Evaluating the Impact of Ventilator-Associated Parameters on Ventilation Free Days of non-ARDS Patients in ICU.

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Research

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Abstract

Background: Critically ill patients are not only mechanically ventilated because of ARDS, what kind of ventilation parameter setting is the optimal ventilation strategy for non-ARDS ICU patients?

Methods: A retrospective cohort study for non-ARDS patients who received mechanical ventilation (MV), performed univariate, multivariate regression analysis, covariate balancing propensity score and inverse-probability-of-treatment weighting, and machines learning models to predict different outcomes. The included predicted factors are four parameters of mechanical ventilation (Driving pressure (DP) and its mediation of tidal volumes (VT) and positive end-expiratory pressure (PEEP), mechanical power (MP)), and the primary outcome was the ventilator-free days (VFD) at day 28.

Results: The study included 2932 patients, low DP, low PEEP and low MP for non-ARDS patients could prolong VFD at day 28, reduce in-hospital mortality and length of hospital stay. However, the VT has no prognostic significance for the population. Among machine learning models with VFD, the randomforest had the best prediction.

Conclusions: For non-ARDS patients who receive invasive ventilation for at least 48 hours, low DP, low PEEP and low MP are beneficial to the population. However, the effect of VT is inconclusive.

1. Background

Mechanical ventilation (MV) could cause ventilator-associated events (VAE), affecting the patients' clinical prognosis'. It is the ventilator's parameter settings, driving pressure (DP) and its mediation of tidal volumes (VT), positive end-expiratory pressure (PEEP) and mechanical power (MP) have a major impact on clinical outcome in patients suffering MV".

Luckily, hospital practice promoted the declining incidence of ARDS, and most patients undergoing MV have no ARDS. There is no consensus on ventilation strategies for non-ARDS patients. Most of the population focus on the above settings from the lessons of ARDS patients based on the protective ventilation.

Therefore, our study aims to discover the association between the four major parameters of MV and the patients' VFD. We hypothesized that the low level of DP, VT, PEEP, and DP may improve the clinical outcome of the patients without ARDS.

2. Methods

2.1 Database

The MIMIC-III database (v1.4) integrated de-identified, comprehensive clinical data of the patients admitted to the ICUs from 2001 to 2012'. Since the study was an analysis of the third party anonymized

publicly available database with institutional review board (IRB) approval, IRB approval was exempted.

2.2 Study Population

Only patients of the first ICU admission of the first hospitalization were recruited. We chose adult patients aged no less than 16 years who consecutively received MV for at least 48 hours. Patients with tracheotomy or death or ARDS according to the Berlin definition during the first 48 hours of ventilation was excluded.

2.3 Data Extraction and Management

Use PostgreSQL (v10.10) to obtain the patients' epidemiological characteristics: age, gender, ethnicity, height, weight, comorbidities, the primary International Classification of Diseases (ICD)–9 diagnosis, the Oxford Acute Severity of Illness Score (OASIS), MV of the first and second day of life and laboratory indicators, and clinical prognosis.

All ventilation variables were extracted as the highest and lowest values per 6 h. Excluding patients with height missing and less than 130 cm, then the predicted body weight (PBW) based on the patient's height and gender was calculated. VT size was normalized for PBW. The patient's DP was obtained by subtracting the PEEP from the plat pressure. Integrated calculation of respiratory rate (RR), peak pressure (P_{peak}), VT and DP for MP (J/min) = $0.098 \times VT \times RR \times (P_{\text{peak}} - 1/2 \times DP)$.

As for the other missing data, we assumed they were missing at random, and less than 10% was replicated with multiple imputation.

2.4 Statistical Analysis

Because patients' condition on the first day was unstable with many confounding factors, the first and second day were analyzed separately, and the ventilator parameters on the second day are utilized for regression analysis. The primary outcome was the VFD at day 28 (defined as the number of days from successfully weaning to day 28). Secondary outcomes included in-hospital mortality, ICU, 30-day, and 1-year mortality, and ICU and hospital length of stay (LOS).

Regression analysis and survival analysis performed on related indicators of MV, including DP, VT, PEEP and MP, influencing factors as age, pH, SpO_2 , mean blood pressure (MBP), $PaCO_2$, temperature, OASIS. According to the cutoff of 13 cmH₂O for DP, the population was divided into the high and low DP group. They were subsequently divided into high and low VT/PEEP subgroups according to the VT threshold of 7.5 mL/kg PBW and the PEEP threshold of 10 cmH₂O, which were eventually divided into 8 subgroups. In addition, obese (body mass index (BMI) ≥ 30 kg/m²), and aged (age ≥ 65) subgroups were added.

Then the model adjusted by covariate balancing propensity score (CBPS) and inverse-probability-of-treatment weighting (IPTW). According to Ary Serpa Neto's method, using $IPTW = 1 / ((z \times CBPS) + ((1 - z) \times (1 - CBPS)))$ Where z was receipt of the eight subgroups to adjust the deviation of dynamic changes on time and ventilation parameters.

The population was divided into the training set and test set (90/10), using 5 folds cross-validation and 5-time repeats. Using the machine learning model including regularization (ridge regression, Least absolute shrinkage and selection operator (LASSO) regression and elastic networks), regression trees and random forests, neural networks, and ensemble learning models. The evaluation of numerical outcome is root mean square error (RMSE), and area under curve (AUC), f-score, error ratio for the analysis of the categorical variables.

A two-tailed $P < 0.05$ was considered statistically significant. All statistical analysis was conducted on the R platform (v3.6.1) (<http://www.R-project.org>).

3 Results

3.1 Patients Characteristics

2932 non-ARDS patients were included in our study, most were male (56.9%), with a median age of 66 years, mainly from the source of emergency (86%), 4.7% of patients had COPD, and 6.1% had asthma. The median of the VFD on the 28th was 20.5 days, the LOS in ICU was 9.7 days, and the hospital stay was 15.9 days. 27.4% of patients died on discharge, and the mortality rate of thirty-day and one-year was 26.5% and 41.5%, respectively.

The median of DP on the first day of the population was 14 cmH₂O, VT was 8 mL/kg PBW, PEEP was 5.5 cmH₂O, and MP was 19.53J/min. On the second day, the median of DP for the patient was 13 cmH₂O, VT was 8.6 mL/kg PBW, and PEEP was 5.3 cmH₂O, and MP was 18.83J/min. [Table 1]

3.2 Primary and Secondary Outcomes

The regression results showed that the DP(OR=-0.17, 95%CI(-0.24,-0.09)), PEEP(OR=-0.44, 95%CI(-0.54,-0.33)) and MP(OR=-0.14, 95%CI(-0.18,-0.11)) of non-ARDS patients after 24 hours of MV were associated with VFD, and this correlation (OR= -0.62, 95%CI(-0.70,-0.54) for DP, OR = 0.65, 95%CI (0.58,0.72) for PEEP, OR= -0.11, 95%CI (-0.14,-0.09) for MP) persisted after IPTW; However, the correlation of VT (OR = 0.10, 95%CI(-0.08,0.29)) after correction (OR = 0, 95%CI(-0.11,0.09)) was still not significant[Table 2]. PEEP and MP were significantly related with the patients' survival [Table 3.1,4]. Only low DP and low PEEP subgroup could prolong the VFD of non-ARDS patients. However, the association gone after the IPTW adjustment. In-hospital mortality was not significantly related to the above parameter settings expect for the low DP and low PEEP subgroup [Table 3.2]. [Figure1]

3.3 Model Training and Performance

Ranking the importance of the correlation and the most relevant factors involved lactate levels, basic respiratory diseases, renal replacement and cardiovascular active drug therapy, OASIS, RR, pH, temperature, plat pressure, peak pressure [Table 5]. In terms of the prediction of VFD, the randomforest had the lowest RMSE prediction of 43.68. As for in-hospital mortality, the gradient-lifting model has the best effect, with AUC was 0.93, error rate was 0.09, f-score was 0.87 [Table 6].

3.4 Subgroup and sensitivity analyses

Low MP was a protective factor for the population not only for the VFD, but the mortality and LOS. The Aged may result in poor clinical outcomes in non-ARDS patients. Interestingly, obesity was also a tricky risk factor for prognosis in patients, they tended to have lower in-hospital mortality and longer hospital stays. [Table 3.3]

4 Discussion

The ventilator settings for non-ARDS patients in this study mainly explored the following clinical problems: 1) low DP, PEEP and MP could prolong VFD, reduce the ratio of mortality and LOS, however, the effect of VT was inclusive. The beneficial effects of combined strategies need to be further explored; 2) Aged patients had worse outcome, and obese patients had longer VFD, lower mortality ratio, and longer hospital stays; 3) The machine learning models on the prognosis of the population were well-predicted.

The lower DP level, the better patient's prognosis. The DP reflects the strain during each respiratory cycle. For ARDS patients, DP is an independent risky and the most critical ventilation factor for survival, the reduced DP could improve survival ratio of the population, and higher DP was connected with postoperative pulmonary complications and high ratio of mortality. However, a retrospective study of MIMIC-II public database showed that the DP on the first 24 hours was not related to the patient's mortality.

Low VT may benefit non-ARDS patients. Low VT was associated with better clinical outcomes, a low mortality ratio, shorter VFD, and lower risk of pulmonary complications, but had little more need for sedation or analgesia. Different ventilation strategies for non-ARDS, such as high VT and low PEEP were better on improving lung compliance, while low VT and low PEEP were associated with shorter LOS. However, the difference of VFD in the 21 days was small in another RCT. In addition, a multi-center retrospective study conducted by PROVENT (Practice of Ventilation in critically ill patients without ARDS at onset of ventilation) in the year of 2016 and 2018 showed that there was little association between VT and clinical prognosis. The results of a trial on protective ventilation in patients without ARDS will soon be on the way. Our analysis shows that VT has little to do with the patient's prognosis, probably because of a clinical consensus on the low VT ventilation strategy.

Low VT may increase alveolar instability, and PEEP could maintain alveolar open, minimize lung damage, and avoid atelectasis and oxygen toxicity³⁵. High PEEP reduced the incidence of ARDS and hypoxemia, but not for VFD and in-hospital mortality, and prophylactic PEEP in non-hypoxic patients could reduce the occurrence of hypoxia and pneumonia. An RCT evaluating the impact on PEEP for non-ARDS patients is still in progress.

MP refers to the energy transferred to the patient's respiratory system during MV which could be an independent predictor of mortality in ARDS patients, and high level of MP was a risk factor for critically ill

patients' clinical prognosis¹⁶. Could it serve as a novel biomarker for the lung in patients without ARDS?

In patients undergoing MV, the aged has bad clinical prognosis, however, obese patients suffering ARDS tended to have lower mortality and fewer VFD, but not for hospital stays compared with the normal-weight patients'. Prognosis studies exclusive for the obese without ARDS are incomplete.

5 Conclusions

Low level of DP, PEEP and MP, not for low VT, are associated with prolonged VFD and low in-hospital mortality in adult critically ill patients.

Abbreviations

ARDS(acute respiratory distress syndrome); ICU(intensive care units); MIMIC(medical information mart for intensive care); MV(machine ventilation); PBW(predicted body weight); DP(driving pressure); VT(tidal volume); PEEP(positive end-expiratory pressure); MP(mechanical power); COPD(chronic obstructive pulmonary disease); CRRT(continuous renal replacement therapy); OASIS(the oxford acute severity of illness score); VFD(ventilator-free days); VAEs(ventilator-associated events); PRoVENT(practice of ventilation in critically ill patients without ARDS at onset of ventilation); BMI(body mass index); CBPS(covariate balancing propensity score); IPTW(inverse-probability-of-treatment weighting); LASSO(least absolute shrinkage and selection operator); ROC(receiver operator characteristic curve); AUC(the area under the curve); RMSE(root mean square error); OR(odds ratios); IQR(interquartile range); XGBoost(extreme gradient boosting).

Declarations

Ethics approval and consent to participate: Since the study was an analysis of the third party anonymized publicly available database with institutional review board (IRB) approval, IRB approval was exempted.

Consent for publication: Written informed consent for publication was obtained from all participants.

Availability of data and materials: The datasets generated analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declared that they have no conflict of interest.

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Author's contributions: Na Liu designed the study, performed the data collection, data analysis, and data interpretation, and wrote the manuscript. Jinxuan Ren designed the study, performed the data interpretation, and reviewed the manuscript. Lina Yu performed the data interpretation, and reviewed the

manuscript. Junran Xie designed the study, performed the data interpretation, and reviewed the manuscript.

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Tables

Table1. Baseline Characteristics of Non-ARDS Patients

characteristic	Median(IQR) or No.(%)
No. of non-ARDS Patients	2932
Female Gender	1265(43.2)
Age	66(52-70)
PBW(Kg)	63.87(54.75-73.11)
COPD	137(4.7)
Asthma	179(6.1)
OASIS	38(32-43)
VasopressorsFirstday	1556(53.1)
RTTFirstday	141(4.8)
Hospital Expire Flag	802(27.4)
Thirtyday Expire Flag	776(26.5)
Oneyear Expire Flag	1218(41.5)
Duration Vent Total Days	6.3(3.7-11.4)
Ventilator-Free Days	20.5(0-24.3)
ICU LOS Days	9.7(6.0-16.2)
Hospital LOS Days	15.9(9.9-25.3)
DAY1	
Heartrate(bpm)	88(77-100)
MeanBP(mmHg)	76(70-83)
Temperature(°C)	37.1(36.6-37.6)
SpO ₂	98.3(96.9-99.3)
Rass	3.0(2.6-3.4)
PaCO ₂ (mmHg)	39.5(35.0-44.0)
FiO ₂	55(45-70)
pH	7.37(7.33-7.42)
Lactate	2.05(1.35-3.15)
Tidal Volume(mL)	557(492-635)
VT(mL/Kg PBW)	8.8(7.7-10.1)
Plateau Pressure(cmH ₂ O)	20.5(17.0-24.0)
PEEP(cmH ₂ O)	5.5(5.0-7.5)
DP(cmH ₂ O)	14(11-16.5)
MP(J/min)	19.53(15.15,25.87)
DAY2	
Heartrate(bpm)	88(77-98)
MeanBP(mmHg)	77(71-85)
Temperature(°C)	37.3(36.8-37.8)
SpO ₂	98.0(96.6-99.1)
Rass	3.1(3.0-3.6)
PaCO ₂ (mmHg)	38.5(34.5-43.5)
FiO ₂	45(40-50)
pH	7.41(7.36-7.44)
Lactate	1.45(1.10-2.05)
Tidal Volume(mL)	540(470-625)
VT(mL/Kg PBW)	8.6(7.5-9.8)

Plateau Pressure(cmH ₂ O)	20(16.5-24.0)
PEEP(cmH ₂ O)	5.3(5.0-9.0)
DP(cmH ₂ O)	13(10.5-16.0)
MP(J/min)	18.83(13.99,25.58)

Table2. Regression Analysis for Ventilator-Free Days

	Univariable Model		Multivariable Model		IPTW	
	Odds Ratio (95% CI)	P Value	Odds Ratio (95% CI)	P Value	Odds Ratio (95% CI)	P Value
DP	-0.17(-0.24,0.09)	1.30e-05	-0.13(-0.20,-0.05)	0.00069	-0.62(-0.70,-0.54)	< 2e-16
VT	0.10(-0.08,0.29)	0.26	0.16(-0.02,0.34)	0.079	0(-0.11,0.09)	0.88
PEEP	-0.44(-0.54,-0.33)	2.00e-16	-0.31(-0.42,-0.20)	1.78e-08	0.65(0.58,0.72)	< 2e-16
MP	-0.14(-0.18,-0.11)	1.25e-14	-0.07(-0.12,-0.03)	0.00207	-0.11(-0.14,-0.09)	< 2e-16
Age	-0.03(-0.04,-0.02)	2.78e-11	-0.02(-0.03,-0.01)	1.40e-07	-0.07(-0.08,-0.05)	< 2e-16
OASIS	-0.26(-0.31,-0.22)	2.00e-16	-0.18(-0.22,-0.01)	4.70e-14	-0.17(-0.20,-0.13)	< 2e-16
pH	25.75(19.72,31.78)	2.00e-16	0.42(0.26,0.59)	3.70e-07	0.78(0.04,0.89)	< 2e-16
SpO ₂	0.65(0.49,0.80)	2.83e-16	0(-0.03,0.04)	0.780	0.05(0.04,0.07)	1.18e-13
MeanBP	0.08(0.04,0.11)	3.22e-05	13.99(7.26,20.71)	4.69e-05	2.42(-0.41,5.24)	0.09
PaCO ₂	0.06(0.02,0.11)	0.007	1.22(0.67,1.78)	1.47e-05	1.21(0.98,1.44)	< 2e-16
Temp	1.81(1.25,2.38)	3.41e-10	0.11(0.06,0.16)	8.14e-06	0.28(0.26,0.30)	< 2e-16

Table3.1 Primary and Secondary Outcomes Analysis of Ventilator Parameters

	DP		VT		PEEP	
	Odds Ratio(95%CI)	P Value	Odds Ratio(95%CI)	P Value	Odds Ratio(95%CI)	P Value
Primary Outcome						
Multivariable Model	-0.13(-0.20,-0.05)	0.0007	0.16(-0.02,0.34)	0.079	-0.31(-0.42,-0.22)	1.78e-08
IPTW	-0.62(-0.70,-0.54)	< 2e-16	0(-0.1,0.1)	0.96	0.44(0.36,0.52)	< 2e-16
Secondary Outcomes						
In-hospital Mortality	0.01(0,0.03)	0.10	-0.03(-0.07,0.01)	0.21	0(0.02,0.03)	0.52
30-Day Mortality	0.01(0,0.03)	0.12	-0.04(-0.09,0)	0.06	0(-0.03,0.03)	0.97
1-Year Mortality	0.02(0,0.03)	0.02	0(-0.05,0.03)	0.65	0(-0.03,0.02)	0.78
ICU Length of Stay	0.70(0.53,0.81)	4.38e-16	2.68(2.46,2.90)	< 2e-16	0.76(0.59,0.93)	< 2e-16
Hospital Length of Stay	1.90(1.70,2.11)	< 2e-16	2.95(2.69,3.22)	< 2e-16	0.65(0.44,0.86)	9.17e-10

Table3.2 Primary and Secondary Outcomes Analysis of Ventilation Subgroups

	Low DP				High DP			
	Low VT	n=464	High VT	n=1070	Low PEEP	n=1285	High PEEP	n=249
	OR(95%CI)	P Value	OR(95%CI)	P Value	OR(95%CI)	P Value	OR(95%CI)	P Value
Primary Outcome								
Multivariable Model	NA	NA	0.15(-0.95,1.24)	0.79	3.34(1.56,5.11)	0.00023	1.96(-0.05,3.97)	0.05
IPTW	NA	NA	-0.31(-0.33,-0.30)	< 2e-16	0.24(-0.09,940)	0.96	0.17(-0.09,910)	0.97
Secondary Outcomes								
In-hospital Mortality	NA	NA	0.06(-0.20,0.33)	0.66	-0.14(-0.55,0.27)	0.49	-0.25(-0.71,0.21)	0.29
30-Day Mortality	NA	NA	0.05(-0.21,0.32)	0.71	-0.04(-0.45,0.38)	0.86	-0.26(-0.73,0.21)	0.28
1-Year Mortality	NA	NA	0.08(-0.16,0.32)	0.53	-0.06(-0.44,0.32)	0.76	-0.26(-0.70,0.17)	0.23
ICU Length of Stay	NA	NA	-0.12(-1.26,1.02)	0.84	-7.50(-9.34,-5.65)	2.49e-15	-2.63(-1.26,1.02)	0.01
Hospital Length of Stay	NA	NA	-0.26(-1.97,1.46)	0.77	-6.27(-9.05,-3.50)	9.75e-06	-2.68(-5.82,0.47)	0.10

Table3.3 Primary and Secondary Outcomes Analysis of Other Subgroups

	MP		Obese		Aged	
	Odds Ratio(95%CI)	P Value	Odds Ratio(95%CI)	P Value	Odds Ratio(95%CI)	P Value
Primary Outcome						
Multivariable Model	-0.09(-0.14,-0.06)	5.15e-06	0.86(0.07,1.65)	3.23e-02	-0.75(-1.59,0.08)	0.08
IPTW	-0.11(-0.14,-0.09)	< 2e-16	-0.67(-0.98,-0.37)	1.64e-05	0.95(0.50,1.39)	3.19e-05
Secondary Outcomes						
In-hospital Mortality	0.013(0.003,0.023)	0.008	-0.29(-0.48,-0.10)	0.003	0.41(0.22,0.61)	3.69e-05
30-Day Mortality	0.01(0.005,0.025)	0.007	-0.28(-0.47,-0.09)	0.004	0.38(0.18,0.58)	0.0002
1-Year Mortality	0.012(0.002,0.021)	0.02	-0.30(-0.47,-0.13)	0.0007	0.68(0.50,0.86)	3.37e-13
ICU Length of Stay	-0.06(-0.12,-0.01)	0.02	2.49(1.72,3.26)	0.39	3.30(2.18,4.42)	8.68e-09
Hospital Length of Stay	0.18(0.11,0.24)	1.28e-07	4.99(4.04,5.94)	< 2e-16	3.04(1.66,4.42)	1.58e-05

Table4. Survival Analysis for Non-ARDS Patients

	Multivariable Model		IPTW	
	Odds Ratio(95%CI)	P Value	Odds Ratio(95%CI)	P Value
DP	0.99(0.98,1)	0.13	0.99(0.98,1.01)	0.45
VT	0.97(0.94,1.01)	0.32	0.99(0.96,1.03)	0.68
PEEP	0.96(0.94,0.98)	8.33e-05	0.96(0.94,0.98)	0.0008
MP	1.007(0.99,1.01)	0.06	1.01(1.00,1.02)	0.048
OASIS	1.03(1.02,1.04)	1.03e-10	1.03(1.02,1.04)	2.88e-11
pH	0.32(0.09,1.15)	0.16	0.49(0.14,1.80)	0.29
SpO ₂	0.95(0.94,0.97)	6.11e-08	0.95(0.94,0.97)	1.35e-07
MeanBP	1(0.99,1.01)	0.78	0.99(0.98,1.01)	0.75
PaCO ₂	0.99(0.98,0.99)	0.03	0.98(0.97,0.99)	0.046
Temp	0.78(0.70,0.86)	1.02e-05	0.7827(0.70,0.87)	9.58e-06
Aged	1.52(1.3,1.77)	2.47e-07	1.5072(1.29,1.76)	3.29e-07
Obese	0.8281(0.70,0.97)	0.02	0.8035(0.68,0.95)	0.009

Table5. Ranked Related Features for Ventilator-Free Days

Selected Features	Gini Index	Selected Features	Variance Coefficient	LASSO	Coefficient
Lactate_min_day2	0.31	Copd	4.52	Ph_mean_day2	14.7
Lactate_max_day2	0.26	Rrtfirstday	4.45	Vt	3.50
OASIS	0.23	Asthma	3.92	Ventfirstday	2.30
Rass_mean_day2	0.20	Resp_rate_total_max_day2	1.12	Driving Force	1.32
Rass_max_day2	0.17	Vasopressorsfirstday	0.94	Ph_min_day2	1.26
Plateau_pressure_max_day2	0.16	Lactate_max_day2	0.89	Rass_mean_day1	1.22
Resprate_min_day2	0.16	Lactate_max_day1	0.86	Asthma	0.94
Peakinsp_pressure_min_day2	0.16	Resprate_total_max_day1	0.85	Rass_mean_day2	0.94
Resprate_set_max_day2	0.15	Lactate_min_day2	0.77	Spo2_max_day1	0.70
Tempc_min_day2	0.15	Lactate_min_day1	0.71	Tempc_mean_day2	0.70

Table6. Machine Learning Model for Clinical Outcomes

Ventilator Free Days		Hospital Expire Flag			
	RMSE		AUC	Error	F-score
L1-Norm	633.63	L1-Norm	0.74	0.24	0.79
L2-Norm	640.96	L2-Norm	0.75	0.24	0.80
Enet	639.46	XGBoost	0.93	0.09	0.87
Rpart	53.61	Rpart	0.82	0.11	0.80
RandomForest	38.97	RandomForest	0.77	0.13	0.70
Neuralnet	110.55	Neuralnet	0.78	0.24	0.80
		Ensemble Learning	0.91	0.10	0.86
		MARS	0.78	0.2	0.72

Figures

Figure 1

Survival Analysis of Non-ARDS Patients After IPTW Analysis