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# Driving pressure is not predictive of ARDS outcome in chest trauma patients under mechanical ventilation

Matteo Arcelli

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UNIVERSITE DE MONTPELLIER
FACULTE DE MEDECINE MONTPELLIER-NIMES

**THESE**

Pour obtenir le titre de
**DOCTEUR EN MEDECINE**

Présentée et soutenue publiquement
Par
**ARCELLI MATTEO**

LE 30/09/2021

TITRE :

# Driving pressure is not predictive of ARDS outcome in chest trauma patients under mechanical ventilation

**Directeur de thèse :** Monsieur le Docteur Severin RAMIN

JURY

**Président :** Monsieur le Professeur Xavier CAPDEVILA

**Assesseurs** (y compris directeur de thèse) :

Monsieur le Professeur Samir JABER

Madame le Docteur Audrey DE JONG

Monsieur le Docteur Severin RAMIN

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| COURTET Philippe | Psychiatrie d'adultes ; addictologie |
| CRAMPETTE Louis | Oto-rhino-laryngologie |
| CRISTOL Jean Paul | Biochimie et biologie moléculaire |
| CYTEVAL Catherine | Radiologie et imagerie médicale |
| DE LA COUSSAYE Jean Emmanuel | Médecine d'urgence |
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| DELAPORTE Eric | Maladies infectieuses ; maladies tropicales |
| DEMOLY Pascal | Pneumologie ; addictologie |

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| MONDAIN Michel | Oto-rhino-laryngologie |
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| PUJOL Pascal | Biologie cellulaire |
| QUERE Isabelle | Chirurgie vasculaire ; médecine vasculaire (option médecine vasculaire) |
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| REYNES Jacques | Maladies infectieuses, maladies tropicales |
| RIPART Jacques | Anesthésiologie-réanimation et médecine péri-opératoire |
| ROUANET Philippe | Cancérologie ; radiothérapie |
| SOTTO Albert | Maladies infectieuses ; maladies tropicales |
| TAOUREL Patrice | Radiologie et imagerie médicale |

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| VANDE PERRE Philippe | Bactériologie-virologie ; hygiène hospitalière |
| YCHOU Marc | Cancérologie ; radiothérapie |

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| AZRIA David | Cancérologie ; radiothérapie |
| BAGHDADLI Amaria | Pédopsychiatrie ; addictologie |
| BLANC Pierre | Gastroentérologie ; hépatologie ; addictologie |
| BORIE Frédéric | Chirurgie viscérale et digestive |
| BOURDIN Arnaud | Pneumologie ; addictologie |
| CAMBONIE Gilles | Pédiatrie |
| CAMU William | Neurologie |
| CANOVAS François | Anatomie |
| CAPTIER Guillaume | Anatomie |
| CARTRON Guillaume | Hématologie ; transfusion |
| CAYLA Guillaume | Cardiologie |
| CHANQUES Gérald | Anesthésiologie-réanimation et médecine péri-opératoire |
| CORBEAU Pierre | Immunologie |
| COULET Bertrand | Chirurgie orthopédique et traumatologique |
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| DADURE Christophe | Anesthésiologie-réanimation et médecine péri-opératoire |
| DAUVILLIERS Yves | Physiologie |
| DE TAYRAC Renaud | Gynécologie-obstétrique, gynécologie médicale |
| DE VOS John | Histologie, embryologie et cytogénétique |

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| DEREURE Olivier | Dermatologie - vénéréologie |
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| GARREL Renaud | Oto-rhino-laryngologie |
| GENEVIEVE David | Génétique |
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| GUIU Boris | Radiologie et imagerie médicale |
| HAYOT Maurice | Physiologie |
| HOUEDE Nadine | Cancérologie ; radiothérapie |
| KLOUCHE Kada | Médecine intensive-réanimation |
| KOENIG Michel | Génétique |
| KOUYOUMDJIAN Pascal | Chirurgie orthopédique et traumatologique |
| LAFFONT Isabelle | Médecine physique et de réadaptation |
| LAVABRE-BERTRAND Thierry | Histologie, embryologie et cytogénétique |
| LAVIGNE Jean-Philippe | Bactériologie-virologie ; hygiène hospitalière |
| LE MOING Vincent | Maladies infectieuses ; maladies tropicales |
| LECLERCQ Florence | Cardiologie |
| MARIANO-GOULART Denis | Biophysique et médecine nucléaire |
| MATECKI Stéfan | Physiologie |
| MORANNE Olivier | Néphrologie |
| MOREL Jacques | Rhumatologie |
| NAVARRO Francis | Chirurgie viscérale et digestive |
| NOCCA David | Chirurgie viscérale et digestive |
| PASQUIE Jean-Luc | Cardiologie |

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| PERNEY Pascal | Médecine interne ; gériatrie et biologie du vieillissement, médecine générale, addictologie |
| PRUDHOMME Michel | Anatomie |
| PUJOL Jean Louis | Pneumologie ; addictologie |
| PURPER-OUAKIL Diane | Pédopsychiatrie ; addictologie |
| ROGER Pascal | Anatomie et cytologie pathologiques |
| TRAN Tu-Anh | Pédiatrie |
| VERNHET Hélène | Radiologie et imagerie médicale |

## PU-PH de 2ème classe

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| CANAUD Ludovic | Chirurgie vasculaire ; médecine vasculaire (option chirurgie vasculaire) |
| CAPDEVIELLE Delphine | Psychiatrie d'Adultes ; addictologie |
| CLARET Pierre-Géraud | Médecine d'urgence |
| COLOMBO Pierre-Emmanuel | Cancérologie ; radiothérapie |
| COSTALAT Vincent | Radiologie et imagerie médicale |
| DAIEN Vincent | Ophtalmologie |
| DORANDEU Anne | Médecine légale et droit de la santé |
| FAILLIE Jean-Luc | Pharmacologie fondamentale ; pharmacologie clinique ; addictologie |
| FUCHS Florent | Gynécologie-obstétrique ; gynécologie médicale |
| GABELLE DELOUSTAL Audrey | Neurologie |
| GAUJOUX Viala Cécile | Rhumatologie |
| GODREUIL Sylvain | Bactériologie-virologie ; hygiène hospitalière |
| GUILPAIN Philippe | Médecine Interne, gériatrie et biologie du vieillissement; addictologie |
| HERLIN Christian | Chirurgie plastique, reconstructrice et esthétique, brulologie |
| IMMEDIATO DAIEN Claire | Rhumatologie |
| JACOT William | Cancérologie ; Radiothérapie |
| JEZIORSKI Eric | Pédiatrie |

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| JUNG Boris | Médecine intensive-réanimation |
| KALFA Nicolas | Chirurgie infantile |
| LACHAUD Laurence | Parasitologie et mycologie |
| LALLEMANT Benjamin | Oto-rhino-laryngologie |
| LE QUINTREC DONNETTE Moglie | Néphrologie |
| LETOUZEY Vincent | Gynécologie-obstétrique ; gynécologie médicale |
| LONJON Nicolas | Neurochirurgie |
| LOPEZ CASTROMAN Jorge | Psychiatrie d'Adultes ; addictologie |
| LUKAS Cédric | Rhumatologie |
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| NAGOT Nicolas | Biostatistiques, informatique médicale et technologies de la communication |
| OLIE Emilie | Psychiatrie d'adultes; addictologie |
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| PEREZ MARTIN Antonia | Chirurgie vasculaire ; médecine vasculaire (option médecine vasculaire) |
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| RIGAU Valérie | Anatomie et cytologie pathologiques |
| RIVIER François | Pédiatrie |
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| MATHIEU Olivier | Pharmacologie fondamentale ; pharmacologie clinique ; addictologie |

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| PANABIERES Catherine | Biologie cellulaire |
| RAVEL Christophe | Parasitologie et mycologie |
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| THEVENIN-RENECéline | Immunologie |

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| DU THANH Aurélie | Dermato-vénéréologie |
| FITENI Frédéric | Cancérologie ; radiothérapie |
| GOUZI Farès | Physiologie |
| HERRERO Astrid | Chirurgie viscérale et digestive |
| HUBERLANT Stéphanie | Gynécologie-obstétrique ; Gynécologie médicale |
| KUSTER Nils | Biochimie et biologie moléculaire |
| MAKINSON Alain | Maladies infectieuses, Maladies tropicales |
| PANTEL Alix | Bactérologie-virologie ; hygiène hospitalière |
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| SZABLEWSKY | Anatomie et cytologie pathologiques |

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| DELABY Constance | Biochimie et biologie moléculaire |
| GUGLIELMI Laurence | Sciences biologiques fondamentales et cliniques |
| HENRY Laurent | Sciences biologiques fondamentales et cliniques |
| HERBET Guillaume | Neurosciences |
| LADRET Véronique | Mathématiques appliquées et applications des mathématiques |
| LAINE Sébastien | Sciences du Médicament et autres produits de santé |
| LE GALLIC Lionel | Sciences du médicament et autres produits de santé |
| LOZZA Catherine | Sciences physico-chimiques et technologies pharmaceutiques |
| MAIMOUN Laurent | Sciences physico-chimiques et ingénierie appliquée à la santé |
| MOREAUX Jérôme | Science biologiques, fondamentales et cliniques |
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| MIOT Stéphanie | Médecine interne ; gériatrie et biologie du vieillissement ; addictologie |
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# Driving pressure is not predictive of ARDS outcome in chest trauma patients under mechanical ventilation

Severin Ramin M.D.[1,2], Matteo Arcelli M.D.[1,2], Karim Bouchdoug M.D.[1,2,3], Thomas Laumon M.D.[1,2], Camille Duflos M.D.[3], Audrey De Jong M.D., Ph.D.[4], Samir Jaber M.D., Ph.D.[4], Xavier Capdevila M.D., Ph.D.[1,2], Jonathan Charbit M.D.[1,2]

[1]Department of Anesthesiology and Critical Care Medicine, Hôpital Lapeyronie, Montpellier, France

[2]OcciTRAUMA network, regional network of medical organization and management for severe trauma in Occitanie.

[3]Department of statistical Analysis, Montpellier, France

[4]Department of Anesthesiology and Critical Care Medicine, Saint Eloi University Hospital, CHU Montpellier, University of Montpellier, Montpellier, France

CORRESPONDING AUTHOR: Severin Ramin, DAR A CHU Lapeyronie, 371 Avenue du Doyen Gaston Giraud, 34090 Montpellier, France. E-mail: severin.ramin@gmail.com

## ABSTRACT

**Background:** The relationship between the driving pressure of the respiratory system (ΔPrs) under mechanical ventilation and worse outcome has never been studied specifically in chest trauma patients. The objective of the present study was to assess in cases of chest trauma the relationship between ΔPrs and severity of acute respiratory distress syndrome (ARDS) or death and length of stay.

**Methods:** A retrospective analysis of severe trauma patients (ISS >15) with chest injuries admitted to the Trauma Center from January 2010 to December 2018 was performed. Patients who received mechanical ventilation were included in our analysis. Mechanical ventilation parameters and ΔPrs were recorded during the stay in the intensive care unit. Association of ΔPrs and ARDS with mortality and outcomes was specifically studied at the onset of ARDS ($\Delta Prs_{-ARDS}$) by receiver operator characteristic curve analysis, Kaplan-Meier curves and multivariate analysis.

**Results:** Among the 266 chest trauma patients studied, 194 (73%) developed ARDS. ΔPrs was significantly higher in the ARDS group versus in the no ARDS group (11.6±2.4 cm $H_2O$ vs 10.9±1.9 cm $H_2O$, $p$=0.04). Among the patients with ARDS, no difference according to the duration of mechanical ventilation was found between the high ΔPrs group ($\Delta Prs_{-ARDS}$ >14 cm $H_2O$) and the low ΔPrs group ($\Delta Prs_{-ARDS}$ ≤14 cm $H_2O$), ($p$=0.75). $\Delta Prs_{-ARDS}$ was not independently associated with the duration of mechanical ventilation (hazard ratio [HR], 1.006; 95% CI, 0.95–1.07; $p$=0.8) or mortality (HR, 1.07; 95% CI, 0.9–1.28; $p$=0.45).

**Conclusion:** A high $\Delta Prs_{-ARDS}$ was not significantly associated with an increase in mechanical ventilation duration or mortality risk in ARDS patients with chest trauma in contrast with medical patients.

**Keywords:**

Acute respiratory distress syndrome, Intensive care unit, Lung injury, Transpulmonary pressure, Ventilator-induced lung injury

# Background

Traumatic chest injuries are responsible for significant morbidity and are the cause of trauma-related death in 20%–25% of cases [1]. Following a trauma, patients affected by thoracic injuries are at risk of significant worsening of respiratory function, leading to mechanical ventilation need and acute respiratory distress syndrome (ARDS) in the most severe cases [2]. Causes of ARDS include direct injuries to the lungs and/or secondary mechanisms induced by the trauma setting (e.g. fat embolism, systemic inflammatory response and abdominal compartment syndrome). These physiopathological phenomena and the influence of harmful factors explain why many cases of ARDS occur more than 48 hours after admission [3]. In addition to these respiratory impairments related to trauma, lung injuries may also be aggravated by deleterious effects of mechanical ventilation, such as barotrauma or biotrauma [4, 5]. To prevent or minimize these expected complications, called ventilator-induced lung injury (VILI), current guidelines for lung-protective ventilation in patients with ARDS suggest the use of a low tidal volume ($V_T$), higher levels of total positive end-expiratory pressure (PEEP) and limitation of the inspiratory plateau pressure of the respiratory system ($P_{PLAT}$) under 30 cm $H_2O$ [6, 7]. Based on the same rational, most experts strongly recommend this therapeutic approach in trauma patients [8]. However, this extrapolation of the medical setting is based on populations affected by ARDS from multiple origins. Post-traumatic ARDS represented only 8% to 13% of these cohorts [3]. Specific studies focusing on populations of trauma patients are lacking.

One of the major determinants of VILI is the driving pressure of the respiratory system (ΔPrs), corresponding to the difference between $P_{PLAT}$ and PEEP [9]. Many studies indeed demonstrated that ΔPrs in case of ARDS was associated with worst outcome [9,10]. ΔPrs is a marker of alveolar collapse as well as lung strain and correlates well with lung stress [11]. ΔPrs

can be represented as the baby lung ventilation. Moreover, those findings remain to be confirmed in trauma patients.

The main goal of the present study was to assess in a population of severe trauma patients with chest injuries the relationship between ΔPrs observed at the onset of ARDS ($\Delta Prs_{-ARDS}$) and outcomes.

# Methods

## Study design

The charts of severe trauma patients (Injury Severity Score [ISS] >15) admitted to Lapeyronie University Hospital (Level I Regional Trauma Center, Montpellier, France; Occitrauma network) over a 9-year period (January 2010 to December 2018) were reviewed retrospectively. We obtained approval from the local scientific and ethics committee of Montpellier University Hospital, Comité d'Organisation et de Gestion de l'Anesthésie Réanimation (COGAR), who stated that informed consent from the patient or next of kin was not required.

## Inclusion criteria

Consecutive trauma patients with chest trauma (Abbreviated Injury Scale [AIS] ≥1) who required invasive mechanical ventilation for a minimum of 48 hours were included in the present study [12]. Exclusion criteria were as follows: minors, immediate death, admission from another hospital, absence of initial computed tomography (CT) scan and incomplete medical records.

## Respiratory management of patients

All patients included in the study were ventilated in our unit using a lung-protective mechanical ventilation protocol as defined in the literature: low tidal volume between 6 and 8 ml/kg of ideal body weight, limited $P_{PLAT}$ and PEEP [13]. Ventilatory parameters were set to avoid intrinsic PEEP. Thoracic drainage was performed if necessary, with surgical dissection by an anterior approach for pneumothoraces (14 Fr) and axillary approach for haemothoraces (24 or 28 Fr). In specific settings such as severe bronchopleural fistulae, unilateral lung injuries, or refractory hypoxemia, an alternative to conventional mechanical ventilation may be used; for example, separated lung ventilation in the prone position, high-frequency percussive ventilation, or veno-venous extracorporeal membrane oxygenation in extreme cases.

## Data collection

The following data were extracted from the medical records: age, sex, mechanism, characteristics of injuries, mortality, duration of mechanical ventilation, length of stay in the intensive care unit (ICU) and hospital length of stay. In addition, ISS and AIS scores were obtained for each body region as well as the Simplified Acute Physiology Score (SAPS) II. Prone position, pH, partial pressure of carbon dioxide in arterial blood ($PaCO_2$), $PaO_2/F_IO_2$, lactate, haemoglobin, base deficit, respiratory rate, $V_T$, PEEP, $P_{PLAT}$, respiratory system compliance (Crs), elastance of respiratory system (Ers), ΔPrs and $PaO_2/F_IO_2$ were recorded. Mechanical power (MP) was also computed as the product of ΔPrs in Newtons (cm $H_2O$ × 0.098), tidal volume and respiratory rate. It was expressed as J/min and was included in the analysis [14]. For the non ARDS group respiratory parameters were collected the day of admission following initial stabilisation. For the ARDS group these parameters were collected on the onset day of ARDS.

In addition, specific data on chest trauma were collected based on the CT scan on admission (size of pulmonary contusions, pneumothoraces, haemothoraces, rib fractures, flail chest and atelectasis) allowing the Thoracic Trauma Severity (TTS) score on admission to be determined on a scale ranging from 0 to 25 points [15, 16].

## Study definitions

ARDS was defined using the Berlin criteria consensus definition [17]: (1) timing: onset within 1 week of a known clinical insult or new or worsening respiratory symptoms; (2) chest imaging: bilateral opacities, not fully explained by effusions, lobar/lung collapse or nodules; (3) origin of oedema: respiratory failure not fully explained by cardiac failure or fluid overload. The ARDS diagnoses were retrospectively reviewed by two physicians (SR and MA). Patients were thus categorized into two groups according to the occurrence (ARDS group) or the absence of ARDS (no ARDS group). Timing was also considered: early ARDS (onset in the first 48 h after admission) and late ARDS (onset 48 h after admission). In the subgroup of ARDS patients, $\Delta Prs\text{-}_{ARDS}$ was the ΔPrs value that was observed at the onset of ARDS. The duration of mechanical ventilation, length of stay in the ICU and hospital length of stay for the ARDS group were extracted from medical records.

## Statistical analysis

The study population was first divided into two groups according to the occurrence of ARDS (ARDS and no ARDS groups) and compared. Quantitative variables were expressed as the mean (standard deviation [SD]) or median (interquartile range, 25%–75%) and compared using the Student t test or Wilcoxon-Mann-Whitney test as appropriate. Qualitative variables were expressed as number (%) and compared using the chi-squared test or Fisher test as appropriate. A descriptive analysis of the ARDS group focused on respiratory parameters was thus

performed. Box plots was used to expose these data. In the case of missing data, the number of missing values is clearly stated for each variable. An a priori threshold for ΔPrs was defined based on previous results in the field (>14 cmH20) [9, 18]. Similarly, the threshold for MP was defined a priori as ≥12 J/min [14].

Thereafter, a specific analysis on predicting severity of ARDS using ΔPrs and ROC curve analysis in the ARDS subgroup was performed. The area under the ROC curve (AUC) was expressed with the 95% confidence interval (CI). A survival analysis for weaning from mechanical ventilation was performed. Weaning from mechanical ventilation is censored by death before extubation. To draw Kaplan-Meier curves, the ARDS subgroup was divided according to the value of ΔPrs or MP. The thresholds defined a priori for ΔPrs and MP (>14 cmH20 and ≥12 J/min respectively) were conserved in this part of the analysis. The log-rank test was used to compare these curves. False-positive and false-negative rates were determined.

Finally, the relationship between ΔPrs or MP and different outcomes (duration of mechanical ventilation, occurrence of death, length of stay in the hospital and in the ICU) were assessed using a multivariate Cox regression analysis. In this analysis, the occurrence of ventilator-associated pneumonia was particularly considered as a confounding factor with the duration of mechanical ventilation. The statistical analysis was performed by CD and KB from the Clinical Research and Epidemiology Unit of Montpellier University Hospital using SAS statistical software (version 9.4; SAS Institute; Cary, NC). Statistical significance was set at a bilateral alpha risk <0.05.

# Results

Among the 1669 patients admitted with chest trauma to our trauma ICU during the study period, 761 (46%) met the inclusion criteria. Of these, 460 (60%) were not eligible for analysis due to duration of mechanical ventilation less than 48 h in 432 cases and a lack of data in 28 cases Finally, 301 patients were included in the study. Of these, 35 patients (11%) were

excluded from our analysis due to early death (traumatic brain injury or early haemorrhagic shock). The 266 remaining patients were thus included in our analysis. The flowchart of the study is presented in **Fig. 1**. Among the study population, 204 patients were male (77%), the mean age was 43.0 (±19.3) years, and the mean ISS was 32 (±10). One-hundred and fifty patients (56%) were classified as AIS ≥3 thoracic trauma, 84 (31%) were AIS ≥3 abdominal trauma and 135 (51%) were AIS ≥3 traumatic brain injury. The mean TTS score was 9.5 (±4.9). The mortality rate was 6%; 15 patients died during the hospital stay. The mean $PaO_2/FiO_2$ ratio on admission was 317 (±173). A total of 194 patients (73%) experienced ARDS in the first week after admission; 52% early ARDS and 48% late ARDS **(Appendix. 1)**. The mean duration of mechanical ventilation was 16.3 (±13.9) days. The main demographic characteristics of the patients are presented in **Table 1**.

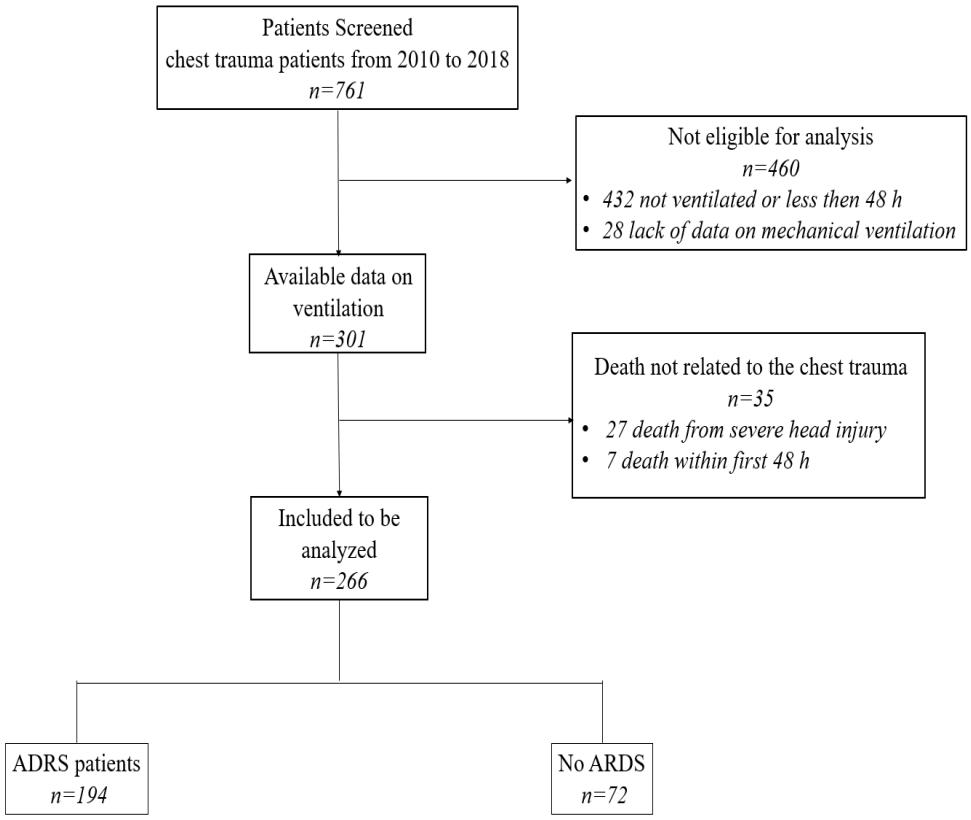


**Figure 1.** Flowchart of the study

**Table 1** Baseline characteristics

| Variable | | Total population | ARDS | | *p* |
|---|---|---|---|---|---|
| | | | No | Yes | |
| | | N=266 | n=72 | n=194 | |
| Sex, n (%) | Men | 204 (76.69) | 50 (69.44) | 154 (79.38) | 0.09 |
| Age (years) | | 43.60 (±19.28) | 34.92 (±16.56) | 46.82 (±19.27) | <0.01 |
| BMI (kg/m$^2$) | | 25.04 (±4.60) | 23.69 (±4.88) | 25.54 (±4.40) | <0.01 |
| SAPS II | | 39.87 (±15.61) | 35.40 (±12.13) | 41.53 (±16.44) | 0.01 |
| ISS | | 31.70 (±9.95) | 31.36 (±9.39) | 31.83 (±10.17) | 0.81 |
| TTS | | 9.49 (±4.86) | 5.73 (±3.29) | 10.88 (±4.62) | <0.01 |
| Thoracic trauma, n (%) | | | | | 0.03 |
| | Mild (AIS 1 or 2) | 116 (43.61) | 41 (56.94) | 75 (38.66) | |
| | Moderate (AIS 3 or 4) | 133 (50.00) | 28 (38.89) | 105 (54.12) | |
| | Severe (AIS 5 or 6) | 17 (6.39) | 3 (4.17) | 14 (7.22) | |
| Pneumothoraces, n (%) | | | | | 0.05 |
| | No | 129 (48.50) | 34 (47.22) | 95 (48.97) | |
| | Mild (AIS 1 or 2) | 58 (21.80) | 23 (31.94) | 35 (18.04) | |
| | Moderate (AIS 3 or 4) | 30 (11.28) | 7 (9.72) | 23 (11.86) | |
| | Severe (AIS 5 or 6) | 49 (18.42) | 8 (11.11) | 41 (21.13) | |
| Hemothoraces, n (%) | | | | | 0.09 |
| | No | 177 (66.54) | 56 (77.78) | 121 (62.37) | |
| | Mild (AIS 1 or 2) | 28 (10.53) | 5 (6.94) | 23 (11.86) | |
| | Moderate (AIS 3 or 4) | 36 (13.53) | 8 (11.11) | 28 (14.43) | |
| | Severe (AIS 5 or 6) | 25 (9.40) | 3 (4.17) | 22 (11.34) | |
| Traumatic brain injury, n (%) | | | | | 0.70 |
| | No | 106 (39.85) | 28 (38.89) | 78 (40.21) | |
| | Mild (AIS 1 or 2) | 25 (9.40) | 9 (12.50) | 16 (8.25) | |
| | Moderate (AIS 3 or 4) | 112 (42.11) | 28 (38.89) | 84 (43.30) | |
| | Severe (AIS 5 or 6) | 23 (8.65) | 7 (9.72) | 16 (8.25) | |
| Abdominal trauma, n (%) | | | | | 0.30 |
| | No | 130 (48.87) | 31 (43.06) | 99 (51.03) | |
| | Mild (AIS 1 or 2) | 52 (19.55) | 12 (16.67) | 40 (20.62) | |
| | Moderate (AIS 3 or 4) | 68 (25.56) | 24 (33.33) | 44 (22.68) | |
| | Severe (AIS 5 or 6) | 16 (6.02) | 5 (6.94) | 11 (5.67) | |
| Hemoperitoneum, n (%) | | | | | 0.08 |

| | | | | | |
|---|---|---|---|---|---|
| | No | 186 (69.92) | 43 (59.72) | 143 (73.71) | |
| | Mild (AIS 1 or 2) | 37 (13.91) | 16 (22.22) | 21 (10.82) | |
| | Moderate (AIS 3 or 4) | 24 (9.02) | 8 (11.11) | 16 (8.25) | |
| | Severe (AIS 5 or 6) | 19 (7.14) | 5 (6.94) | 14 (7.22) | |
| pH at entry | | 7.34 (±0.09) | 7.37 (±0.08) | 7.34 (±0.09) | 0.01 |
| Base deficit at entry | | 5.72 (±3.59) | 5.64 (±3.89) | 5.75 (±3.48) | 0.43 |
| Lactates at entry | | 3.58 (±2.59) | 3.58 (±2.40) | 3.59 (±2.66) | 0.94 |
| Haemoglobin at entry | | 11.54 (±2.64) | 11.33 (±2.84) | 11.62 (±2.56) | 0.47 |

Data are expressed as mean ±SD, or as number of patients (percentage) as appropriate

BMI, body mass index; SAPS II, Simplified Acute Physiology Score 2; ISS, Injury Severity Score; TTS, Thoracic Trauma Severity score; AIS, Abbreviated Injury Score

ΔPrs was significantly higher in the ARDS group than in the no ARDS group; 11.8 (±2.9) cm $H_2O$ vs 12 (±2.03) cm $H_2O$ ($p$=0.04). $P_{PLAT}$ and MP showed the same behaviour; 18 (±3) cm $H_2O$ vs 16 (±2) cm $H_2O$, ($p$<0.001) and 11.5 (±3.6) J/min vs 9.6 (±3.0) J/min ($p$<0.001), respectively. The characteristics of the ventilatory parameters and outcomes of the patients are presented in **Table 2**.

**Table 2** Respiratory characteristics and outcome

| Variable | | Total population | ARDS | | *p* |
|---|---|---|---|---|---|
| | | | No | Yes | |
| | | N=266 | n=72 | n=194 | |
| $PAO_2/FiO_2$ at entry | | 317.03 (±173.30) | 494.54 (±166.90) | 251.14 (±121.95) | < 0.01 |
| Worst $PaO_2/FiO_2$ | | 232.49 (±120.65) | 397.13 (±75.90) | 171.39 (±63.26) | < 0.01 |
| ARDS severity, n (%) | | | | | |
| | Mild | 64 (24.06) | | 64 (32.99) | |
| | Moderate | 100 (37.59) | | 100 (51.55) | |
| | Severe | 30 (11.28) | | 30 (15.46) | |
| Early ARDS, n (%) | | | | | |
| | <48 h | 101 (37.97) | | 101 (52.06) | |
| | ≥48 h | 93 (34.96) | | 93 (47.94) | |
| Day of occurrence of ARDS | | 2.22 (±2.41) | | 2.22 (±2.41) | |
| Driving pressure (ΔPrs; cm $H_2O$) | | 11.58 (±2.70) | 10.96 (±2.03) | 11.81 (±2.89) | 0.04 |
| Driving pressure, n (%) | | | | | 0.27 |
| | <14 cm $H_2O$ | 230 (86.47) | 65 (90.28) | 165 (85.05) | |
| | >14 cm $H_2O$ | 36 (13.53) | 7 (9.72) | 29 (14.95) | |
| Mean Driving pressure over the first 5 days (cm $H_2O$) | | 11.47 (±2.24) | 10.93 (±1.84) | 11.68 (±2.34) | 0.02 |
| Plateau pressure ($P_{PLAT}$; cm $H_2O$) | | 17.26 (±3.09) | 16.23 (±2.31) | 17.64 (±3.26) | < 0.01 |
| Static compliance (Crs ; cm $H_2O$) | | 47.53 (±11.45) | 47.69 (±8.42) | 47.47 (±12.40) | 0.53 |
| Mechanical power (MP; cm $H_2O$) | | 11.00 (±3.50) | 9.60 (±2.98) | 11.52 (±3.55) | < 0.01 |
| VAP, n (%) | | | | | < 0.01 |
| | No | 110 (41.35) | 47 (65.28) | 63 (32.47) | |
| | Yes | 156 (58.65) | 25 (34.72) | 131 (67.53) | |
| Death (, n (%) | | | | | 0.08 |
| | No | 251 (94.36) | 71 (98.61) | 180 (92.78) | |
| | Yes | 15 (5.64) | 1 (1.39) | 14 (7.22) | |
| Length Duration of mechanical ventilation (days) | | 16.32 (±13.89) | 12.30 (±12.34) | 17.81 (±14.16) | < 0.01 |
| 28 Free days free of ventilation | | 13.05 (±9.95) | 16.78 (±9.36) | 11.67 (±9.83) | < 0.01 |
| Length of stay in ICU (days) | | 26.32 (±20.43) | 20.72 (±18.02) | 28.40 (±20.92) | < 0.01 |
| Length of hospital stay (days) | | 36.22 (±28.57) | 30.47 (±19.08) | 38.37 (±31.15) | 0.03 |

Data are expressed as mean±SD, or as number of patients (percentage) as appropriate.VAP, ventilator-acquired pneumonia

The results of the descriptive analysis are shown in **Fig. 2** for the subgroup analysis of the ARDS group. The AUC of the ROC curve for $\Delta Prs_{-ARDS}$ in predicting the severity of ARDS was 0.59 (95% CI, 0.48–0.71; *p*=0.06) for moderate and severe ARDS **(Appendix. 2).** and 0.60 (95% CI, 0.58–0.61; *p*=0.04) for severe ARDS. A $\Delta Prs_{-ARDS}$ value >14 cm $H_2O$ had a sensitivity of 20.8% (95% CI, 13.8%–27.7 %), a specificity of 88.9% (95% CI, 81.1%–96.6%), a predictive positive value of 79.4 (95% CI, 65.8%–93 %) and a negative predictive value of

35.2 (95% CI, 27.8%–42.6 %) for predicting severe ARDS.

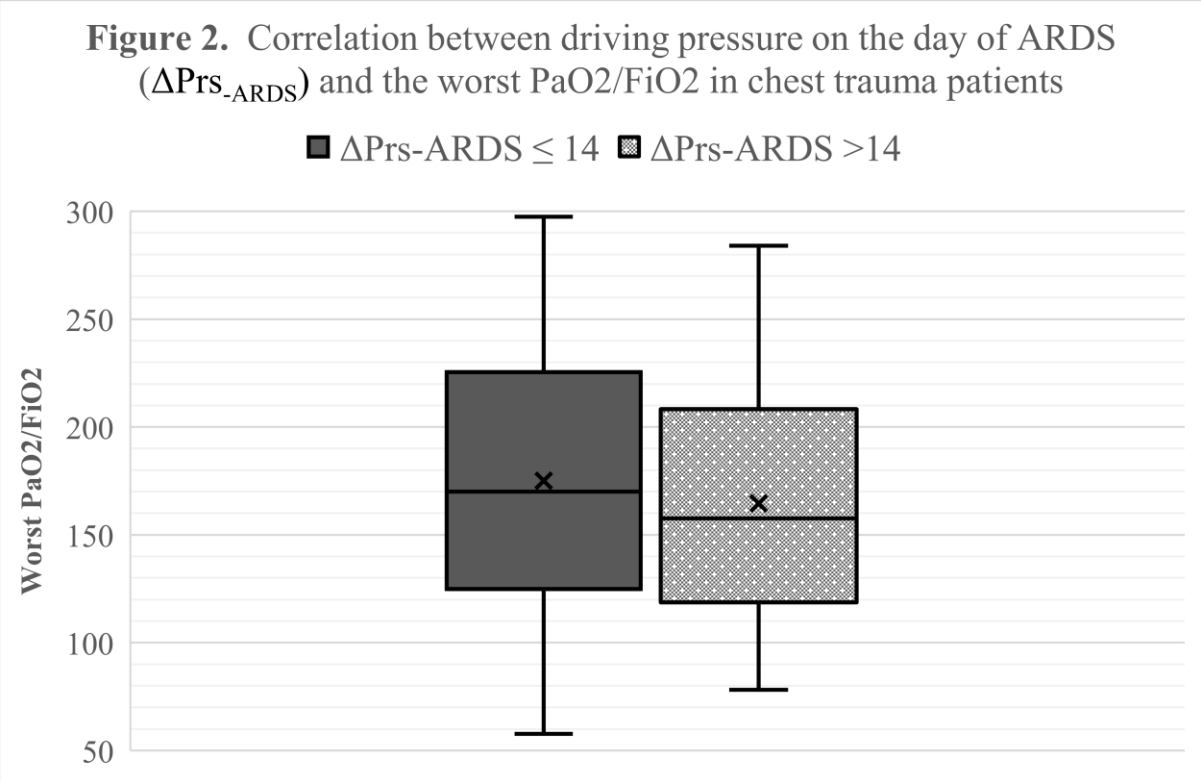


**Figure 2.** Correlation between driving pressure on the day of ARDS ($\Delta Prs_{-ARDS}$) and the worst PaO2/FiO2 in chest trauma patients

In the survival analysis using the a priori $\Delta Prs_{-ARDS}$ threshold >14 cm $H_2O$, the duration of mechanical ventilation did not differ between the high and the low driving pressure groups HR= 0.82 (95% CI, 0.57-1.2), p=0.3 **Fig. 3.** This was also observed for ICU length of stay (*p*=0,78) and hospital length of stay (*p*=0.75). Kaplan-Meier curves using MP are presented in **(Appendix. 3).** In the multivariate analysis, $\Delta Prs_{-ARDS}$ was not found to be independently associated with the duration of mechanical ventilation (hazard ratio [HR], 1.01; 95% CI, 0.95–1.07; *p*=0.8) or mortality (HR, 1.07; 95% CI, 0.9–1.28; *p*=0.45) **Table 3.** When considering $\Delta Prs_{-ARDS}$ in two groups (≤14 cm $H_2O$ and >14 cm $H_2O$) no association was found for mortality or duration of mechanical ventilation **Table 3**. Similarly, no other respiratory parameters, such as $P_{PLAT}$ (HR, 0.98; 95% CI, 0.93–1.02; *p*=0.33), Crs (HR, 0.98; 95% CI 0.98–1.00; *p*=0.12) and MP (HR, 0.98; 95% CI, 0.94–1.02; *p*=0.22), were found to be independently associated with duration of mechanical ventilation or mortality **(Appendix. 4).**

**Table 3** Multivariate cox regression analysis results on duration of ventilation (ΔPrs as a continuous variable) and $\Delta Prs_{-ARDS}$ according to the group (superior or inferior to 14 cm $H_2O$) outcome

| Variable | Modality | Hazard ratio | 95% confidence interval | *p* |
|---|---|---|---|---|
| **Duration of ventilation** | | | | |
| Age (years) | +1 year | 0.99 | 0.99-1.00 | <0.04 |
| SAPS II | +1 point | 0.97 | 0.96–0.99 | <0.0001 |
| ISS | +1 point | 0.99 | 0.97–1.01 | 0.25 |
| Chest injury | | | | |
| Reference | AIS <2 | | | |
| | ≥2 AIS ≤4 | 0.95 | 0.7–1.29 | 0.75 |
| | AIS >4 | 0.51 | 0.26–0.97 | 0.04 |
| Head injury | | | | |
| Reference | No injury | | | |
| | AIS <2 | 0.91 | 0.56–1.48 | 0.7 |
| | ≥2 AIS ≤4 | 0.84 | 0.6–1.18 | 0.31 |
| | AIS >4 | 0.45 | 0.25–0.81 | 0.007 |
| $\Delta Prs_{-ARDS}$ | +1 cm $H_2O$ | 1.01 | 0.95–1.08 | 0.84 |
| **Group outcome[a]** | | | | |
| Mortality | $\Delta Prs_{-ARDS}$ ->14 cm $H_2O$ | 1.42 | 0.44–4.54 | 0.56 |
| Ventilation duration | $\Delta Prs_{-ARDS}$ >14 cm $H_2O$ | 0.9 | 0.61–1.33 | 0.59 |

[a]Cox model for mortality was adjusted on SAPS II and arterial pH. Cox model for ventilation duration was adjusted on age, SAPS II, ISS, AIS thorax, AIS skull, haemoperitoneum, driving pressure in trauma ICU and ventilator-associated pneumonia

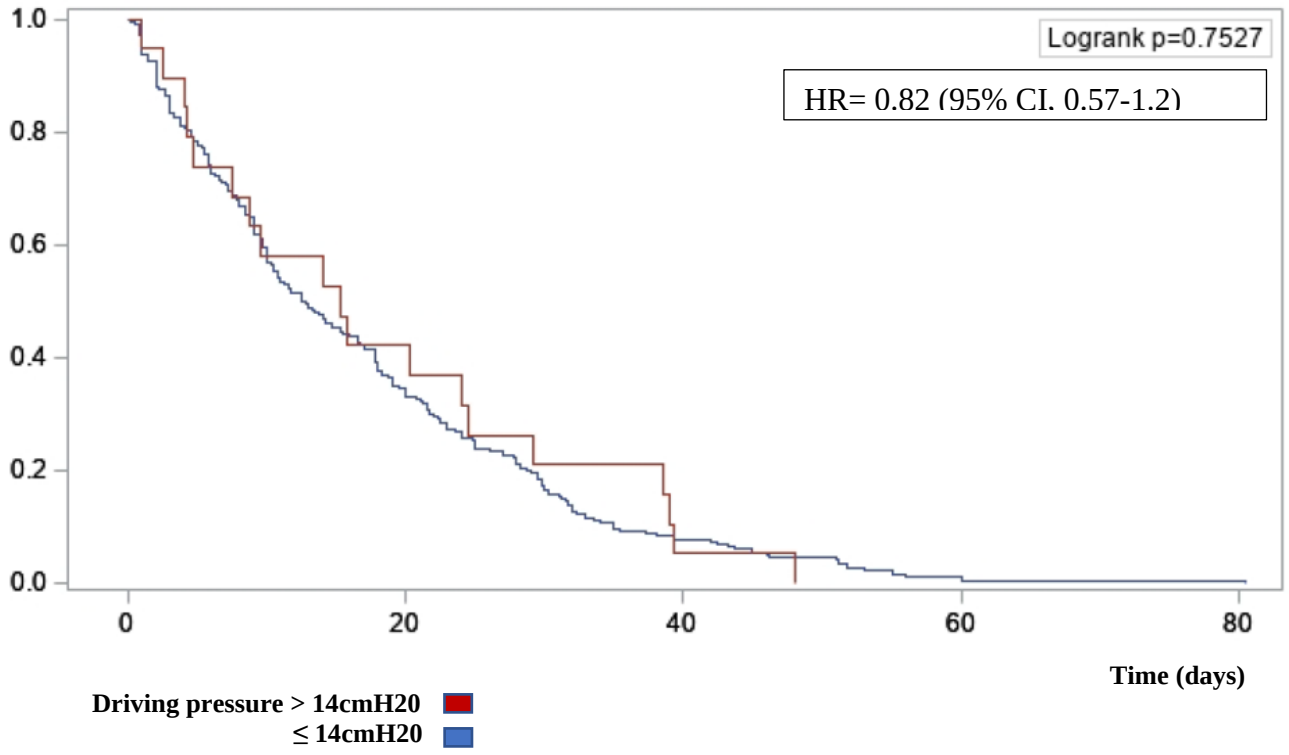


**Figure 3.** Kaplan-Meier curves for time to weaning from mechanical ventilation according to driving pressure

# Discussion

This is the first study to assess the association of ΔPrs with outcomes in a specific population of chest trauma patients. The main finding is that the ΔPrs value at the onset of ARDS was not associated with the duration of mechanical ventilation, mortality risk or ICU length of stay either in survival analysis or multivariate analysis. Our analysis demonstrates therefore that ΔPrs is an unreliable predictor of outcomes in this specific population.

Nowadays, ΔPrs, usually called the driving pressure, is used universally in clinical practice to reflect lung strain and correlates well with the mechanical stress generated by $V_T$ on the ventilated lung [11]. ΔPrs also means respiratory system compliance for a given $V_T$. Thus, a high ΔPrs may indicate impairment of respiratory system compliance by a decrease in the

functional size of the lung. This phenomenon, called baby lung within context of ARDS, is related to alveolar collapse.

Many studies have demonstrated that ΔPrs is associated with mortality in patients with ARDS [9, 10, 18]. However, these previous studies focused on ARDS in medical settings. The morbid association between ΔPrs and mortality may nevertheless be altered in different clinical situations. Thus, De Jong et al [18] have reported that in obese patients with ARDS, ΔPrs was not associated with mortality. Similarly, our data suggest the absence of a relationship between ΔPrs and outcomes in the case of patients with ARDS related to trauma. One of the main physiopathological explanations for this difference observed between the medical and trauma contexts could be significant modifications of chest wall compliance related to traumatic injuries. Traumatic parietal dehiscence increases chest wall compliance, which may lead to an increase in ΔPrs [19]. Thus, ΔPrs reflects both chest wall and lung compliance and it may be directly modified by strong variation in chest wall compliance in cases of severe chest trauma. ΔPrs = ΔPcw + ΔPl, ΔPcw being the chest wall driving pressure and ΔPl being the transpulmonary driving pressure., ΔPl would offer a better reflection of actual lung compliance and alveolar collapse [20]. Similarly, to obese patients, in chest trauma patients, much of the pressure provided by the ventilator will be used to distend the chest wall rather than the lung. Hence, there may not be an increase in transpulmonary pressure with accompanying lung overdistension. The only way to monitor the ΔPl of real interest from bench to bedside is to measure oesophageal pressure which is an estimation of pleural pressure and allows to determine ΔPcw. Thus, physicians may quickly differentiate a high ΔPrs due to an increase in ΔPcw, without a real lung injury, or inversely a high ΔPrs with a normal ΔPcw, a sign of lung pathology.

ARDS related to chest trauma represents a low percentage of case of ARDS and has its own specific properties. Its incidence is estimated to be between 10% and 30% of critically ill

trauma patients, mainly depending on the severity of the trauma in injured patients. Surprisingly, trauma-related ARDS is known to be twice less likely to lead to death than medical ARDS [21]. Our cohort presents similar results with a low mortality rate in the ARDS group (7%). Traumatic ARDS is characterized by a typical immunological profile different from ARDS in a medical setting. The early phase following trauma is thus characterized by an important and uncontrolled inflammatory response in the lung tissues. The importance of this inflammatory response depends on the intensity of the initial trauma but also on the genetic profile of the patient. A previous work by Xiao et al. [22] in a severe trauma population showed that the early leukocyte genomic response was simultaneously associated with increased expression of genes involved in the systemic inflammatory, innate immune, and compensatory anti-inflammatory responses, as well as in the suppression of genes involved in adaptive immunity. All these modifications induce a massive release of damage-associated molecular pattern molecules from injured tissues [23]. Massive release of epithelial biomarkers such as sRAGE, for example, is responsible for dysfunction of the capillary-alveolar barrier, increase in inflammation, and oxidative stress favouring fibrosis in cases of ARDS [24, 25]. These specific characteristics explain the specificities of ARDS after chest trauma, its lower lethality rate, and maybe the absence of association between ΔPrs and outcomes in the trauma context.

The present study has some limitations. First, its design was monocentric with a retrospective analysis, which limits extrapolation of the results. However, the data were collected prospectively with the ICU software, and the management of patients with ARDS was standardized according to international recommendations. Only a few data are missing regarding the driving pressure (28 of 329; 8%) in trauma patients under mechanical ventilation. Second, no threshold analysis was performed according to the ΔPrs. Patients who died from traumatic brain injury or from haemorrhagic shock in first 48 h after admission were excluded from our study. Consequently, only 15 non-survivors are present in our final analysis. This

may lead to a lack of power and threshold analysis is impossible. However, previous work also used a threshold of 14 cm $H_2O$ for ΔPrs [9, 18]. Third, patients in our cohort were severely injured with a mean ISS of 32, and about 25% of the cohort also had abdominal injuries. Increase in abdominal pressure may also be involved in the change in chest wall compliance and create an analysis bias. It is therefore impossible to exclusively attribute our results only to chest injuries. However, multiple traumas are a frequent situation, which makes our study close to real life.

# Conclusion

The results of the present study demonstrate that driving pressure in a specific population of chest trauma patients was a poor predictor for ARDS severity and had no correlation with worse outcomes. Changes in chest compliance due to traumatic injuries could explain this unexpected observation. Therefore, our results suggest that the use of transpulmonary pressure would be relevant in chest trauma patients to directly monitor injured lungs and guide an optimal mechanical ventilation strategy. Further studies will be necessary to prove the positive impact of transpulmonary pressure on chest trauma management.

# Declarations

## Ethics approval and consent to participate

We obtained approval from the local scientific and ethics committee of Montpellier University Hospital, Comité d'Organisation et de Gestion de l'Anesthésie Réanimation (COGAR), who stated that informed consent from the patient or next of kin was not required.

## Consent for publication

Informed consent from the patient or next of kin was not required.

## Availability of data and materials

All data are extracted from medical record.

## Competing interests

The authors declare no competing interests.


## Funding

Support was provided solely from institutional and departmental resources.


## Authors' contributions

S.R., M.A, and K.B collected clinical data for this study; S.R., M.A, and K.B collected pharmaceutical and blood requirements. J.C, S.R, A. DJ, C.D prepared the draft of the study and conducted the statistical analysis. S.R. and M.A. wrote the article, which was revised by S.J, T.L, A.DJ and X.C.


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**Fig. 1** Flowchart of the study

**Fig. 2** Correlation between $\Delta Prs_{-ARDS}$ and the worst $PaO_2/FiO_2$ in ARDS patients.

**Fig. 3** Kaplan-Meier curves for time to weaning from mechanical ventilation according to driving pressure level

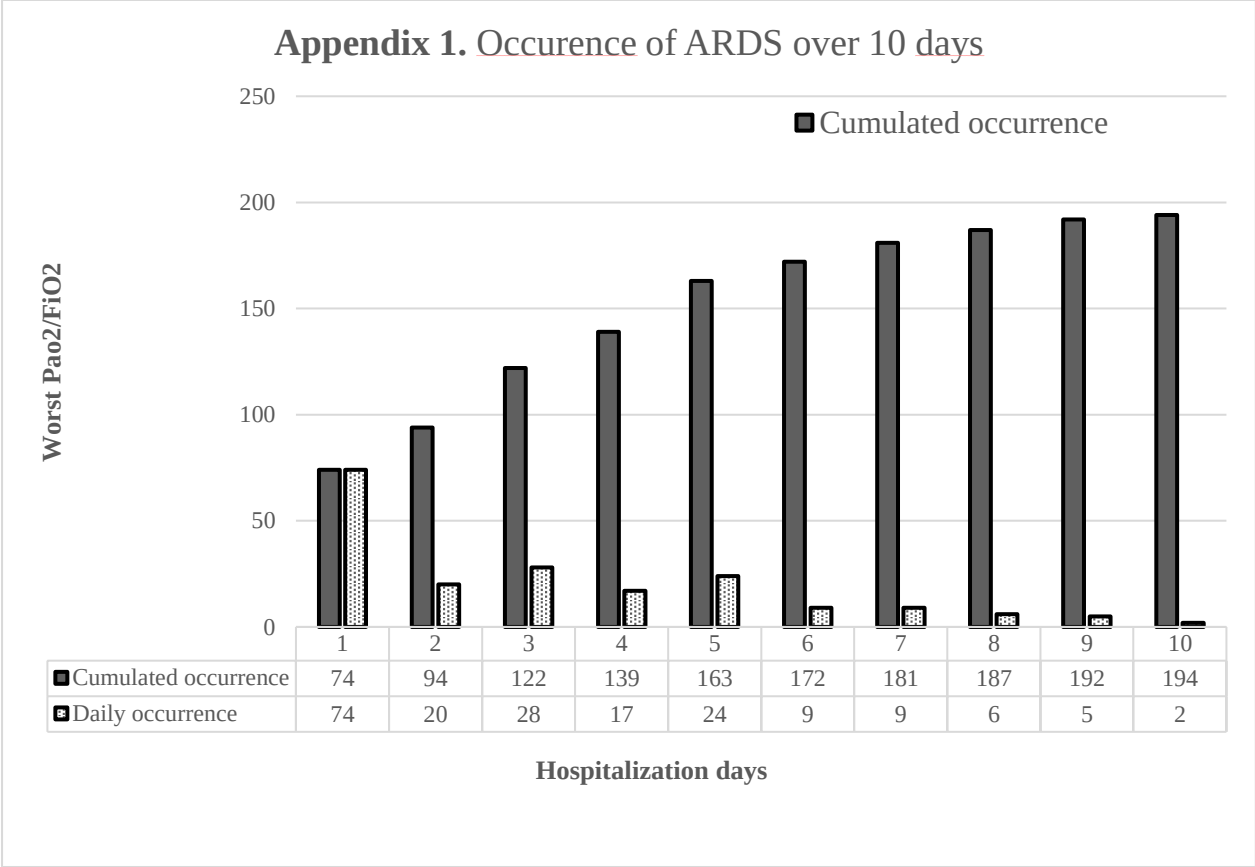
**Appendix. 1** Occurrence of ARDS over 10 days

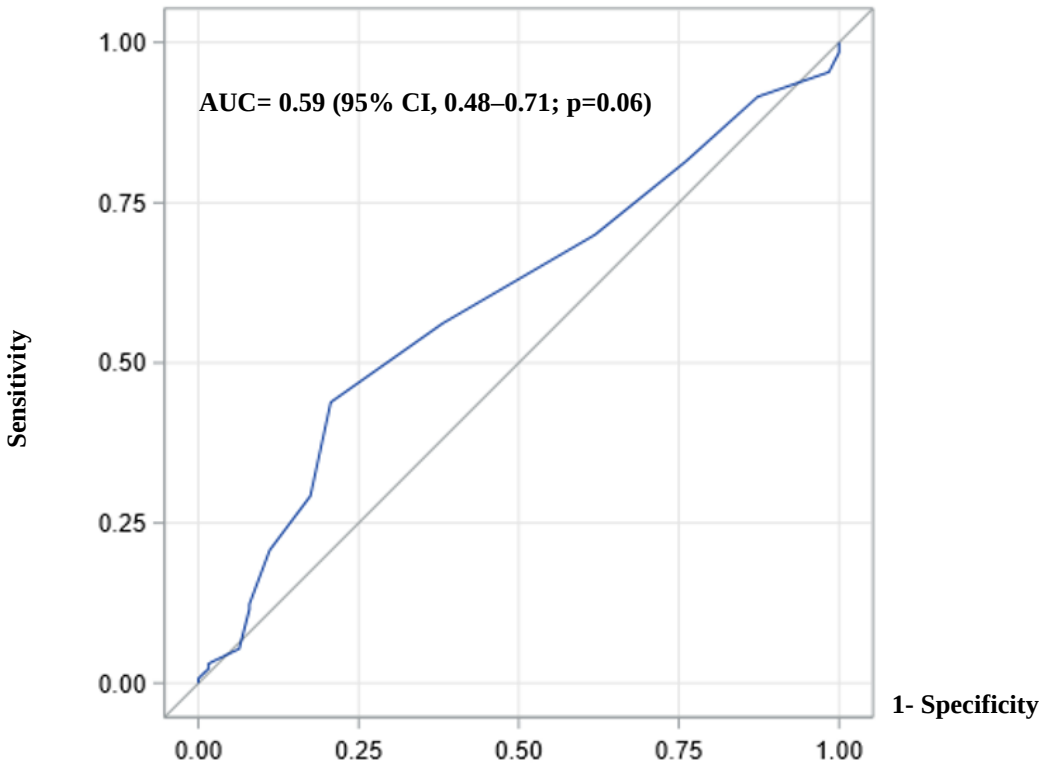
**Appendix. 2** ROC curve for predicting moderate and severe ARDS using driving pressure.

**Appendix. 3** Kaplan-Meier curves for time to weaning from mechanical ventilation according to mechanical power level

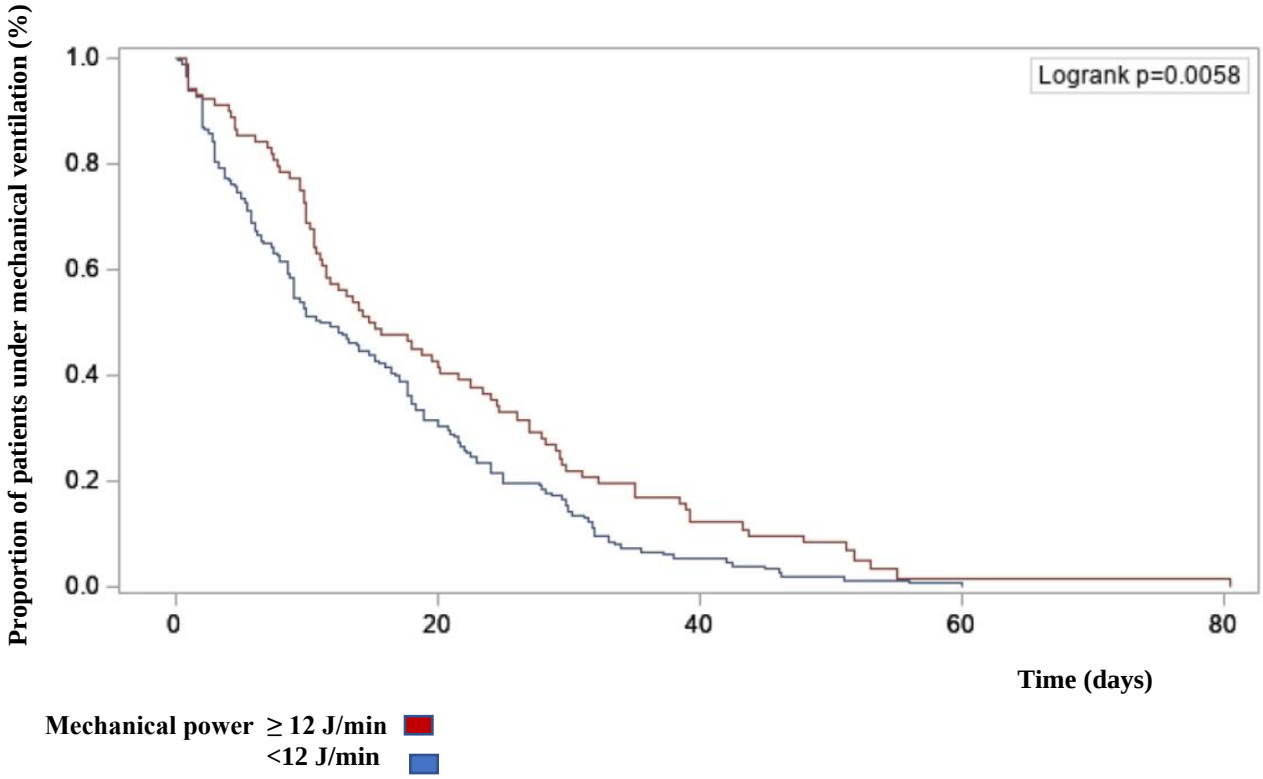
**Appendix. 4** Multivariate cox regression analysis results using plateau pressure or compliance or mechanical power as a predictive variable instead of driving pressure

## Annexes




**Appendix 2.** Roc curve for predicting moderate and severe ARDS using driving pressure




**Appendix 3.** Kaplan-Meier curves for time to weaning from mechanical ventilation according to mechanical power level

| Variable[a] | Modality | Hazard ratio | 95% confidence interval | *p* |
|---|---|---|---|---|
| Plateau pressure | +1 cm $H_2O$ | 0.98 | 0.93–1.02 | 0.33 |
| Plateau pressure | <25 cm $H_2O$ | 0.84 | 0.36–1.92 | 0.67 |
| Compliance | +1 ml/cm $H_2O$ | 0.99 | 0.98–1.00 | 0.12 |
| Compliance | >31 ml/cm $H_2O$ | 1.16 | 0.67–2.01 | 0.6 |
| Mechanical power | +1 J/min | 0.98 | 0.94–1.02 | 0.22 |
| Mechanical power | <12 J/min | 0.92 | 0.68–1.23 | 0.57 |

Cox models for each variable were adjusted on age, SAPS II, ISS, AIS thorax, AIS skull, haemoperitoneum, driving pressure in trauma ICU and ventilator-associated pneumonia

**Appendix 4.** Multivariate cox regress ion analysis results using plateau pressure or compliance or mechanical power as a predictive variable instead of driving pressure

# *SERMENT*

- *En présence des Maîtres de cette école, de mes chers condisciples et devant l'effigie d'Hippocrate, je promets et je jure, au nom de l'Etre suprême, d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la médecine.*

- *Je donnerai mes soins gratuits à l'indigent et n'exigerai jamais un salaire au-dessus de mon travail.*

- *Admis (e) dans l'intérieur des maisons, mes yeux ne verront pas ce qui s'y passe, ma langue taira les secrets qui me seront confiés, et mon état ne servira pas à corrompre les mœurs, ni à favoriser le crime.*

- *Respectueux (se) et reconnaissant (e) envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.*

- *Que les hommes m'accordent leur estime si je suis fidèle à mes promesses. Que je sois couvert (e) d'opprobre et méprisé (e) de mes confrères si j'y manque.*

## Résumé

**Introduction :** La relation entre la pression motrice du système respiratoire (ΔPrs) sous ventilation mécanique et la survie n'a jamais été étudiée spécifiquement chez les patients ayant subi un traumatisme thoracique. L'objectif de cette étude était d'évaluer en cas de traumatisme thoracique la relation entre la ΔPrs et la sévérité du syndrome de détresse respiratoire aiguë (SDRA) ainsi que le décès et la durée du séjour.

**Matériel et méthodes :** Une analyse rétrospective des patients traumatisés sévères (ISS >15) avec des traumas thoraciques admis au centre régional de traumatologie de janvier 2010 à décembre 2018 a été réalisée. Les patients ayant reçu une ventilation mécanique ont été inclus dans notre analyse. Les paramètres de ventilation mécanique et la ΔPrs ont été enregistré pendant le séjour en réanimation. L'association de la ΔPrs et de la survie a été spécifiquement étudiée au début du SDRA (ΔPrs-ARDS) par analyse de courbe ROC, courbes de Kaplan-Meier ainsi qu'une analyse multivariée.

**Résultats :** Parmi les 266 patients ayant subi un traumatisme thoracique, 194 (73 %) ont développé un SDRA. La ΔPrs était significativement plus élevé dans le groupe SDRA par rapport au groupe sans SDRA (11,6 ± 2,4 cm H2O vs 10,9 ± 1,9 cm H2O, p = 0,04). Parmi les patients avec SDRA, aucune différence dans la durée de ventilation mécanique n'a été retrouvée entre le groupe ΔPrs-ARDS >14 cm H2O) et le groupe (ΔPrs-ARDS ≤14 cm H2O) (p=0,75) bas). ΔPrs-ARDS n'était pas associé de manière indépendante à la durée de ventilation mécanique (rapport de risque [HR], 1,006 ; IC à 95 %, 0,95-1,07 ; p = 0,8) ou à la mortalité (HR, 1,07 ; IC à 95 %, 0,9 à 1,28 ; p = 0,45).

**Conclusion :** Une ΔPrs-ARDS élevé n'était significativement pas associé à une augmentation de la durée de la ventilation mécanique ou du risque de mortalité chez les patients atteints de SDRA avec traumatisme thoracique, contrairement aux patients médicaux.

**Mots clés:**

Syndrome de détresse respiratoire aiguë, Unité de soins intensifs, Lésion pulmonaire, Pression transpulmonaire, Lésion pulmonaire induite par la ventilation