with a mean age of 49.8 years and a Body Mass Index (BMI) of 24.7 kg/m^2. Of those patients, 76.1% had moderate ARDS, and 23.9% severe ARDS. The incidence of positive P_L-exp was 41.3%. The factors significantly related to the included BMI and initial PEEP settings.

Conclusions: Our study demonstrated an incidence of positive P_L-exp of 41.3%. Adjusting PEEP settings may be beneficial for ARDS patients with high BMI within Vietnamese populations. Further research is necessary to optimize and individualize PEEP settings in ARDS patients to improve clinical outcomes.

Keywords: respiratory distress syndrome; body mass index; positive-pressure respiration

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*Corresponding author: Tu Ngoc Nguyen. Department of Emergency and Critical Care Medicine, University of Medicine and Pharmacy at Ho Chi Minh City, Ho Chi Minh City, Vietnam. E-mail: ngoctu@ump.edu.vn

1. INTRODUCTION

Critically ill patients frequently encounter increased chest wall weight and elevated pleural pressures, often resulting from multiple factors such as edema, pleural effusions, increased abdominal hypertension, and other causes [1,2]. These conditions can lead to alveolar derecruitment, increased lung elastance, and subsequent hypoxemia in Acute Respiratory Distress Syndrome (ARDS) [1]. A major challenge in ARDS treatment is effectively titrating positive end-expiratory pressure (PEEP) to align with the physiological characteristics of each patient. Transpulmonary pressure, reflecting the mechanical stiffness of the chest wall, may accurately represent the shear stress applied to the alveoli injuries [3]. Positive transpulmonary end-expiratory pressure (P_L-exp) has been evidenced to improve blood oxygenation and respiratory mechanics in previous studies [4,5]. However, titrated PEEP guided by esophageal pressure has been less frequently studied in Vietnamese populations, limiting clinicians ability to make individualized PEEP adjustments for ARDS patients. Therefore, our study aims to determine the incidence of positive P_L-exp in the initial PEEP setting and identify factors related to adjustments of PEEP-guided by positive P_L-exp to optimize and individualize PEEP settings in ARDS patients.

2. MATERIALS AND METHODS

2.1. Population study

We collected data from all patients aged 16 and above who were admitted to the mixed Intensive Care Unit (ICU) of Cho Ray Hospital, a tertiary hospital in Vietnam. Our study, conducted from November 2021 to October 2023, focused on patients diagnosed with moderate to severe ARDS according to the Berlin Definition criteria [6]. Exclusion criteria encompassed various conditions such as contraindications for esophageal pressure catheter placement, receipt of extracorporeal membrane oxygenation or prone position ventilation, severe coagulopathy, history of lung transplant, history of chronic obstructive pulmonary disease, presence of an active bronchopleural fistula, neuromuscular disorders, severe coagulopathy, pulmonary embolism, lung transplants, absence of adequate tools, or a declined to participate in the study, see Fig. 1.

2.2. Measurements and ventilation strategy

Patients eligible for the study were subjected to mechanical ventilation using the ELISA 800 Ventilator (Löwenstein, Germany) under the ARDSNet protocol (Table 1), targeting optimal respiratory function [7]. The ventilation strategy involved low tidal volumes set at 6–8 mL/kg of predicted body weight (PBW), while maintaining the plateau pressure (Pplat)≤30 cm H_2O. In scenarios where the plateau pressures>30 cm H_2O, a reduction in VT to as low as 4 mL/kg PBW was implemented, subsequently establishing a plateau pressure threshold of 35 cm H_2O. The protocol set the arterial oxygen saturation target within the range of 88%–95%, or partial pressure of arterial oxygen (PaO_2) between 55–80 mmHg. Arterial pH of 7.30 to 7.45, respiratory rates were limited to a maximum of 35 breaths per minute. Adjustments in PEEP were meticulously managed to optimize oxygenation while minimizing the risk of adverse hemodynamic effects. An esophageal pressure balloon (Nutrivent™, Mirandola, Italy) was inserted, and patients were sedated and given muscle relaxations when necessary. This facilitated the measurement of esophageal pressure (Pes) and enabled the calculation of transpulmonary pressure using the formulae: Transpulmonary end-inspiration pressure (P_L-insp) = Plateau pressure – Pes-insp, and transpulmonary end-expiration pressure = PEEPtotal – Pes-exp. Patients were divided into two groups based on P_L-exp: the constant PEEP group (P_L-exp>0 cm H_2O) and the adjusted PEEP group (P_L-exp> 10 or <0 cm H_2O). Finally, PEEP was modified to achieve a P_L-exp minimal range of 0–10 cm H_2O. Intrinsic PEEP levels were monitored before and after each adjustment, and the inspiratory/expiratory ratio was carefully regulated to avert the presence of auto-PEEP.

2.3. Data collection

We recorded patient demographics including age, sex, body mass index (BMI), ARDS risk factors, and scores including Sequential Organ Failure Assessment (SOFA)

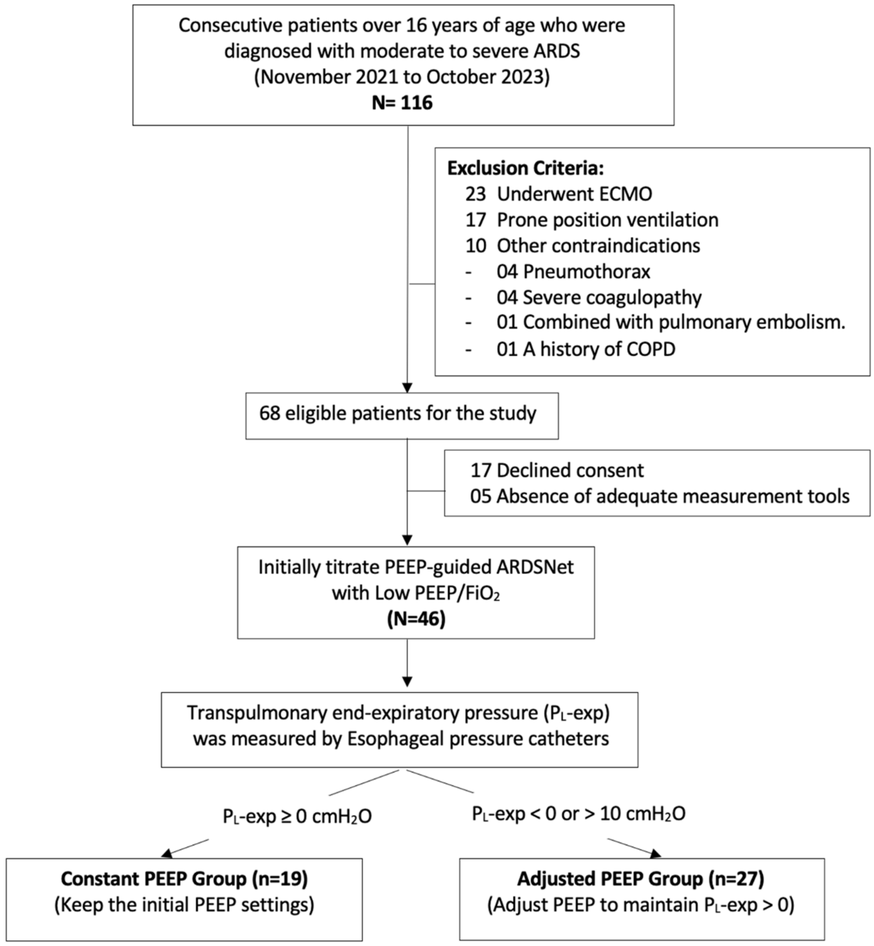

Fig. 1. Flowchart of the study. ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; ECMO, extracorporeal membrane oxygenation; PEEP, positive end-expiratory pressure; P_L-exp, transpulmonary end-expiratory pressure.

score, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, Vasopressor Index Score (VIS), and Radiographic Assessment of Lung Edema (RALE) score at ICU admission. Respiratory mechanics parameters were also collected encompassing airway driving pressure (DP), plateau pressure (Pplat), transpulmonary end-expiratory/inspiratory pressure, esophageal end-expiratory/inspiratory pressure (Pes-exp/insp), and respiratory system compliance (Crs). The primary outcome was the incidence of positive P_L-exp with secondary outcomes included ventilator days, hospital stay duration, and in-hospital mortality.

2.4. Statistics analysis

Categorical variables are expressed as numerical data and percentages, and their analysis was conducted using Fisher's exact test. Prior to analysis, continuous variables were assessed for normality using the Shapiro-Wilk test. Variables with a normal distribution are presented as mean±SD, while those non-normally distributed variables are reported as the median (25th–75th percentile). Comparisons of continuous variables between the Constant PEEP group and the Adjusted PEEP group were conducted using student's t-test or the Mann-Whitney U test, as appropriate. Risk factors associated with adjusting PEEP were explored through both univariable and multivariable logistic regression, with odds ratios (OR) and 95% confidence interval (CI) estimated. All statistical analyses were performed by R 3.6.2, and a two-sided p-value<0.05 was considered statistically significant.

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Table 1. Ventilator settings using ARDSNet low PEEP/FiO_2 and transpulmonary end-expiratory pressure strategy

ARDSNet - Low PEEP/FiO_2		Transpulmonary end-expiratory pressure (P_L-exp)	
FiO_2 (%)	PEEP (cm H_2O)	FiO_2	P_L-exp (cm H_2O)
30	5	40	0
40		50	
40	8	50	2
50		60	
50	10	60	4
60		70	
70		70	6
70	12	80	
70	14	80	8
80		90	
90		90	10
90	16	100	
90	18		
100	20–24		

PEEP, positive end-expiratory pressure.

2.5. Medical ethics

The study was approved by the Institutional Review Board of Cho Ray Hospital's Ethics Committee in Biomedical Research (Approval Number 1229/GCN-HĐĐĐ) on November 3, 2021. All participants written informed consent or their legally authorized representatives. The study was conducted in adherence to the ethical principles of the Declaration of Helsinki.

3. RESULTS

3.1. Characteristic of patients

Our cohort comprised 46 patients, with a mean age of 49.8 years, and a male predominance of 69.6%. The mean BMI was 24.7 kg/m². The majority of patients (76.1%) were classified as having moderate ARDS ($PaO_2/FiO_2<200$), while 23.9% had severe ARDS ($PaO_2/FiO_2<100$). Common observed risk factors for ARDS included pneumonia (39.1%) and sepsis or septic shock (37.0%). Lung contusion and pancreatitis each accounted for 8.7% of cases, with four patients presenting with each condition. Other contributing factors comprised 6.5% of cases. Respiratory mechanics revealed a median plateau pressure of 27.0 cm H_2O [IQR 24.0–29.0], airway DP of 17.0 cm H_2O [IQR 14.0–20.0], and respiratory system compliance (Crs) of 23.8 mL/cm H_2O [IQR 19.7–27.7], as summarized in Table 2.

3.2. Incidence and factors related to adjusting positive end-expiratory pressure (PEEP) to positive transpulmonary end-expiratory pressure (P_L-exp)

In our study, patients were stratified into two distinct group based on the PEEP-guided P_L-exp: a Constant PEEP group (comprising19 patients) and an Adjusted PEEP group (comprising 27 patients). The findings of our study indicated that the incidence of positive P_L-exp at 41.3% (19 out of 46 patients) and 58.7% of the patients required adjustments in PEEP to achieve a P_L-exp within the range of 0–10 cm H_2O. Notably, none of the patients had a P_L-exp>10 cm H_2O, nor was there a reduction in the initial PEEP setting. All 19 patients in the Constant PEEP group had an increase in PEEP, with the median of PEEP changes at 2 cm H_2O [IQR 2–4].

Respiratory parameters showed variations between the groups. Airway DP displayed a significant variance, with medians of 15 cm H_2O [IQR 13–16.8] in the Constant PEEP group and 19 cm H_2O [IQR 16.2–20.9] in the Adjusted PEEP group ($p=0.001$). Similarly, respiratory system compliance (Crs) also demonstrated significant difference, with a median of 26.5 mL/cm H_2O [IQR 24.3–29.2] in the Constant PEEP group compared to 20.6 mL/cm H_2O [IQR 18.3–24.5] in the Adjusted PEEP group ($p=0.001$). Adjust PEEP level was +2 cm H_2O [IQR 2–4] and the respiratory mechanics for the two groups are presented in Table 2.

Regarding the secondary outcomes, including mortality rate, duration of mechanical ventilation, and length of hospital stay, our analysis revealed no significant differences between the constant PEEP group and the adjusted PEEP group. Furthermore, our regression analysis, utilizing both univariable and multivariable logistic regression with a Backward stepwise approach, identified BMI, and initial PEEP settings as significant factors associated with adjusting PEEP to achieve a P_L-exp above zero, as detailed in Table 3.

Table 2. Baseline characteristics of the patients in two groups of PEEP settings guided transpulmonary pressure

Variable	Total (n=46)	Constant PEEP group (n=19)	Adjusted PEEP group (n=27)	p-value
Characteristics of patients				
Age (year)	49.8±15.5	50.6±18.7	49.1±13.2	0.517
Male, n (%)	32 (69.6)	14 (73.7)	18 (66.7)	0.854
BMI (kg/m^2)	24.2 [21.4–27.4]	22.1 [19.5–23.7]	26.2 [24.2–29.3]	<0.001*
Actual body weight (kg)	67 [55.0–75.0]	55 [51.5–62.5]	70 [64.5–80]	0.001*
SOFA score	10.0 [8.0–13.8]	11 [8–14]	10 [8–12]	0.522
APACHE II score	19.0 [16.3–26.8]	21 [17.5–25.5]	19 [16–27.5]	0.591
CCI score	2 [1–3]	2 [1–3]	1 [1–3]	0.782
VIS score	5.6 [0–13.5]	5.3 [0–16.4]	5.9 [0–12.8]	0.954
Lactate (mmol/L)	2.2 [1.5–3.1]	2.35 [1.84–3]	1.9 [1.56–3.26]	0.321
Heart rate (beat/min)	114 [101–128]	120 [104–131]	110 [101–127]	0.455
Mean arterial pressure (mmHg)	86.7 [76.7–93.8]	86.7 [79.0–91.0]	86.7 [75.5–98.2]	0.606
ARDS classification, n (%)				
Moderate (PaO_2/FiO_2<200)	35 (76.1)	15 (78.9)	20 (74.1)	1
Severe (PaO_2/FiO_2<100)	11 (23.9)	4 (21.1)	7 (25.9)	
Air blood gas				
pH	7.4 [7.35–7.45]	7.4 [7.34–7.44]	7.4 [7.35–7.47]	0.655
$PaCO_2$ (mmHg)	39.9 [35.2–43.3]	42.1 [36.4–44.3]	39 [34.4–42]	0.174
PaO_2 (mmHg)	81.4 [67.2–97.4]	81.4 [70.1–104]	77 [65.6–93.2]	0.468
Respiratory parameters				
Tidal volume (mL)	400 [380–400]	400 [380–400]	400 [390–410]	0.377
Respiratory rate (rate/min)	22.0 [20.0–25.0]	24 [20–26]	22 [20–24.5]	0.417
PEEP (cm H_2O)	10 [8–10]	10 [10–12]	8 [8–10]	0.002*
FiO_2 (%)	60 [52–80]	60 [57–78]	60 [50–80]	0.867
Airway driving pressure (cm H_2O)	17.0 [14.0–20.0]	15 [13–16.8]	19 [16.2–20.9]	0.001*
Plateau pressure (cm H_2O)	27.0 [24.0–29.0]	25 [22.5–27]	28 [26–29]	0.065
Crs (mL/cm H_2O)	23.8 [19.7–27.7]	26.5 [24.3–29.2]	20.6 [18.3–24.5]	0.001*
Adjusting PEEP	2 [0–2]	0 [0–0]	2 [2–4]	<0.001*
Outcomes				
Ventilator days (days)	12 [8–20]	12.0 [9.5–17.5]	12.0 [8.0–22.0]	0.729
Length of hospital stay (days)	19.0 [14.0–25.8]	16.0 [14.0–21.0]	21.0 [14.0–27.0]	0.241
In-hospital mortality, n (%)	18 (39.1)	8 (42.1)	10 (37.0)	0.728

Data are presented as n (%) for categorical variables and the median (interquartile range) for nonparametric variables.
APACHE-II, Acute Physiologic Assessment and Chronic Health Evaluation-II; BMI, body mass index; CCI, Charlson Comorbidity Index; Crs, compliance respiratory system; SOFA, Sequential Organ Failure Assessment; FiO_2, fraction of inspired oxygen; PaO_2, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure; VIS, Vasopressor Index Score.

4. DISCUSSION

Critically ill patients frequently experience elevated chest wall weight and increased pleural pressures, secondary risk factors such as edema, pleural effusions, increased abdominal hypertension, and other causes [1,2]. These conditions contribute to alveolar derecruitment, increased lung elastance, and subsequent hypoxemia [1]. Prior investigations have underscored the efficacy of PEEP settings guided by esophageal pressure, targeting a positive P_L-exp [4,5]. The Pes-guided PEEP group showed significantly better oxygenation with a 42% increase in PaO_2/FIO_2 and a 45% increase in respiratory system compliance at 72 hours. Due to the significant impact on oxygenation, this trial was terminated

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Table 3. Analysis of univariate and multivariate logistic regression with backward stepwise selection on adjusting PEEP

Variables	Univariable analysis			Multivariable analysis		
	OR	95%CI	p-value	Adjusted OR	95%CI	p-value
BMI (kg/m^2)	1.44	1.14–1.82	0.002	1.50	1.12–2.02	0.007
Weight (kg)	1.12	1.04–1.20	0.002	NA	NA	NA
Initial PEEP setting (cm H_2O)	0.57	0.38–0.85	0.006	0.54	0.3–0.98	0.044
Airway DP (cm H_2O)	1.40	1.12–1.75	0.003	NA	NA	NA
Crs (ml/cm H_2O)	0.81	0.7–0.93	0.004	0.81	0.7–1.01	0.069

CI, confidence interval; BMI, body mass index; Crs, compliance respiratory system; DP, driving pressure; OR, odd ratio; PEEP, positive end-expiratory pressure; NA, not applicable.

prematurely. Settings that achieve a transpulmonary pressure greater than zero were recommended, especially in patients with a stiff chest wall or high pleural pressure [1,8]. Our study unveiled a 41.3% of incidence of positive P_L-exp among ARDS patients (19 out of 46 patients). Moreover, our findings highlighted that BMI and initial PEEP settings played pivotal roles in the adjusting PEEP to maintain positive P_L-exp, We observed no significant disparities in secondary outcomes, including in-hospital mortality and length of hospital stay, between the constant and adjusted PEEP groups.

Certainly, ensuring PEEP levels to maintain a P_L-exp greater than zero has been shown to mitigate atelectasis and the cyclical opening and closing of alveoli, improving pulmonary mechanics and oxygenation [9]. In our study, the initial PEEP set approach to the low PEEP-FiO_2 strategy of the ARDSNet was associated with an increase in PEEP in 58.7% (27/46) of patients to achieve positive P_L-exp. The EPVent trial conducted by Talmor et al. [5] which involved 61 ARDS patients, a Pes-guided PEEP titration strategy was compared with the low PEEP/FIO_2 strategy. The findings revealed that 90% of patients in the Pes-guided PEEP strategy group required an increase in PEEP to achieve a transpulmonary end-expiratory pressure above zero. Similarly, Wang et al. [10] reported on 23 traumatic ARDS patients where the esophageal pressure group had a mean of 12±4 cm H_2O, higher than the PEEP titration value of 8±3 cm H_2O in the ARDSNet group, with a significance of $p<0.05$. Additionally, the lack of notable variance in secondary outcomes, including in-hospital mortality and length of hospital stay between the two groups, underscores the safety associated with PEEP adjustment. Therefore, it is suggested that in patients with moderate and severe ARDS, adhereing to the ARDSNet low PEEP/FiO_2 table settings may still hold promise for lung recruitability.

Given the complexities of mechanical ventilation in high BMI patients, it is imperative to take into account the physiological changes. Bime et al. [11] highlighted that increased abdominal pressure and added mass of the chest wall in obese patients often necessitate the use of higher PEEP levels to reduce the risk of atelectasis compared to non-obese. Similarly, Pirrone et al. [12] demonstrated that the PEEP values employed in clinical practice (11±3 cm H_2O) may be inadequate for optimazing ventilation in obese patients.

In Asian populations, where individuals typically have smaller anthropometric measurements compared ot those in European or American cohorts, the application of tritrated PEEP guided by esophageal pressure has been less explored. Additionally, it is notable that the World Health Organization has set a lower threshold for obesity in Asia-Pacific populations (BMI≥25 kg/m^2) compared to the general standard (BMI 30≥kg/m^2) [13–15]. In our study, the high BMI associated with increased PEEP to maintain positive P_L-exp due to high BMI patients present with increased chest wall elastance and decreased pulmonary compliance, leading to lower or negative transpulmonary pressure values [16,17] Consistent with our findings, Mezidi et al. [18] reported that COVID-19 ARDS patients with a BMI>30 require higher PEEP (16 cm H_2O versus 10 cm H_2O) levels to achieve positive P_L-exp. Furthermore, Kassis et al. also highlighted the specific challenges in obese patients due to these alterations in chest wall elastance. They pointed out that the DP in such cases does not accurately reflect the true transpulmonary DP [17]. Therefore, we suggeste monitoring of transpulmonary pressure to titrate PEEP adjustments in patients with high BMI.

The research is subject to several limitations. Firstly, the single-center design and relatvely small sample size may limit the generalizability of the findings to larger and more diverse populations. Additionally, the absence of intra-abdominal pressure measurements in our study is noteworthy. These limitations should be considered with caution when interpreting the results, emphasizing the need for more comprehensive future studies to build upon our findings.

5. CONCLUSION

The study showed that the incidence of positive P_L-exp at 41.3% and adjusting PEEP may be beneficial in patients with high BMI in moderate to severe ARDS patients within Vietnamese populations. We suggest monitoring the transpulmonary pressure to individualize PEEP in high BMI patients. Further research is necessary to optimize and individualize PEEP settings in ARDS patients.

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Conflict of interest

No potential conflict of interest relevant to this article was reported.

ORCID

Tu Ngoc Nguyen
https://orcid.org/0000-0002-6832-9510
Ngan Hoang Kim Trieu
https://orcid.org/0000-0001-8723-7964
Thanh Chi Pham
https://orcid.org/0009-0003-6619-2535
Linh Thanh Tran
https://orcid.org/0000-0001-5595-8855
Xuan Thi Phan
https://orcid.org/0000-0003-0846-0688
Thao Thi Ngoc Pham
https://orcid.org/0000-0002-8312-2390

Authors' contributions

Data curation: TN Nguyen, NHK Trieu, TC Pham.
Methodology: TN Nguyen, TC Pham.
Investigation: TN Nguyen, NHK Trieu, TC Pham, LT Tran.
Writing - original draft: TN Nguyen, NHK Trieu.
Writing - review & editing: TN Nguyen, NHK Trieu, TC Pham, LT Tran, XT Phan, TTN Pham.

Availability of data and material

Upon reasonable request, the datasets of this study can be available from the corresponding author.

Ethics Approval

The study was approved by the Ethics Committee in Biomedical Research of Cho Ray Hospital (No. 1229/GCN-HĐĐĐ) on November 3, 2021.

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