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CHARACTERIZATION OF CRITICALLY ILL PATIENTS WITH ARDS REQUIRING PROLONGED MECHANICAL VENTILATION

IOANNIS ANDRIANOPOULOS

INTERNIST INTENSIVIST

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«Η έγκριση της διδακτορικής διατριβής από το Τμήμα Ιατρικής του Πανεπιστημίου Ιωαννίνων δεν υποδηλώνει αποδοχή των γνωμών του συγγραφέα Ν. 5343/32, άρθρο 202, παράγραφος 2 (νομική κατοχύρωση του Ιατρικού Τμήματος)».

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«Χαρακτηριστικά βαρέως πασχόντων ασθενών με ARDS και ανάγκη για παρατεταμένο μηχανικό αερισμό»

ΟΡΙΣΜΟΣ ΕΠΤΑΜΕΛΟΥΣ ΕΞΕΤΑΣΤΙΚΗΣ ΕΠΙΤΡΟΠΗΣ: 1178α/Ο7-1Ο-2Ο25

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5. Σταμάτης Κωνσταντίνος, Επίκουρος Καθηγητής Εντατικής Θεραπείας με έμφαση στη Χειρουργική του Τμήματος Ιατρικής του Πανεπιστημίου Ιωαννίνων
6. Βερονίκη Φωτεινή, Επίκουρη Καθηγήτρια Εντατικής Θεραπείας με έμφαση στην Αναισθησιολογία του Τμήματος Ιατρικής του Πανεπιστημίου Ιωαννίνων
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Σπυρίδων Κονιτσιώτης

Καθηγητής Νευρολογίας

Η παρούσα Διδακτορική Διατριβή εκπονήθηκε με την οικονομική υποστήριξη του Ελληνικού Ιδρύματος Έρευνας και Καινοτομίας (ΕΛ.ΙΔ.Ε.Κ.) στο πλαίσιο της Δράσης «2η Προκήρυξη ερευνητικών έργων ΕΛ.ΙΔ.Ε.Κ. για την ενίσχυση Μεταδιδακτορικών Ερευνητών/τριών» (Αριθμός Έργου: 80-1/15.10.2020 στον Ηλία Σιέμπο.

Πρόλογος

Γράφοντας αυτόν τον πρόλογο, αναλογίζομαι τι είναι η διδακτορική διατριβή για μένα. Είναι φιλοδοξία ή ματαιοδοξία; Η προσθήκη ενός «Δρ» μπροστά από ένα όνομα ή ενός «PhD» μετά από αυτό; Μήπως μια προϋπόθεση για την επιδίωξη μιας ακαδημαϊκής θέσης ή μήπως, ένα «παιδικό» όνειρο;

Από τα εφηβικά μου χρόνια άρχισα να διαβάζω τα έργα του A.J. Cronin, ενώ αργότερα στράφηκα στη μελέτη της ζωής επιφανών επιστημόνων, όπως ο Άγιος Λουκάς ο Ιατρός και ο καθηγητής Ιατρικής Κ. Γαρδίκας. Με εντυπωσίασε βαθιά η αφοσίωσή τους στην επιστήμη και την έρευνα. Κατά τη φοίτησή μου στο πανεπιστήμιο, η πρόσβαση στη μεγάλη βιβλιοθήκη και στα πολυάριθμα επιστημονικά περιοδικά και βιβλία με εισήγαγε στον μαγευτικό κόσμο της επιστήμης και της έρευνας. Ένιωσα την επιθυμία να συμμετέχω και εγώ σε αυτό το κόσμο.

Δεν ήταν, όμως, μόνο τα αναγνώσματα, ήταν και τα παραδείγματα που είχα γύρω μου. Πρώτα από όλα μέσα στο σπίτι μου, από τον πατέρα, μου που ως γιατρός παθολόγος ο ίδιος με έμαθε (και ακόμα με μαθαίνει) τι σημαίνει να μελετώ, να διψώ για νέα γνώση, να μαθαίνω από τον ασθενή και για τον ασθενή. Δεύτερον, από τον αείμνηστο παθολόγο κο Νικόλαο Ακριτίδη που μαζί με τον πατέρα μου αποτελούν τα πρότυπα του σωστού γιατρού. Όπως, άλλωστε επεσήμανε ο καθηγητής M.J. Tobin η ιατρική διδάσκεται ως τέχνη «apprenticeship», και επομένως πρέπει κανείς να μαθητεύει σε σπουδαίους δασκάλους. Εγώ είχα την ευλογία να έχω τέτοιους από την αρχή της καριέρας μου. Εκτός όμως από όλα τα παραπάνω, αυτοί οι δύο μου μετέδωσαν και αυτή την ώση - τη θέληση - για συνεχή βελτίωση και νομίζω ότι η ενασχόλησή μου με την έρευνα εκπληρώνει ένα μέρος αυτού του συναισθήματος. Χάρις στην έρευνα μελετώ, καταλαβαίνω τα νοσήματα καλύτερα, εμβαθύνω στα θέματα, τροποποιώ τηη κλινική μου πρακτική και μαθαίνω από τα αποτελέσματα των ενεργειών μου. Με λίγα λόγια, νιώθω ότι γίνομαι καλύτερος γιατρός.

Επίσης, η έρευνα μου διδάσκει ταπεινότητα. Δεν μπορείς παρά να νιώσεις δέος μπροστά στο άπειρο της γνώσης και να συνειδητοποιήσεις την αδυναμία σου να τη συλλάβεις με το περιορισμένο μυαλό σου στην ολότητά της, καθώς και τα όρια των ικανοτήτων σου. Η έρευνα είναι κατεξοχήν ομαδική προσπάθεια και συνεργαζόμενος με ανθρώπους που είναι πολύ καλύτεροι από εμένα σε αυτήν, είναι ένα πολύ καλό (και οδυνηρό) μάθημα ενάντια στην αλαζονεία, στην έπαρση που μπορεί να έχει κάθε άνθρωπος, και ειδικά ένας γιατρός.

Εκτός από τα παραπάνω, η έρευνα για μένα δεν παύει να είναι μια εξερεύνηση, ένα μυστήριο, μια δυνατότητα να νιώθω όπως και οι ήρωες - ερευνητές των νεανικών μου χρόνων. Μέσω της έρευνας, μου δίνεται η δυνατότητα να αναζητώ κάθε φορά κάτι καινούργιο, να βγαίνω από την καθημερινή μου ρουτίνα και αυτό είναι κάτι που με αναζωογονεί τόσο ως γιατρό όσο και ως άνθρωπο. Με κάνει να αισθάνομαι νέος˙ είναι ένα αντίδοτο στη σκληρή, γεμάτη άγχος, δυσκολίες και απογοητεύσεις πραγματικότητα.

Για να διεξαχθεί, όμως, μια έρευνα, όπως προανέφερα, απαιτείται η συμβολή πολλών ανθρώπων. Είθισται στο πρόλογο μιας διδακτορικής διατριβής να ευχαριστούν οι υποψήφιοι διδάκτορες όλους εκείνους που συνέβαλαν άμεσα ή έμμεσα στην αποπεράτωση αυτού του πονήματος. Ομολογώ ότι βρίσκω τρομερά δύσκολο να εκφράσω με λόγια την ευγνωμοσύνη μου προς όλους όσοι με βοήθησαν για την ολοκλήρωση αυτού του εγχειρήματος.

Πρώτα από όλα θα ήθελα να ευχαριστήσω τα μέλη της τριμελούς επιτροπής μου: τον καθηγητή Βασίλειο Κουλούρα, και τους καθηγητές Γεώργιο Παπαθανάκο και Ηλία Σιέμπο. Ευχαριστώ πολύ για το ενδιαφέρον τους προς το πρόσωπό μου, την καθοδήγησή τους, το χρόνο και την υπομονή τους. Για τους δύο πρώτους, θέλω να εκφράσω την ευγνωμοσύνη μου για τη μακρόχρονη συνεργασία μας. Για τον Ηλία Σιέμπο, που ήταν ο εμπνευστής και καθοδηγητής αυτής της ερευνητικής μου προσπάθειας, θα πω ότι, αν για τη μαθητεία μου στη κλινική ιατρική αναγνωρίζω πρωτίστως τον πατέρα μου και το Ν. Ακριτίδη, για τη μαθητεία μου στην έρευνα αναγνωρίζω πρωτίστως τον κ. Ηλία Σιέμπο.

Ιδιαίτερες ευχαριστήριες στην καθηγήτρια της Ιατρικής Σχολής του Πανεπιστημίου Κρήτης, κα. Κατερίνα Βαπορίδη, στον επίκουρο καθηγητή του ΕΚΠΑ, κ. Στέλιο Κόκκορη και στους υποψηφίους διδάκτορες Ελένη Παπουτσή, Βασίλη Γιαννακούλη και Παναγιώτη Κρεμμύδα. Η συμβολή τους ήταν sine qua non για την πραγματοποίηση αυτού του εγχειρήματος. Αν και στο εξώφυλλο αυτό του πονήματος υπάρχει μόνο το όνομά μου, πιστεύω ότι χωρίς τη βοήθειά τους αυτή η διδακτορική διατριβή δε θα μπορούσε να πραγματοποιηθεί.

Θερμές ευχαριστίες οφείλω και στους συναδέλφους μου στη ΜΕΘ του Π.Γ.Ν.Ι. για την αγάπη τους και την καθημερινή μας αλληλεπίδραση που με κάνει καλύτερο ως γιατρό και ως ερευνητή.

Έρευνα δεν μπορεί να πραγματοποιηθεί χωρίς ασθενείς, οι οποίοι αποτελούν τόσο το μέσο όσο και το σκοπό για τον οποίο η έρευνα διεξάγεται. Συλλογιζόμενος αυτό, οφείλω να εκφράσω ευγνωμοσύνη προς αυτούς, επίσης.

Τέλος, θα ήθελα να ευχαριστήσω ιδιαιτέρως την οικογένειά μου: Τον πατέρα μου Γιώργο, που του χρωστώ το «ζην» και το «ευ ζην», τους γονείς μου, Δημήτρη και Αλίκη που με στηρίζουν με την αγάπη τους, τη σύζυγό μου Φωτεινή, που με αγαπά, με ενθαρρύνει και με υπομένει, και τα παιδιά μου, Αγγελική, Ανθία και Γιώργο, την αδελφή μου Άρτεμις, και τα αδέλφια μου Μαριάννα, Δημήτρη, Ιακώβη, Γιώργο και Νατάσα. Χάρις σε αυτούς και τους φίλους μας μπορώ να χαίρομαι τη ζωή.

Σε όλους εσάς θα ήθελα να αφιερώσω το παρόν πόνημα εκφράζοντας την απέραντη ευγνωμοσύνη μου.

Τρίτη, 04/11/2025

Μνήμη Αγίου Γεωργίου Καρσλίδη

Table of Contents

Short Curriculum Vitae

I was born in Argos in 1983.

In 2001 I was admitted to the Medical School of University of Ioannina from which I graduated in 2007 with a grade of 8.2.

After completing my compulsory military service as a Doctor and my primary care service as a junior doctor in northwestern Greece I continued my training in England in 2010.

From August 2010 to October 2013, I worked in Peterborough City Hospital, James Paget University Hospital NHS Trust and Norfolk and Norwich University Hospital NHS Trust where I finished my Core Medical Training, passed my MRCP exam and worked as an SpR in Endocrinology for the last two months.

For family reasons, I returned to Greece and continued my Internal Medicine training in “Agios Dimitrios” General Hospital of Thessaloniki, and I became board certified in Internal Medicine in September 2015.

Subsequently I trained in Intensive Care at Ioannina University Hospital and after finishing my training successfully I became board certified in Intensive Care in July 2018.

Since 2018 I have been working as a Consultant in Intensive Care at Ioannina University Hospital.

Apart from my clinical duties, I have been involved in the training of medical students and intensive care residents as well as have been an instructor in ALS, BASIC and ICF courses.

I hold two MSc degrees one in Hematopathology, University of York, UK and another in Medical Chemistry, University of Ioannina, Greece.

I have been an author/collaborator in 25 peer-reviewed articles, and in 33 abstracts in International Congresses. I have been co-authoring in 8 chapters of medical books, and I have delivered more than 10 presentations at various medical conferences in Greece and presented 12 abstracts in international congresses over the last three years.

A. GENERAL PART - INTRODUCTION

A1. Acute Respiratory Distress Syndrome - Definition

Acute Respiratory Distress Syndrome (ARDS) was initially defined in 1967 by Ashbaugh et al (1). Since then, several attempts have been made to revise the diagnostic criteria. Berlin definition, published in 2012 has been up until very recently the globally accepted definition (2). According to the above, ARDS has been defined as: a syndrome with acute onset (< 1 week), bilateral lung infiltrates on imaging, hypoxemia, and absence of features that suggest that lung edema is of cardiogenic origin.

ARDS is a syndrome that describes a clinical condition that has several causes grossly categorized in two categories as direct (due to direct lung injury) or indirect (cause of injury is extrapulmonary). Most common causes are pneumonia and sepsis followed by aspiration, trauma, transfusion and pancreatitis (Table 1).

Table 1. Most common causes of ARDS.

ARDS causes	
Direct	**Indirect**
Pneumonia	Extrapulmonary sepsis
Aspiration	Pancreatitis
Near drowning	Transfusion
Toxic inhalation	Severe trauma
Lung contusion	Cardiopulmonary bypass
Ischemic reperfusion injury	Eclampsia
Fat embolism	Burns

Epidemiology of ARDS

ARDS is not a rare entity. In fact, it is more common than initially considered and it appears that up to 23% of mechanically ventilated patients match the Berlin definition criteria

(3, 4). The very recent pandemic due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) led to overwhelming of Intensive Care Units (ICUs) with ARDS patients, higher mortality, and mandated an increased need for research on ARDS mechanism of disease and management.

Outcomes of ARDS

Mortality

Mortality in ARDS is significant. In a multicenter trial involving 459 ICUs from 50 countries, overall hospital mortality in ARDS was 40% (3). Disease severity appears to affect hospital mortality as patients with severe ARDS have a higher mortality estimated to 46.1% in the same study. Interestingly, ARDS appears to have an attributable mortality of 15% in ICU patients when compared to non-ARDS ICU patients (5). Apart from disease severity several factors appear to affect mortality in ARDS patients such as severity scores, non-pulmonary organ failure on admission, age, comorbidities, sociogeographic variations, lung mechanics as well as trajectory of disease with rapidly improving ARDS having a better prognosis from other ARDS cases (6-10).

Cost

The cost of ARDS appears to be significant. In a recent systematic review of 22 studies, patients with ARDS had a higher inpatient cost compared to other causes of ICU admission (11). Also, outpatient cost after hospital discharge is not negligible.

Long Term Sequalae

Apart from a significant mortality, ARDS patients are considered of high risk for Post Intensive Care Syndrome (PICS)(12). Six months after the discharge from hospital they continue to suffer from physical disability, mental health impairment, a significant percentage

is jobless and have reduced functional autonomy that is even worse than non-ARDS patients (13).

Pathophysiology of ARDS

ARDS pathophysiology is complex, heterogeneous and our knowledge of it is incomplete. Cornerstones of the syndrome appear to be the injury in the endothelial and alveolar barrier. Such an injury causes increased fluid permeability leading to injury alveoli to be filled with protein-rich edema. This fluid accumulation causes both an impairment in gas exchange and a reduction in lung compliance. Impairments in oxygenation and mechanics are thought to coincide and reflect the severity of ARDS (Figure 1) (14).

Heterogeneity of ARDS

ARDS is heterogeneous. First of all, there are several causes that lead to ARDS and based on these etiologies pathophysiology can significantly vary. Pathological specimens vary significantly whether the cause of ARDS is due to direct acute lung injury (ALI) or indirect (15). Histopathological specimens from patients with ARDS of direct acute lung injury (ALI) show a predominance in epithelial damage, have thicker and more heterogeneously distributed hyaline membranes, more oedema and more fibrosis while specimens from non-direct ALI show predominance of endothelial damage, thinner and more evenly distributed layers of hyaline deposits and less edema (Figure 2)(16, 17).

Second, trajectory of the syndrome is very heterogenous as some patients may recover rapidly while others can have a more prolonged trajectory of disease (18).

Third, while hypoxemia is universal, lung mechanics can significantly vary, and lung compliance can vary from being essentially normal up to significantly impaired. Due to this great heterogeneity, the observed mortality rate in ARDS patients varies significantly as well as the response to specific treatments with a characteristic example being dexamethasone's effectiveness in Coronavirus disease 2019 (COVID-19) associated ARDS (19). As a result of the above, the cause, timing of interventions, and underlying pathophysiology can significantly affect the outcome and treatment effectiveness.

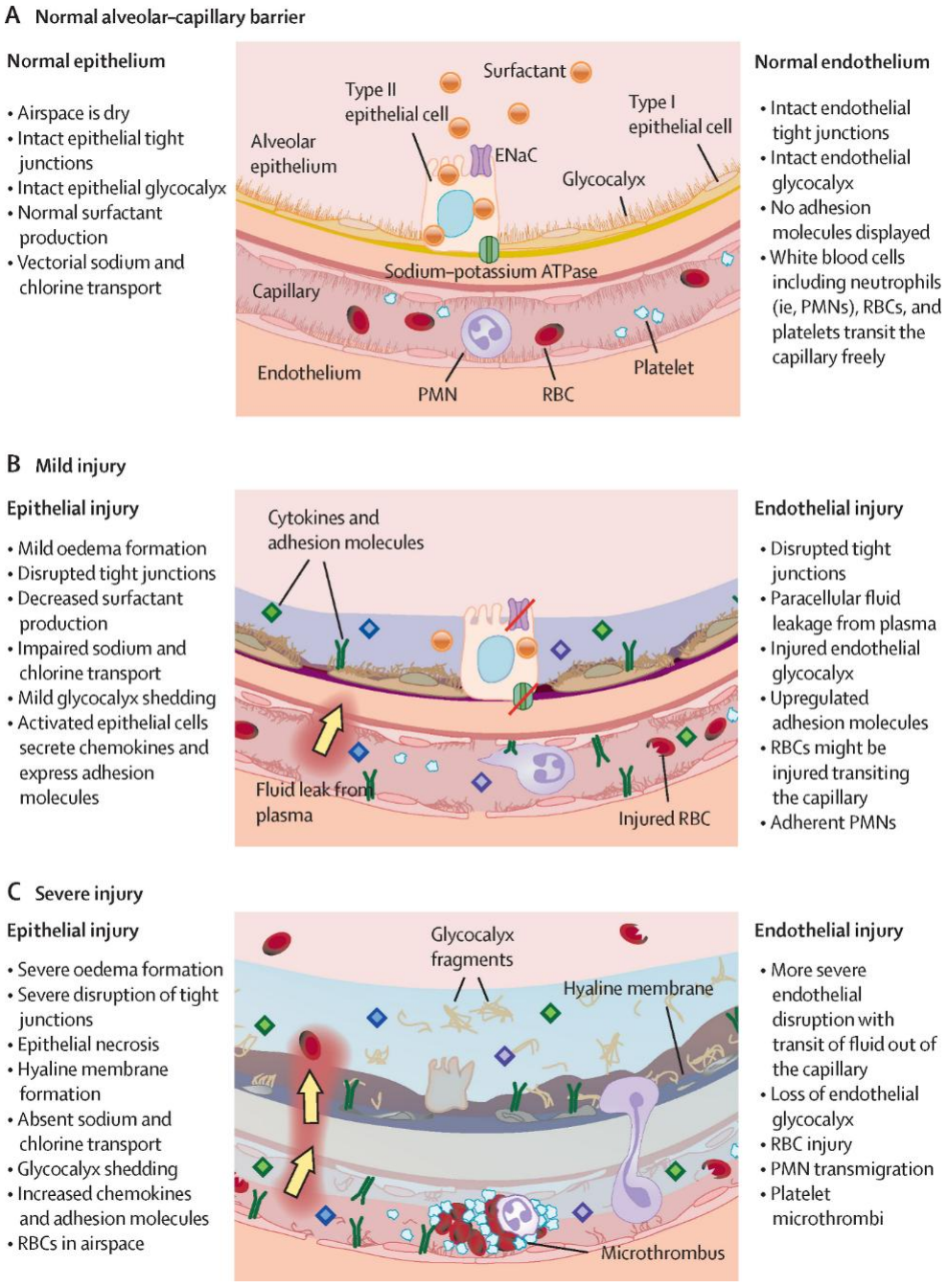


Figure 1. Endothelial and alveolar injury in ARDS among different severity stages. In normal lungs endothelial and epithelial tight junctions as well as glycocalyx are intact, production of surfactant is normal and there is absence of inflammation. In mild ARDS injury, tight junctions become disrupted, sodium and chloride pumps are dysregulated, glycocalyx is injured and mild edema is formed as well there is presence of inflammation with expression of adhesion molecules. In severe ARDS injury, there is severe disruption of epithelial and endothelial tight junctions, loss of glycocalyx, epithelial cell necrosis and hyaline membrane formation, severe edema and inflammation as well as formation of microthrombi [image reprinted from (14) with permission from Elsevier].

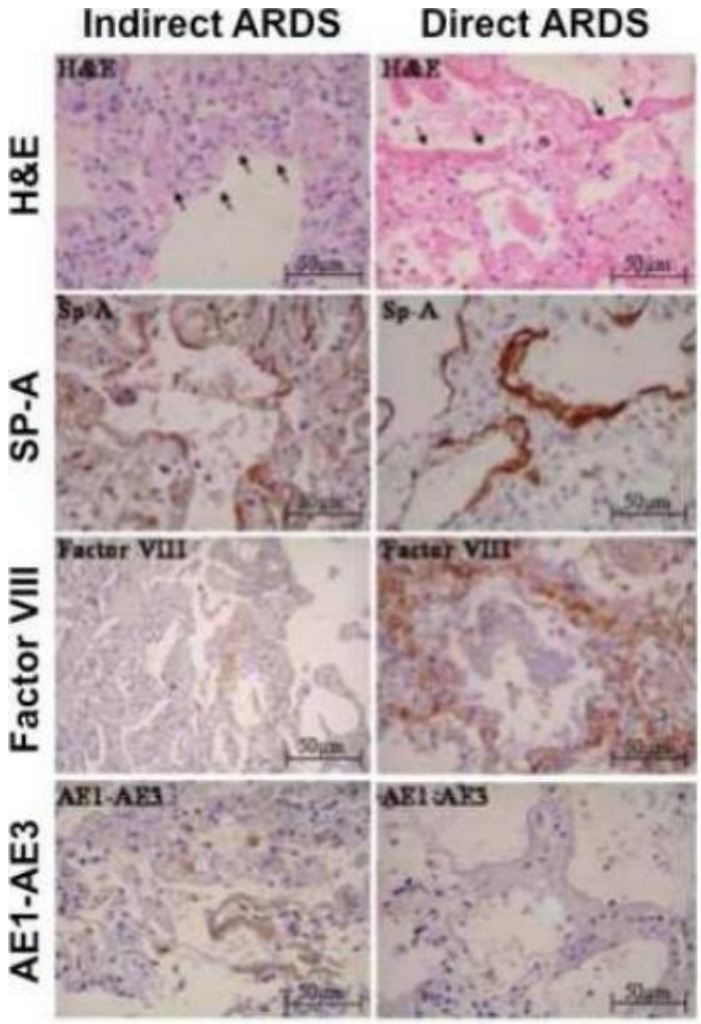


Figure 2. Differences in pathophysiology among direct and indirect ARDS. Specimens from direct ARDS have thicker hyaline membranes in H&E (arrows) and SP-A (brown color) stains, lack pan-cytokeratin staining (AE1-AE3) suggesting epithelial injury, while indirect ARDS shows absence of VIII factor an endothelial cell marker suggestive of endothelial injury [image reprinted from (17) with permission from Elsevier].

In terms of heterogeneity and lung mechanics, it was observed that several patients with ARDS due to the COVID-19 presented a dissociation between severe hypoxemia and relatively well-preserved compliance (20, 21). A subsequent secondary analysis of the LUNG SAFE study revealed that approximately one in eight patients meeting the hypoxemia criterion of ARDS exhibited preserved compliance, confirming this dissociation between oxygenation and compliance in patients presenting with ARDS regardless of etiology (22). The above observations were limited to the first days after the onset of ARDS, i.e., at early stages.

The number of ARDS patients dramatically increased during the COVID-19 pandemic, as did patients who required prolonged mechanical ventilation (23). During the pandemic, it was observed that many patients after several days of mechanical ventilation exhibited an 'opposite' dissociation between oxygenation and compliance, characterized by mild-moderate hypoxemia but significantly reduced compliance. Again, differences in compliance and oxygenation show the significant heterogeneity of ARDS but raise also the issue of different clinical trajectories and outcomes among ARDS patients. Clinical experience suggests that initial presentation cannot accurately predict ARDS outcome and the heterogeneity of the trajectory of disease requires studying of clinical characteristics in subsequent days following admission.

ARDS and Clinical Studies

The publication of the Acute Respiratory Management in ARDS (ARMA) study in 2000 was a cornerstone study by showing that patients ventilated with high tidal volumes (VT) (12 ml/kg Ideal Body Weight) have increased mortality compared to patients ventilated with a low VT (6 ml/kg) and a plateau pressure < 30 cm H_2O (24). This study has shifted the management of ARDS to what we nowadays refer to as lung protective ventilation.

After the publication of the ARMA study, ARDS network pursued whether the utilization of higher positive end-expiratory pressure (PEEP) [Assessment of Low tidal Volume and elevated End-expiratory volume to Obviate Lung Injury, (ALVEOLI) Study], different feeding protocols [Early Versus Delayed Enteral Nutrition, (EDEN) Study], the use of b-agonists [Albuterol to Treat Acute Lung Injury, (ALTA) Study] or statin [Statins for Acutely Injured Lungs from Sepsis (SAILS) Study] had any positive effect on patients, but all studies were negative (25-28).

The Fluids and Catheter Treatment Trial (FACTT) trial did indeed show that the use of a conservative fluid balance approach resulted in a reduction in the duration of mechanical ventilation and improvement of the lung function (29). The Prevention and Early Treatment of Acute Lung Injury (PETAL) network succeeded ARDS network consortium and pursued with further trials on ARDS management such as the use of neuromuscular blockage [Reevaluation of Systemic Early Neuromuscular Blockade (ROSE Trial)] or Vitamin-D replacement [Vitamin D

to Improve Outcomes by Leveraging Early Treatment (VIOLET) Trial] (30, 31). These studies also failed to show a statistically significant benefit from the intervention.

To summarize, while ARDS and PETAL network succeeded in organizing large, randomized control trials (RCTs), the great majority of these studies showed no benefit from the intervention despite reasonable pre-trial hypotheses. A key factor for RCTs on ARDS not showing any benefit from pharmacological interventions is the heterogeneity of ARDS population involved in these studies.

A2. Prolonged Mechanical Ventilation in ARDS

Definition and Risk Factors of ARDS in ICU

A proportion of ICU patients will require mechanical ventilation for several days. Therefore, these patients are defined as requiring prolonged mechanical ventilation (PMV) and may be considered as “difficult to wean”. Thus far several definitions have been used for PMV with the most commonly used cut-off points being 96 hours, 7, 14 and 21 days (32). Long term outcome of these patients is significantly affected and these patients are associated with worse mortality, higher healthcare utilization scores and higher readmission rates (33).

Several risk factors for PMV have been proposed, including age, comorbidities, severity of disease and cause of admission. Nevertheless, due to great heterogeneity among studies the available evidence is not strong and the list of factors is incomplete (32).

Prolonged Mechanical Ventilation Specifically in ARDS Patients

As mentioned earlier, trajectory of ARDS is heterogenous. Indeed, there are patients whose hypoxemia improves rapidly (i.e., within 24 hours), others whose severe hypoxemia persists for several days , and still others who receive PMV (7, 9, 34). Patients with ARDS, as opposed to those without ARDS, are indeed four times more likely to receive PMV (35). In a retrospective study performed in three cohorts of ARDS patients out of 1574 patients that were alive and under mechanical ventilation in day 3, 995 patients were either dead or

required mechanical ventilation at day 14; of these patients only 31.4% (312/995) survived to exit the mortality, suggesting a significant mortality of patients requiring more than 14 days of mechanical ventilation (36).

Based on studies involving unselected critically ill patients (i.e., not specifically patients with ARDS), PMV poses a constant challenge for the treating clinicians as it is associated with poor outcomes (37, 38). Also, it is very costly as, for example, patients with PMV occupy 30% of general ICU beds (33, 35). Given its immense clinical and financial burden on health-care systems, PMV has emerged as an important research priority (39). PMV was indeed recognized as an important research priority as early as 2005 at a National Association for Medical Direction of Respiratory Care (NAMDRC) Consensus Conference. That Consensus Conference report stated that "the number of patients meeting the definition of PMV will likely continue to increase" over time and that "predicting mortality outcomes is vital" (40). Nevertheless, subsequent relevant evidence specifically involving patients with ARDS is limited and there is scarce data on the prevalence and risk factors for mortality, as well as the trajectory of lung mechanics in these ARDS patients.

A3. ARDS Prolonged Mechanical Ventilation and Acute Kidney Injury

ARDS is associated with non-negligible attributable mortality (5, 41)(42,43). Mortality of patients with ARDS significantly increases with the development of acute kidney injury (AKI)(42). The prevalence of AKI, which is around 30% in unselected critically ill patients, further increases to around 45% in patients with ARDS (43-45). This increase in prevalence of AKI in patients with ARDS has been attributed, at least partially, to injurious mechanical ventilation leading to ventilator-induced lung injury (46). According to the concept of biotrauma, ventilator-induced lung injury may propagate an inflammatory response, which in turn may mediate injury of multiple organs, including kidney (47-50).

Preclinical and limited clinical data suggest that acute lung injury mediates AKI through multiple pathophysiological pathways that involve not only release of inflammatory mediators (as noted above), but also vasoconstriction of renal vessels, activation of the renin-angiotensin-aldosterone system and reduction in the renal blood flow by reduction of the cardiac output (51, 52). In addition, an increase in the afterload of right ventricle, as it is often

the case in patients with ARDS, is associated with higher central venous pressure and therefore a higher risk for AKI (48).

Conversely, AKI may lead to increased fluid accumulation in the lung, which in turn worsens lung compliance and increases driving pressure (48). In other words, high driving pressure may not be a contributor (as a marker of ventilator-induced lung injury) to but rather a consequence of AKI in patients with ARDS. The latter nuance ('*was high driving pressure a contributor to or a consequence of AKI?*') could not be assessed in previous meticulous large observational studies involving patients with ARDS, because they focused on AKI which was already present at the time of onset of ARDS (53-56).

Whether AKI is a risk factor for prolonged mechanical ventilation or whether prolonged mechanical ventilation is a risk factor for AKI remains to be addressed.

B. SPECIFIC PART

B1. Introduction

In the general part of the thesis, we presented the general knowledge of ARDS. We highlighted its high prevalence in ICUs as well as its association with significant heterogeneity, morbidity and mortality. In addition, we focused on the subgroup of patients that require prolonged mechanical ventilation. We identified gaps in our knowledge of patients with ARDS who require prolonged mechanical ventilation in terms of prevalence, mortality, risk factors as well as the trajectory of lung mechanics and the role of extrapulmonary organ dysfunction, such as AKI.

Purpose of Thesis

As a consequence of the lack of current evidence on prevalence, outcome and clinical characteristics of patients with ARDS that require PMV, we pursued with investigating the characteristics of this subgroup of patients.

Research Hypothesis

Having the above considerations into mind, we endeavored to take advantage of the large high-quality databases of randomized controlled trials conducted by the ARDS Network and assess three hypotheses/questions:

- First question to address was to estimate temporal trends of prevalence and mortality of PMV and to identify risk factors associated with mortality of patients with ARDS receiving PMV. This knowledge is important to understand the burden of PMV on ARDS patients and identify potentially modifiable risk factors.
- Second, whether the dissociation between oxygenation and compliance becomes prevalent in persistent ARDS regardless of etiology, or rather it is a particular feature of

COVID-19 related ARDS. This knowledge may be important given that a nonnegligible proportion of patients with ARDS require prolonged mechanical ventilation; i.e., they remain under ventilation more than 21 days after intubation(40). Based on our observation, we endeavored to systematically examine the presence of this combination of mild-moderate hypoxemia and significantly impaired compliance, focusing specifically on patients with ARDS requiring prolonged mechanical ventilation.

- Third, we endeavored to study the association of ARDS, PMV and the development of AKI. In order to achieve that, we focused on examining whether high driving pressure is associated with subsequent development of AKI.

B2. Methods

Thesis Design and Study Population

To address the above hypotheses we used data from two cohorts. The first cohort included all patients enrolled in seven ARDS and PETAL network trials: ARMA, ALVEOLI, FACTT, ALTA, EDEN , SAILS and ROSE trials (24-30). The second cohort consisted of patients with ARDS related to COVID-19 (CARDS) admitted between October 2020 and January 2022 (i.e., when the alpha and delta SARS-CoV-2 variants were prominent) in two academic ICUs at tertiary hospitals in Crete and Ioannina, Greece.

For each hypothesis the study populations were defined by the specific parameters of the research question.

In order to investigate the temporal trend and prevalence of PMV in ARDS patients as well as to identify potential risk factors for mortality, we performed a secondary analysis by obtaining individual patient data from subjects enrolled in the following six randomized controlled trials conducted by the ARDS Network: ARMA, ALVEOLI, FACTT, ALTA, EDEN, and SAILS trial (24-29).

To investigate the prevalence of oxygenation-compliance dissociation observed in CARDS patients with persistent ARDS as well as its prevalence in non-COVID-19 associated ARDS we utilized data from two cohorts: The first cohort of our study (“ARDSNet” cohort)

consisted of patients with ARDS enrolled in four prospective therapeutic clinical trials conducted by the ARDS Network, namely FACTT, ALTA, EDEN, and SAILS (26-29). The second cohort for our study consisted of patients with CARDS in the two academic ICUs at tertiary hospitals in Crete and Ioannina, Greece.

To investigate the role of persistent ARDS and mechanical ventilation in the development of AKI we used individual patient-level data from seven ARDS Network and Prevention and Early Treatment of Acute Lung Injury (PETAL) Network randomized controlled clinical trials; namely, ARMA, ALVEOLI, FACTT, ALTA, EDEN, SAILS and ROSE trials (24-30).

We were granted access to data after submitting a prospective protocol to the Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC) of the National Heart, Lung, and Blood Institute (NHLBI). Because the data would be received in de-identified form (non-human subjects research), the Institutional Review Board of Evangelismos Hospital waived the need of informed consent and approved the study (protocol number 140/5-5-2022). For the CARDS cohort, the Institutional Review Board at each participating study site (Ioannina: University Hospital of Ioannina, and Crete: University Hospital of Heraklion) approved of the data collection and waived the need for informed consent owing to the observational study design and the collection of de-identified data.

Study Definitions

With regard to the definition of PMV, we used the NAMDRC Consensus Conference report, we used a threshold of 21 days which is the one most commonly use(39, 40). Accordingly, PMV was defined as the requirement for invasive mechanical ventilation for more than 21 consecutive days after trial enrollment.

We used a threshold for low PaO_2:FiO_2 a value below 150, which has been used to identify patients with significant hypoxemia likely to benefit from prone position, and for low compliance a value below 30 mL/cm H_2O, which has been shown to be associated with sustained high driving pressure and weaning failure (57-59). Accordingly, we considered four combinations of oxygenation and compliance in our study:

- mild-moderate hypoxemia/low compliance,
- mild-moderate hypoxemia/high compliance,

- severe hypoxemia/high compliance, and
- severe hypoxemia/low compliance.

We defined AKI according to the Kidney Disease Improving Global Outcome (KDIGO) criteria (60, 61). Because of unavailability of hourly urine output data, we only used the serum creatinine criterion as per previous similar studies (53). We defined baseline creatinine as the lowest value of creatinine on the day of onset of ARDS (day 1). After exclusion of patients with early AKI (i.e., those who met the AKI criteria within the first two days following onset of ARDS), we classified the study population into two groups: “late AKI” and “no AKI”. The “late AKI” group included patients who developed AKI more than two days but no longer than seven days following onset of ARDS. This threshold of two days to define late AKI has been previously used in the literature (62). The “no AKI” category included patients who did not develop AKI during index stay in the ICU.

Collection of Data

From the seven included ARDS Network and PETAL Network randomized controlled trials, we extracted data on demographics (age, sex, body mass index and race), comorbidities (data on hypertension, chronic pulmonary disease and cardiovascular disease were not available for ARMA and ALVEOLI trials), risk factors of ARDS, organ failure (namely cardiovascular, coagulation and hepatic) at baseline, fluid balance, creatinine (up to day 7 after ARDS onset) and respiratory variables. We collected data on 90-day mortality, organ failure-free days, ventilator-free days and ICU-free days. Organ failures were defined according to the various components of Sequential Organ Failure Assessment (SOFA) score. Specifically, cardiovascular failure was defined as a systolic blood pressure ≤ 90 mm Hg or the requirement for vasopressors, coagulation failure as platelet concentration ≤ 80,000/µL, and hepatic failure as the concentration of bilirubin ≥ 2 mg/dL. Regarding respiratory system mechanics, we retrieved data on PEEP, plateau pressure (Ppl), tidal volume per predicted body weight (VT/PBW) and driving pressure (defined as Ppl minus PEEP). Data on driving pressure were available for consecutive days 2 to 6 following onset of ARDS. As baseline values for these parameters, we used the data of day 2, due to their unavailability on day 1. Their mean values were estimated by dividing the sum of values (up to day 6 or day of development of AKI

whatever came first) with the total number of measurements. The mean value was used as a surrogate of the trajectory of each parameter across time.

To investigate the dissociation of hypoxemia-compliance in ARDS, we first analyzed all patients at baseline and evaluated the prevalence of each of the four above-described combinations. Data from all patients were included in this analysis (no exclusion criteria). We subsequently focused on patients who were on mechanical ventilation and had available data on oxygenation (as assessed by PaO_2:FiO_2) and respiratory system compliance on day 21.

Main Outcomes

Primary end point for the first hypothesis investigating the prevalence, mortality and clinical characteristics of the study was 90-day mortality and secondary end points were risk factors for mortality among ARDS patients requiring prolonged mechanical ventilation.

In order to investigate the dissociation of compliance and hypoxemia in ARDS patients, primary endpoint was the change in prevalence of the combination of mild-moderate hypoxemia/low compliance over time from baseline to day 21. Secondary endpoints included the difference in the prevalence of the combination of mild-moderate hypoxemia and low compliance between the ARDSNet cohort and the CARDS cohort; the trajectory of oxygenation among patients with either low or high compliance (using the abovementioned threshold of 30 mL/cm H_2O) from baseline to day 21; the mortality at day 21 based on the oxygenation-compliance combination at baseline, and the 60-day mortality based on the oxygenation-compliance combination on day 21.

The primary endpoint in the study investigating the role of ARDS and mechanical ventilation in the development of AKI was the development of late AKI. Secondary outcomes were 90-day mortality, organ failure-free days, ventilator-free days, and ICU-free days; the latter were defined as previously in the literature (7, 63).

Statistical Analysis

We presented continuous variables as median with interquartile range (IQR) and compared them using the non-parametric Mann-Whitney U test (for 2 groups) or the Kruskal-

Wallis test (for multiple groups). We presented categorical variables as percentages and compared them using the Chi-squared or Fisher's exact test, as appropriate. We estimated the prevalence and mortality of PMV across time via a simple linear regression model, with time as the independent variable and within-study prevalence of PMV (or, respectively, mortality of patients with PMV) as the dependent variable. To identify risk factors associated with mortality of patients with ARDS receiving PMV, we utilized a multivariate binary logistic regression model with 90-day mortality (i.e., the primary outcome of the present analysis) as the dependent variable, using all available information on mortality and risk factors. In the light of previous contributions involving the general ICU population, we considered the following risk factors for inclusion in the model: age, baseline severity of illness [as assessed by the Acute Physiology and Chronic Health Evaluation (APACHE III) score], malignancy, pneumonia as the cause of ARDS, persistent severe ARDS (defined as previously), coagulation failure and hepatic failure during the first 21 days after trial enrolment, and tracheostomy (33, 34, 38, 64, 65). We presented relevant results as odds ratio (OR) and 95% confidence intervals (CI).

For the study investigating late AKI development in ARDS patients, we estimated the association between driving pressure and development of late AKI via binary logistic regression analyses, with driving pressure as the independent variable and the development of late AKI as the dependent variable. We used multivariable logistic regression analyses to adjust for confounding factors known to be associated with development of AKI, such as age, sex, body mass index, presence of diabetes mellitus, organ failures (namely, cardiovascular, coagulation, and hepatic) and fluid balance (29). We also adjusted for respiratory variables other than driving pressure, such as PaO_2:FiO_2, respiratory rate, tidal volume, respiratory system compliance and PEEP. We tested for collinearity between variables by calculating variance inflation factor (VIF); a VIF < 5 was considered to rule out collinearity (66). We also assessed the linearity of the relationship between baseline driving pressure and late AKI using cubic splines. We performed repeated measurements using two-way repeated measures ANOVA. We performed and compared three multivariate regressions to delineate which of the following remains a significant factor for late AKI prediction: Ppl, PEEP or both, expressed as a difference, namely driving pressure. Firstly, we defined a reference clinical model including the same baseline variables used in the previous logistic regressions. Then, three separate multivariate logistic regression analyses were conducted to assess the performance

of the predictive models, after adding the individual risk factors to the reference model individually. Improvements in the model were evaluated by difference in the area under the curves (AUCs) (ΔAUC) and DeLong test. We also quantified the improvement of each factor on late AKI risk prediction with the net reclassification improvement (NRI), which measures how much a new model improves the classification of individuals compared to a reference model. It assesses whether the new model more accurately reclassifies individuals into appropriate risk categories. A positive NRI indicates that the new model improves classification compared to the reference model. We considered statistical significance at a level of 0.05; all P values were two-sided.

All p values were two-sided and thought to denote statistical significance if equal to or less than 0.05. We performed statistical analyses using SPSS software version 28.0 (SPSS, Inc., Chicago, IL), R software version 4.2.1 (R Foundation for Statistical Computing) and GraphPad Prism version 9.0.0, (GraphPad Software, La Jolla, California, USA).

B3. Results

Temporal Trends of Prevalence and Mortality of PMV

Out of 4216 patients with ARDS enrolled in six ARDS Network trials, 646 (15.3%) patients received PMV(24-29). Figure 3 presents temporal trends of prevalence of PMV in clinical trials of ARDS. Prevalence of PMV gradually declined from 18.4% in the ARMA (published in 2000) trial to 10.9% in the SAILS (2014) trial (R2=0.728, p=0.031). During the same time period, prevalence of patients with ARDS who were discharged alive without receiving PMV gradually increased from 52.3% in the ARMA trial to 65.6% in the SAILS trial (R2=0.780, p=0.020; Figure 3).

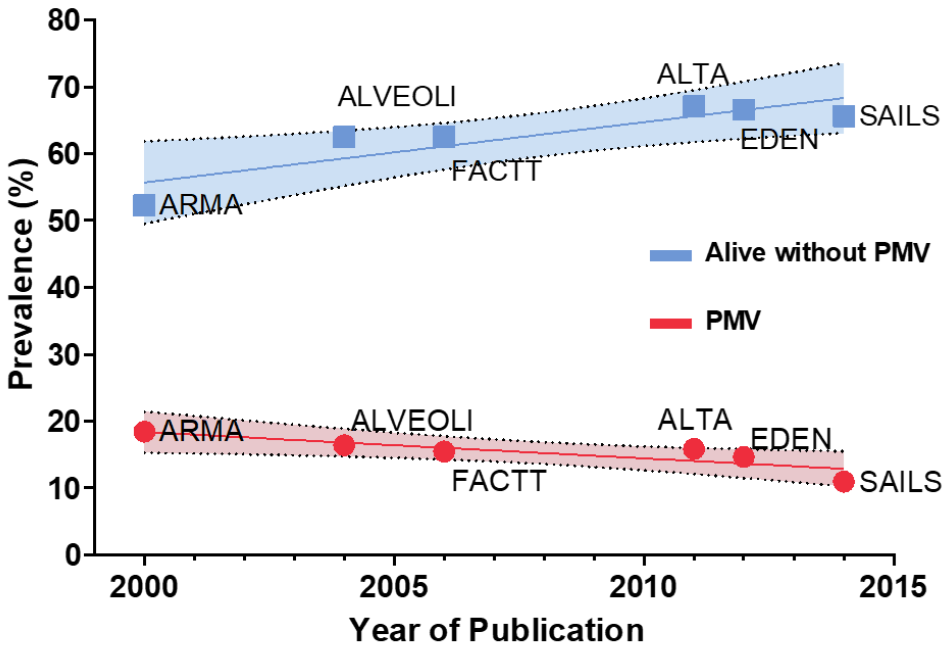


Figure 3. Temporal trends of prevalence of prolonged mechanical ventilation (PMV) in clinical trials of ARDS. Prevalence of PMV gradually declined from the ARMA to the SAILS trial. During the same time period, prevalence of patients with ARDS who were discharged alive without receiving PMV gradually increased.

This was also the case (i.e., prevalence of PMV gradually declined, while percentage of patients with ARDS who discharged alive without receiving PMV gradually increased) in the subgroup analyses involving only medical patients or only patients with pulmonary causes of ARDS, but not in the subgroup analyses involving only surgical patients or only patients with extrapulmonary causes of ARDS (Figure 4).

Figure 5 presents temporal trends of 90-day mortality of patients with ARDS receiving PMV. Mortality of patients receiving PMV did not change over time in clinical trials of ARDS ($R2=0.271$, $p=0.290$) and remained as high as 36.8% (Figure 5).

This was also the case (i.e., mortality of patients receiving PMV did not change over time) in the subgroup analyses involving only medical patients or only surgical patients or only patients with pulmonary causes of ARDS or only patients with extrapulmonary causes of ARDS (Figure 6).

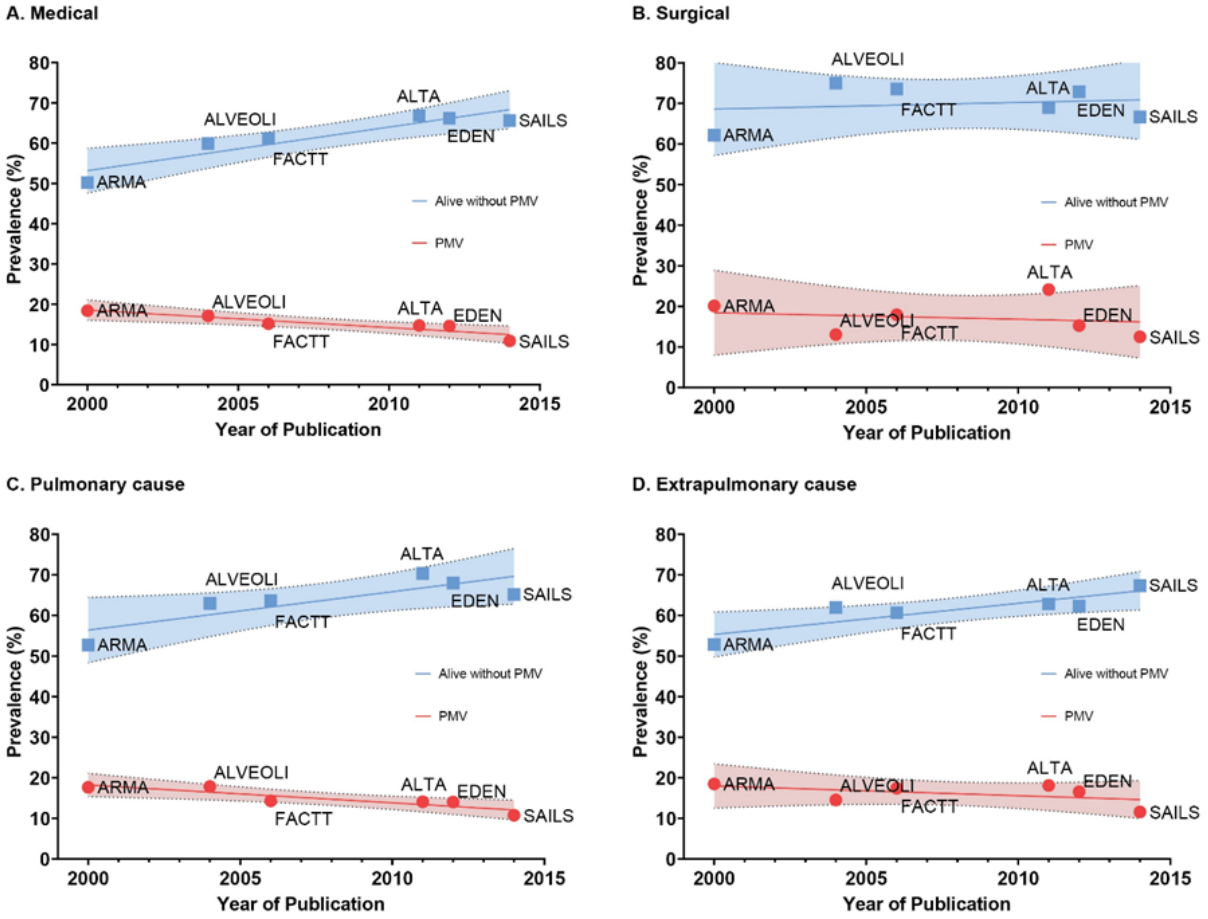


Figure 4. Temporal trends of prevalence of prolonged mechanical ventilation (PMV) in subgroup analyses involving (A) only medical patients; (B) only surgical patients; (C) only patients with pulmonary causes of acute respiratory distress syndrome (ARDS); and (D) only patients with extrapulmonary causes of ARDS. In the subgroup analysis involving only medical patients (i.e., after exclusion of patients with ARDS following trauma or elective surgery), prevalence of PMV gradually declined (R2=0.828, p=0.012), while percentage of patients with ARDS who were discharged alive without receiving PMV gradually increased (R2=0.862, p=0.008). (B) In the subgroup analysis involving only surgical patients (i.e., patients with ARDS following trauma or elective surgery), neither prevalence of PMV declined (R2=0.038, p=0.713) nor percentage of patients with ARDS who were discharged alive without receiving PMV increased (R2=0.032, p=0.734). (C) In the subgroup analysis involving only patients with pulmonary causes (namely, pneumonia and aspiration) of ARDS, prevalence of PMV gradually declined (R2=0.794, p=0.017), while percentage of patients with ARDS who were discharged alive without receiving PMV gradually increased (R2=0.695, p=0.039). (D) In the subgroup analysis involving only patients with extrapulmonary causes of ARDS, prevalence of PMV did not decline (R2=0.241, p=0.322), while percentage of patients with ARDS who were discharged alive without receiving PMV gradually increased (R2=0.760, p=0.024).

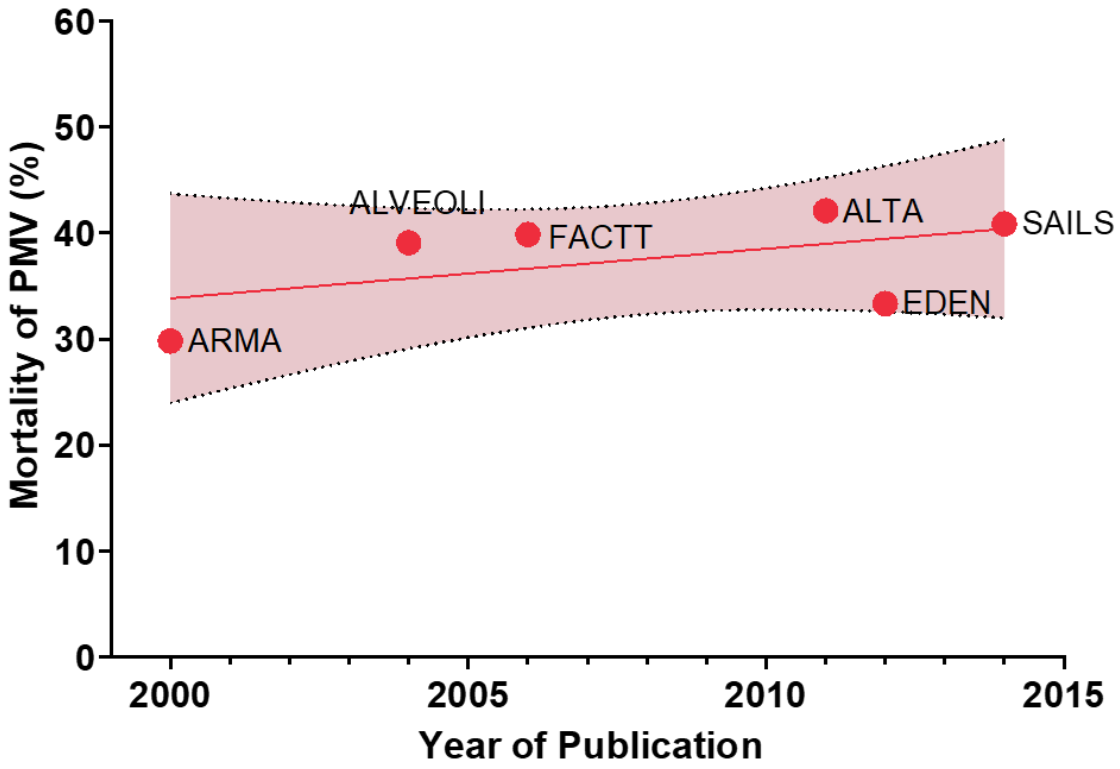


Figure 5. Temporal trends of 90-day mortality of patients with acute respiratory distress syndrome receiving prolonged mechanical ventilation. Mortality of patients with ARDS receiving PMV did not change over time in clinical trials conducted by the ARDS Network.

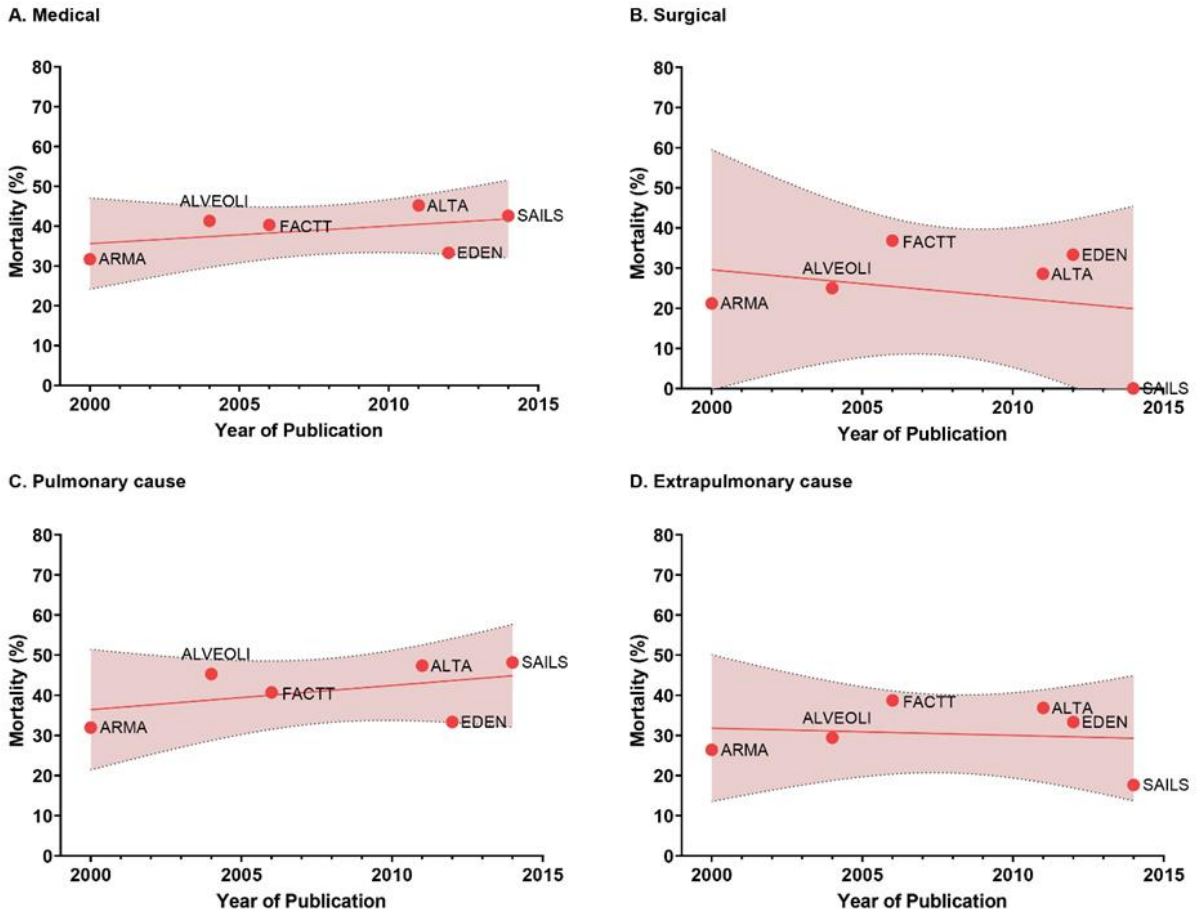


Figure 6. Temporal trends of 90-day mortality of patients with acute respiratory distress syndrome (ARDS) receiving prolonged mechanical ventilation (PMV) in subgroup analyses involving (A) only medical patients; (B) only surgical patients; (C) only patients with pulmonary causes of ARDS; and (D) only patients with extrapulmonary causes of ARDS. Mortality of patients receiving PMV did not change over time in the subgroup analyses involving (A) only medical patients (i.e., after exclusion of patients with ARDS following trauma or elective surgery) (R2=0.197, p=0.379) or (B) only surgical patients (i.e., patients with ARDS following trauma or elective surgery) (R2=0.081, p=0.585) or (C) only patients with pulmonary causes (namely, pneumonia and aspiration) of ARDS (R2=0.210, p=0.360) or (D) only patients with extrapulmonary causes of ARDS (R2=0.016, p=0.813).

Baseline Characteristics and Clinical Course of Patients with PMV

To better reflect modern clinical practice, the remainder of our analyses considered only data from the three most recently published ARDS Network trials; namely, ALTA, EDEN, and SAILS (all published after 2010) (26-28). Of the 1853 patients with ARDS enrolled in these trials, 250 (13.5%) patients received PMV (26-28).

Table 2 presents baseline characteristics and initial management of the 250 patients with ARDS receiving PMV. Out of those 250 patients, 92 (36.8%) died by day 90. Non-survivors, as opposed to survivors, were older [59.0 (44.3-69.0) vs 51.5 (42.0-63.0) years; p=0.012], had higher APACHE III score [102.0 (83.5-123.3) vs 93.0 (78.0-106.0); p=0.006], were more likely to have malignancy [12 (13.0%) vs 3 (3.9%); p<0.001], were more likely to have pneumonia as a cause of ARDS [65 (70.7%) vs 91 (57.6%); p=0.040] and had higher baseline partial pressure of arterial oxygen to fraction of inspired oxygen ratio (PaO_2:FiO_2) [157.8 (106.5-192.4) vs 118.1 (89.7-160.0); p<0.001]. There was no difference between non-survivors and survivors in terms of initial management, such as ventilator settings and cumulative fluid balance (Table 2).

Table 3 presents the clinical course of the 250 patients with ARDS receiving PMV. Non-survivors, as opposed to survivors, were more likely to experience coagulation failure dysfunction [64 (69.6%) vs 60 (38.0%); p<0.001] and hepatic failure dysfunction [35 (38.0%) vs 39 (24.7%); p=0.026] during the first 21 days after trial enrollment. Also, non-survivors, as opposed to survivors, were less likely to receive tracheostomy [30 (32.6%) vs 88 (55.7%); p<0.001] during the first 21 days after trial enrolment (Table 3).

Risk Factors Associated with Mortality of Patients with ARDS Receiving PMV

Table 4 presents a multivariable binary logistic regression analysis to identify risk factors associated with 90-day mortality of patients with ARDS receiving PMV. Risk factors independently associated with mortality were age (OR 1.03, 95% CI 1.01-1.0605), malignancy (OR 6.35, 95% CI 1.55-26.08 5.77, 95% CI 1.45-22.95), pneumonia as the cause of ARDS (OR 2.48, 95% CI 1.26-4.89 2.56, 95% CI 1.32- 4.97), coagulation failure dysfunction (OR 4.02, 95% CI 2.05-7.9OR 4.17, 95% CI 2.17-8.01) and hepatic failure dysfunction (OR 2.12, 95% CI 1.08-4.17 2.07, 95% CI 1.07-4.00) during the first 21 days after trial enrollment. Tracheostomy

during the first 21 days after trial enrollment was negatively associated with mortality (OR 0.34, 95% CI 0.18-0.64) (Table 4).

Table 2. Baseline characteristics and initial management of 250 patients with ARDS receiving PMV.

Variable[a]	**Total (n=250)**	**Non-survivors (n=92)**	**Survivors (n=158)**	**p value**
Age (years)	55.0 (42.0-65.0)	59.0 (44.3-69.0)	51.5 (42.0-63.0)	0.012
Female sex	119 (47.6%)	46 (50.0%)	73 (46.2%)	0.562
Race				0.613
White	161 (64.4%)	61 (66.3%)	100 (63.3%)	
Black	42 (16.8%)	17 (18.5%)	25 (15.8%)	
Hispanic or Latino	38 (15.2%)	11 (12.0%)	27 (17.1%)	
Other	8 (3.2%)	2 (2.2%)	6 (3.8%)	
Body Mass Index (kg/m^2)	29.2 (23.3-35.6)	28.0 (22.9-34.6)	30.2 (23.7-36.3)	0.149
APACHE III score	96.0 (79.0-114.0)	102.0 (83.5-123.3)	93.0 (78.0-106.0)	0.006
Usage of vasopressors within 24 hours prior to trial enrollment	154 (61.6%)	60 (65.2%)	94 (59.5%)	0.370
Comorbidity				
Any comorbidity	162 (64.8%)	67 (72.8%)	95 (60.1%)	0.043
Malignancy[b]	15 (6.0%)	12 (13.0%)	3 (1.9%)	< 0.001
Cardiovascular disease[c]	120 (48.0%)	46 (50.0%)	74 (46.8%)	0.629
Liver disease[d]	16 (6.4%)	8 (8.7%)	8 (5.1%)	0.258
Chronic pulmonary disease	36 (14.4%)	17 (18.5%)	19 (12.0%)	0.161
Immunosuppression[e]	37 (14.8%)	23 (25.0%)	14 (8.9%)	< 0.001
Cause of ARDS				
Pneumonia	156 (62.4%)	65 (70.7%)	91 (57.6%)	0.040
Sepsis	48 (19.2%)	15 (16.3%)	33 (20.9%)	0.375
Trauma	13 (5.2%)	4 (4.3%)	9 (5.7%)	0.773
Aspiration	19 (7.6%)	4 (4.3%)	15 (9.5%)	0.139
Physiological parameters on the day of trial enrolment[f]				

VT (ml/kg)	6.2 [6.0-7.4]	6.4[6.0-7.8]	6.1 (5.9-7.1)	0.220
RR (breaths/ minute)	26.0 (20.0-31.0)	26.0 (20.0-31.0)	26.0 (21.0-32.0)	0.474
PEEP (cm H_2O)	10.0 (5.0-12.0)	10.0 [5.0-12.0]	10.0 [5.3-14.0]	0.143
Pdriving (cm H_2O)	15.0 (12.0-20.0)	15.0 (12.0-18.0)	16.0 (12.0-20.0)	0.310
PaO_2:FiO_2	129.5 [94.7-176.0]	157.8 [106.5-192.4]	118.1 [89.7-160.0]	< 0.001
Cumulative fluid balance (ml, days 0-2)	365 (503-7290)	3934.0 (503.0-7652.0)	3581.5 (395.5-7123.5)	0.359

Abbreviations: ARDS, acute respiratory distress syndrome; PMV, prolonged mechanical ventilation; APACHE, Acute Physiology and Chronic Health Evaluation; VT, tidal volume; RR, respiratory rate; PEEP, positive end-expiratory pressure; Pdriving, driving pressure; PaO2: FiO2, partial pressure of arterial oxygen to fraction of inspired oxygen ratio.

[a] Data are presented as number (percentage) or median [interquartile range].

[b] Malignancy includes solid tumor with metastasis, leukemia and lymphoma.

[c] Cardiovascular disease includes prior myocardial infarction, hypertension, congestive heart failure, peripheral vascular disease and prior stroke with sequelae.

[d] Liver disease includes cirrhosis and hepatic failure with coma or encephalopathy.

[e] Immunosuppression refers to radiation, chemotherapy or administration of systemic steroids (greater than or equal to 0.3 mg/kg/day prednisone or equivalent) within the past six months.

[f] Trial enrollment (specifically, randomization) occurred a median of 1.0 day [1.0-2.0] after intubation and a median of 1.0 day [0.0-1.0] after diagnosis of ARDS. There were no statistically significant differences regarding the median time from intubation to trial enrollment (p=0.772) or regarding the median time from diagnosis of ARDS to trial enrollment (p=0.860) between the three randomized controlled trials (14-16).

Table 3. Clinical course during the first 21 days after trial enrollment of the 250 patients with ARDS receiving PMV.

Variable[a]	Total (n=250)	Non-survivors (n=92)	Survivors (n=158)	p value
Persistent severe ARDS[b]	50 (20.0%)	18 (19.6%)	32 (20.3%)	0.982
Non-pulmonary organ dysfunction[c]	231 (92.4%)	91 (9.9%)	140 (88.6%)	0.003
Coagulation dysfunction	124 (49.6%)	64 (69.6%)	60 (38.0%)	< 0.001
Renal dysfunction	139 (55.6%)	56 (60.9%)	83 (52.5%)	0.201
Cardiovascular dysfunction	207 (82.8%)	82 (89.1%)	125 (79.1%)	0.043
Hepatic dysfunction	74 (29.6%)	35 (38.0%)	39 (24.7%)	0.026

Abbreviations: ARDS, acute respiratory distress syndrome; [a] Data are presented as number (percentage). [b] Persistent severe ARDS was defined as partial pressure of arterial oxygen to fraction of inspired oxygen ratio ≤100 mmHg on the second day after trial enrollment(34). If that value was not available, then the next available value up to day 7 after trial enrollment was considered. [c] Non-pulmonary organ dysfunctions were defined as follows: coagulation dysfunction as platelets <100 10^3/mm^3; hepatic dysfunction as bilirubin ≥2 mg/dL; cardiovascular dysfunction as usage of vasopressors, and renal dysfunction as creatinine ≥2 mg/dL at any time up to day 21 after trial enrollment.

Table 4. Multivariable binary logistic regression analysis to identify risk factors associated with 90-day mortality of patients with ARDS receiving PMV.

Risk factor	OR	95% CI	p value
Age (increments of 1 year)	1.03	1.01-1.05	0.005
APACHE III (increments of 1)	1.00	0.99-1.01	0.708
Malignancy	5.77	1.45-22.95	0.013
Pneumonia as the cause of ARDS	2.56	1.32-4.97	0.005
Persistent severe ARDS[a]	1.19	0.56-2.53	0.656
Coagulation dysfunction[b]	4.17	2.17-8.01	< 0.001
Hepatic dysfunction[c]	2.07	1.07-4.00	0.030

Abbreviations: ARDS, acute respiratory distress syndrome; OR, odds ratio; CI, confidence intervals; APACHE, Acute Physiology and Chronic Health Evaluation. [a] Persistent severe ARDS was defined as partial pressure of arterial oxygen to fraction of inspired oxygen ratio ≤ 100 mm Hg on the second day after trial enrollment (34). If that value was not available, then the next available value up to day 7 after trial enrollment was considered. [b] Coagulation dysfunction was defined as platelets <100 10^3/mm^3 at any time up to day 21 after trial enrollment. [c] Hepatic dysfunction was defined as bilirubin ≥2 mg/dL at any time up to day 21 after trial enrollment.

Oxygenation and Compliance Subphenotypes

Characteristics of Included Patients in the Two Cohorts

Figure 7 and figure 8 present the patient flow diagram for both cohorts (ARDSNet and CARDS). In the ARDSNet cohort, out of the 2909 patients with ARDS, the majority of patients (67%) were liberated from mechanical ventilation ("extubated" group) by day 21, 19% of patients had died ("deceased" group) by day 21, 10% remained on mechanical ventilation but did not have data on compliance, mostly because they were ventilated on assisted or partially assisted modes ("ventilated in assisted modes" group) by day 21, and 4% of patients were on mechanical ventilation and had available data on oxygenation and compliance ("ventilated in control modes" group) on day 21. In the CARDS cohort, out of the 349 patients, 17% were in the "extubated" group, 41% in the "deceased", 15% in the "ventilated in assisted modes" and 28% were in the "ventilated in control modes" group.

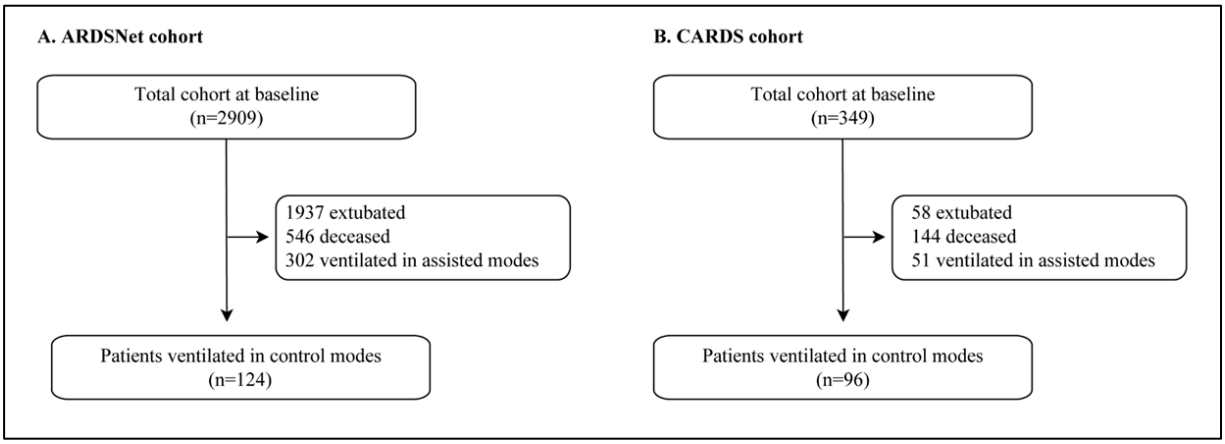


Figure 7. Patient flow diagram.

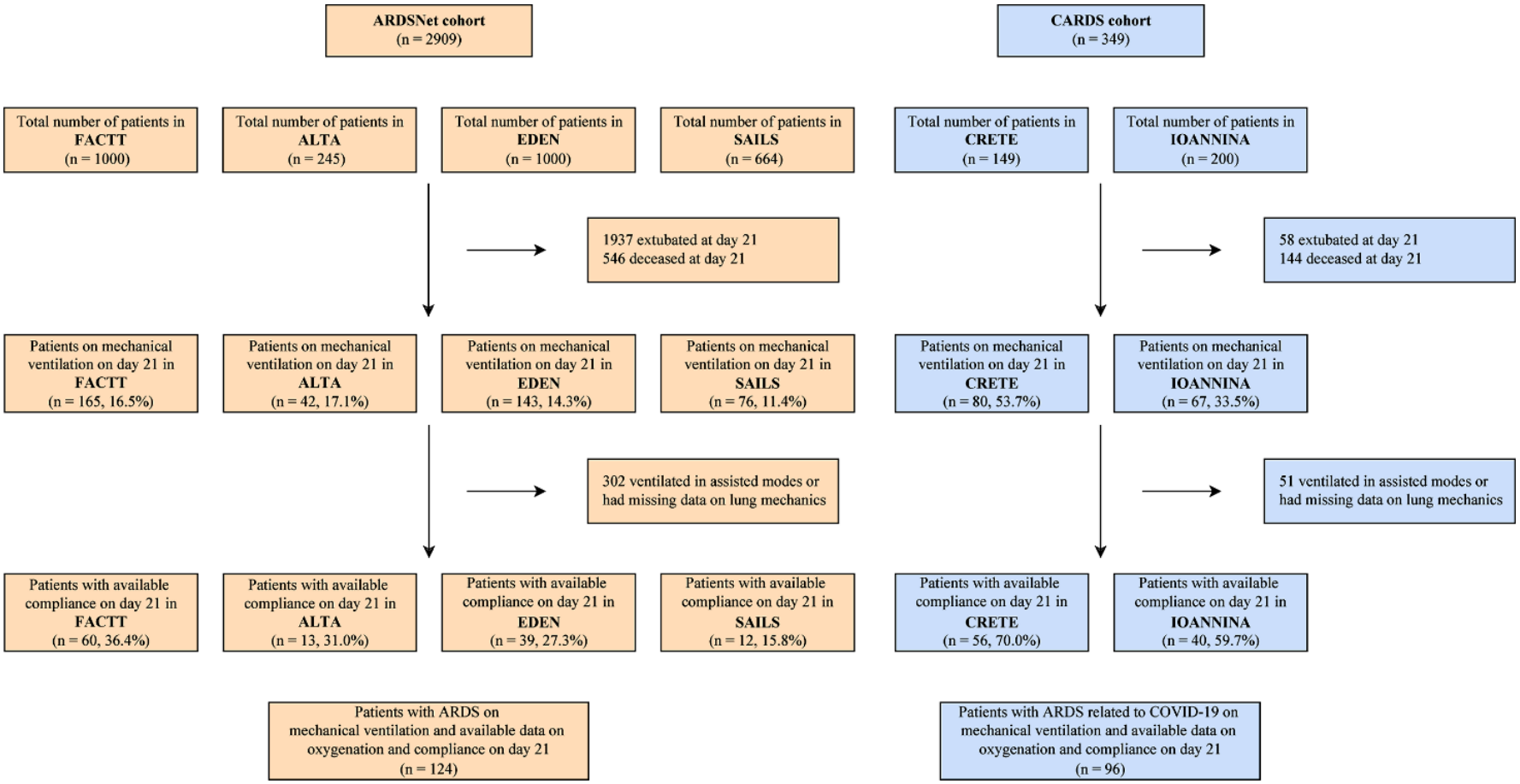


Figure 8. Detailed patient flow diagram for both study cohorts. The “extubated” group consisted of patients who were liberated from mechanical ventilation by day 21; the “deceased” group consisted of patients who died by day 21; and the “ventilated in assisted modes” group consisted of patients who remained on mechanical ventilation but did not have data on compliance, mostly because they were ventilated on assisted or partially assisted modes by day 21 (details on the modes of ventilation are not available for patients in the FACTT ARDSNet trial). The “ventilated in control modes” group consisted of patients who were on mechanical ventilation and had available data on oxygenation and compliance on day 21.

Table 5 presents the baseline characteristics of patients categorized based on their status on day 21 (i.e., ventilated in control or assisted modes, extubated, or deceased) in the ARDSNet and CARDS cohorts. The combination of mild-moderate hypoxemia and low compliance at baseline was less common among patients ventilated in control modes compared to other groups in the ARDSNet cohort but not in the CARDS cohort (Table 5).

Table 6 presents the comparison of baseline characteristics of patients included in the ARDSNet versus the CARDS cohort. Regardless of their status on day 21, patients in the ARDSNet cohort were younger, had higher total SOFA score, higher non-respiratory SOFA score and lower respiratory system compliance at baseline compared to patients in the CARDS cohort. The combination of mild-moderate hypoxemia but low compliance at baseline was more common in the ARDSNet cohort than in the CARDS cohort (Table 6).

Table 5. Baseline characteristics of patients according to status on day 21 of ARDSNet and CARDS cohort.

			ARDSNet cohort			CARDS cohort		
	Ventilated in Control modes[1] (n=124)	**Ventilated In Assisted modes[1] (n=302)**	**Extubated (n=1937)**	**Deceased (n=546)**	**Ventilated in Control modes[1] (n=96)**	**Ventilated in Assisted modes[1] (n=51)**	**Extubated (n=58)**	**Deceased (n=144)**
Age	52.5 (41.0-65.8)	54.0 (42.0-65.0)	50.0 (39.0-60.0)*	58.0 (45.0-71.0)*	71.0 (61.0-75.8)	69.0 (61.0-74.0)	63.5 (53.0-75.0)**	72.0 (64.0-77.0)
Female sex n (%)	50 (40.3)	138 (45.7)	975 (50.3)	246 (45.1)	32 (33.3)	20 (39.2)	23 (39.7)	45 (31.5)
Baseline SOFA score	7 (5-9)	7 (5-9)	6 (4-8)#	8 (6-10)#	4 (4-6)	4 (4-8)	4 (4-6)##	5 (4 -7)##
Non-respiratory SOFA	3 (1-6)	4 (2-6)$	3 (1-5)	5 (3-7)$	1 (0-3)	1 (0-4)	1 (0-2)	1 (0-3)
PaO_2:FiO_2 at baseline	103 (81-147)˚	146 (107-195)	50 (106-200)	127 (89-177)˚	120 (88-153)	131 (110-181)	118 (101-158)	101 (76-147)˚
Crs at baseline	27 (22-35)	28 (21-36)	30 (23-40)¨	28 (21-38)	36 (30-45)	40 (35-48)	38 (33-45)	32 (26-39)¨¨
MH-LoC at baseline[2]	13/108 (12.0)•	56/223 (25.1)	357/1527 (23.4)	76/405 (18.8)	2/94 (2.1)	0/43 (0.0)	2/55 (3.6)	6/128 (4.7)

Age, baseline SOFA, non-respiratory SOFA and lung mechanics at baseline are presented as median with interquartile range (IQR) and compared using the Kruskal-Wallis test. Sex is presented as percentage and compared using the chi-squared test. Pairwise comparisons were corrected using the Bonferroni method, and statistical significance was considered at an α level of 0.05. Abbreviations: ARDS, acute respiratory distress syndrome; CARDS, COVID-19-related acute respiratory distress syndrome; n, number; SOFA, sequential organ failure assessment; PaO_2:FiO_2, partial pressure of arterial oxygen to fraction of inspired oxygen ratio; Crs, compliance; MH-LoC, mild-moderate hypoxemia and low compliance. [1] The "ventilated in control modes" group consisted of patients who were on mechanical ventilation and had available data on oxygenation and compliance on day 21; the "ventilated in assisted modes" group consisted of patients who remained on mechanical ventilation but did not have data on compliance, mostly because they were ventilated on assisted or partially assisted modes by day 21; the "extubated" group consisted of patients who were liberated from mechanical ventilation by day 21; and the "deceased" group consisted of patients who died by day 21. [2] Due to missing data on respiratory system compliance at baseline, the total number of patients is less for this variable (shown as denominator). * Deceased vs. all other groups p<0.05, and extubated vs. ventilated in assisted modes p<0.001; # Deceased vs. all other groups, and extubated vs. ventilated in control, assisted modes p<0.05; $ Deceased vs. extubated, ventilated in control modes, and ventilated in assisted modes vs. extubated p<0.001; ˚Deceased vs. all other groups p<0.05, and ventilated in control modes vs. ventilated in assisted modes, extubated p<0.001; ¨ Extubated vs. deceased, ventilated in assisted modes p<0.05; • Ventilated in control modes vs. ventilated in assisted modes, extubated p<0.05.** Extubated vs. ventilated in control modes, deceased p<0.05; ## Deceased vs. extubated p<0.05; ˚˚ Deceased vs. ventilated in assisted modes p<0.01; ¨¨ Deceased vs. all other groups p<0.01.

Table 6. Baseline characteristics of patients according to status on day 21.

	Ventilated in Control modes[1]			Ventilated in Assisted modes[1]			Extubated			Deceased		
	ARDSNet (n=124)	**CARDS (n=96)**	**p value**	**ARDSNet (n=302)**	**CARDS (n=51)**	**p value**	**ARDSNet (n=1937)**	**CARDS (n=58)**	**p value**	**ARDSNet (n=546)**	**CARDS (n=144)**	**p value**
Age	52.5 (41.0-65.8)	71.0 (61.0-75.8)	< 0.001	54.0 (42.0-65.0)	69.0 (61.0-74.0)	< 0.001	50.0 (39.0-60.0)	63.5 (53.0-75.0)	< 0.001	58.0 (45.0-71.0)	72.0 (64.0-77.0)	< 0.001
Female sex % (n)	50 (40.3)	32 (33.3)	0.288	138 (45.7)	20 (39.2)	0.389	975 (50.3)	23 (39.7)	0.109	246 (45.1)	45 (31.5)	0.003
Total SOFA score	7 (5-9)	4 (4-6)	< 0.001	7 (5-9)	4 (4-8)	< 0.001	6 (4-8)	4 (4-6)	< 0.001	8 (6-10)	5 (4-7)	< 0.001
Non-respiratory SOFA score	3 (1-6)	1 (0-3)	< 0.001	4 (2-6)	1 (0-4)	< 0.001	3 (1-5)	1 (0-2)	< 0.001	5 (3-7)	1 (0-3)	< 0.001
PaO_2:FiO_2 at baseline	103 (81-147)	120 (88-153)	0.266	146 (107-195)	131 (110-181)	0.289	150 (106-200)	118 (101-158)	0.003	127 (89-177)	101 (76-147)	< 0.001
Crs at baseline[2]	27 (22-35)	36 (30-45)	< 0.001	28 (21-36)	40 (35-48)	< 0.001	30 (23-40)	38 (33-45)	< 0.001	28 (21-38)	32 (26-39)	0.001
MH-LoC at baseline[2]	13/108 (12.0)	2/94 (2.1)	0.007	56/223 (25.1)	0/43 (0.0)	< 0.001	357/1527 (23.4)	2/55 (3.6)	< 0.001	76/405 (18.8)	6/128 (4.7)	< 0.001

Abbreviations: ARDS, acute respiratory distress syndrome; CARDS, COVID-19-related ARDS; n, number; SOFA, sequential organ failure assessment; PaO2:FiO2, partial pressure of arterial oxygen to fraction of inspired oxygen ratio; Crs, compliance; MH-LoC, mild-moderate hypoxemia and low compliance.
[1] Study population consisted of patients who were ventilated in control modes and had available data on oxygenation and Crs on day 21. Most of the patients on mechanical ventilation without available data on mechanics were on assisted modes (details on the modes of ventilation are not available for patients in the FACTT ARDSNet trial). [2] Due to missing data on respiratory system compliance at baseline, the total number of patients is less for this variable (shown as denominator).

Trajectory of Oxygenation and Compliance from Baseline to Day 21

In the ARDSNet cohort, the combination of mild-moderate hypoxemia but low compliance increased among patients ventilated in control mode from a prevalence of 22.2% at baseline to 42.7% on day 21 ($p<0.001$). A sensitivity analysis including only patients who were randomized to the control group showed similar results, specifically the combination of mild-moderate hypoxemia but low compliance increased from a prevalence of 23.1% at baseline to 47.8% on day 21 ($p<0.001$). Likewise, in the CARDS cohort, the combination of mild-moderate hypoxemia but low compliance increased from a prevalence of 3.1% at baseline to 33.3% on day 21 ($p<0.001$). The prevalence of the combination of mild-moderate hypoxemia but low compliance on day 21 was similar in both the ARDSNet and CARDS cohorts ($p=0.155$).

After limiting our analysis to only those patients ventilated in control modes on day 21, the combination of mild-moderate hypoxemia but low compliance increased from a prevalence of 7.4% (12.0% and 2.1% in the ARDSNet and CARDS cohort, respectively) at baseline to 38.6% (42.7% and 33.3% in the ARDSNet and CARDS cohort, respectively) on day 21 ($p<0.001$ for all comparisons). Alluvial plots to depict the change in prevalence of the different combinations over time from baseline to day 21 are shown in Figure 9.

In the sensitivity analysis including only patients from the ARDSNet cohort with pneumonia as the primary risk factor of ARDS (Table 7), the combination of mild-moderate hypoxemia but low compliance increased from a prevalence of 5.4% at baseline to 34.6% on day 21 ($p<0.001$).

Among patients who had low compliance, in whom the underlying pathophysiology, edema or atelectasis causing the impairment in mechanics, would be expected to affect oxygenation, oxygenation appeared to improve over time (Figure 10A-B). This was also the case for patients who had high compliance (Figure 10C-D).

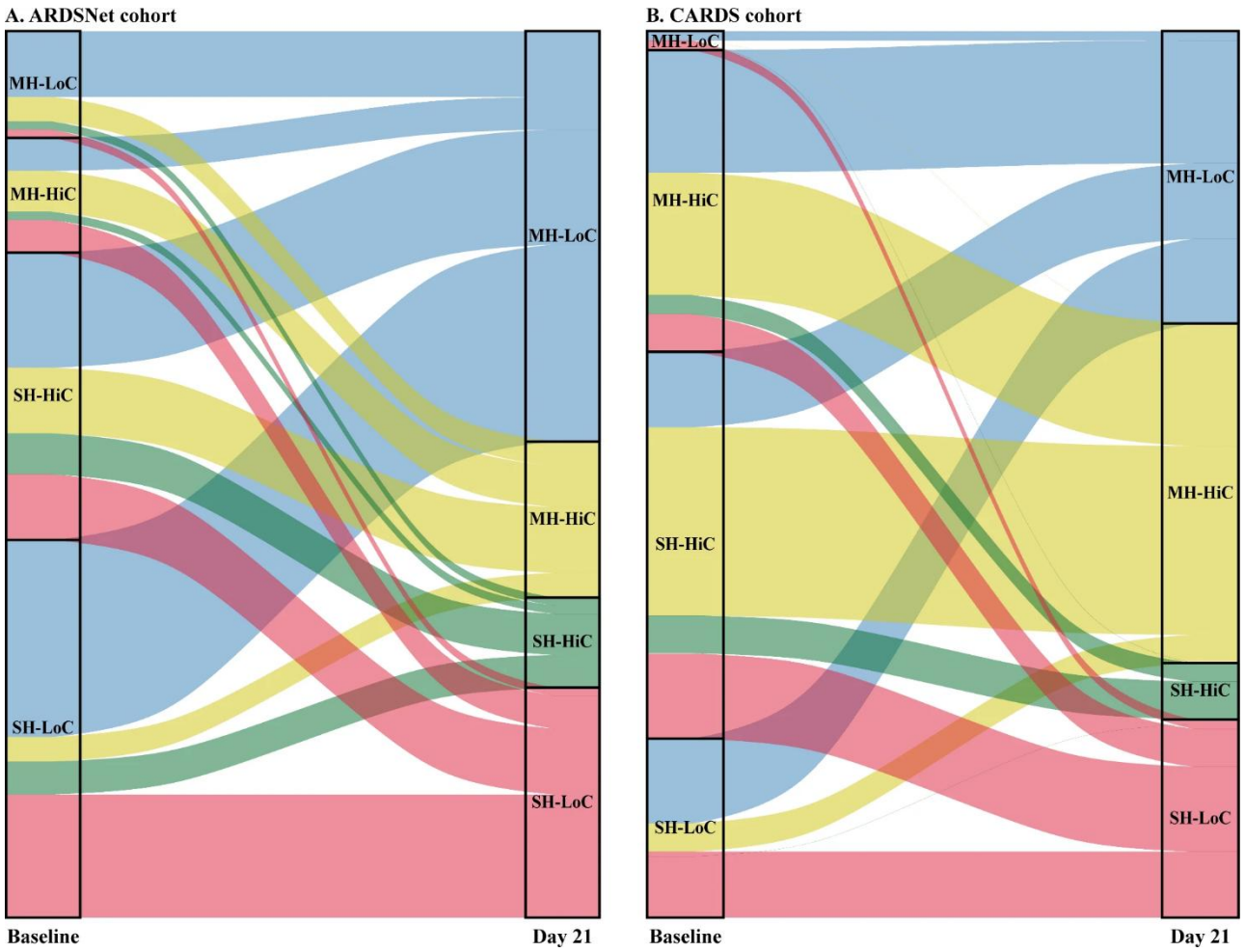


Figure 9. Alluvial plot of changes in prevalence of different combinations of oxygenation and compliance over time from baseline to day 21, among patients who remained on controlled ventilation and had available data on oxygenation and compliance, in (A) the ARDSNet cohort, and (B) the CARDS cohort. Each block represents a different combination, and the height of a block represents the number of patients in this combination. Combinations at baseline are illustrated with different colors. Each stream field between two blocks represents the change in the number of patients in the respective combinations from baseline to day 21, and the height of a stream field is proportionate to this number of patients. A total of 108 and 94 patients with available data on oxygenation and compliance on both baseline and day 21 are included in the alluvial plot of the ARDSNet and CARDS cohort, respectively. (MH-HiC: mild-moderate hypoxemia/high compliance; MH-LoC: mild-moderate hypoxemia/low compliance; SH-HiC: severe hypoxemia/high compliance; and SH-LoC: severe hypoxemia/low compliance).

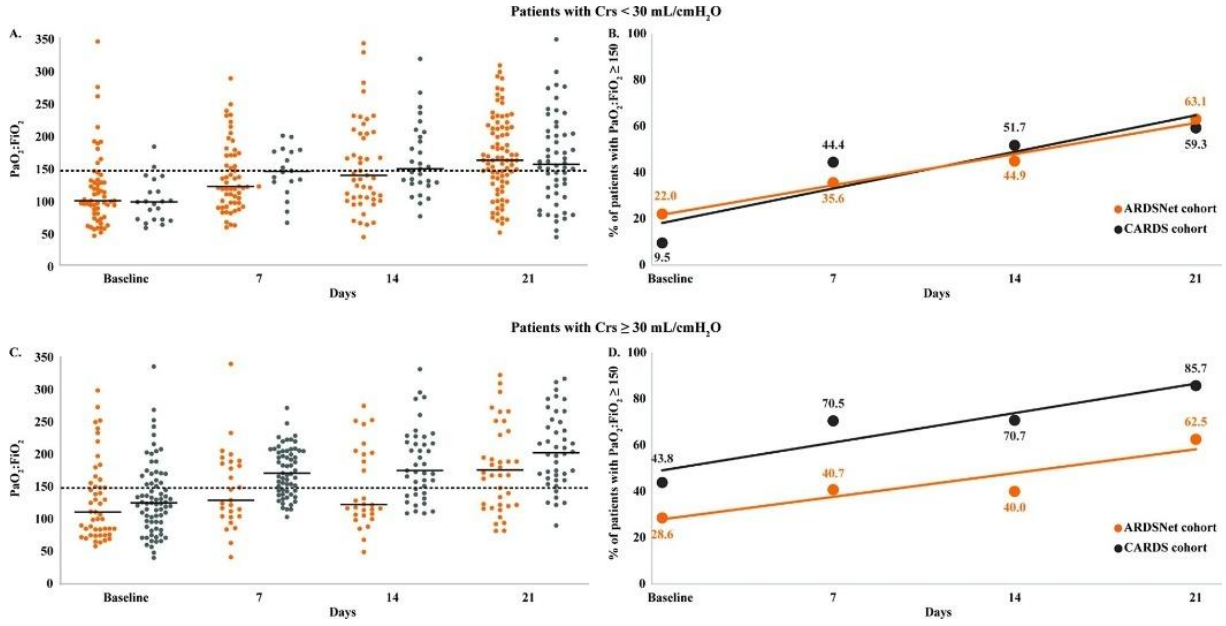


Figure 10. (A) Trajectory of oxygenation, as assessed by the partial pressure of arterial oxygen to fraction of inspired oxygen ratio (PaO2:FiO2), (line at median), and (B) percent of patients with mild-moderate hypoxemia, among patients with low compliance at baseline and on days 7, 14 and 21 in the two independent cohorts (ARDSNet and CARDS). (C) Trajectory of oxygenation, as assessed by the partial pressure of arterial oxygen to fraction of inspired oxygen ratio (PaO_2:FiO_2), and (D) percent of patients with mild-moderate hypoxemia, among patients with high compliance at baseline and on days 7, 14 and 21 in the two independent cohorts.

Table 7. Baseline characteristics and lung mechanics of patients with pneumonia as primary risk factors for ARDS.

Variable	ARDSNet cohort (n=66)	CARDS cohort (n=96)	p value
Age	51.5 (42.0-63.3)	71.0 (61.0-75.8)	< 0.001
Female sex % (n)	31 (47.0)	32 (33.3)	0.080
Baseline SOFA score	6 (5-8)	4.0 (4.0-6.0)	< 0.001
Baseline non-respiratory SOFA score	3 (1-5)	1.0 (0.0-3.0)	< 0.001
PaO_2:FiO_2	99 (76-130)	120 (88-153)	0.058
Crs	27 (21-35)	36 (30-45)	< 0.001
MH-LoC	6/55 (10.9)	2/94 (2.1)	0.052
60-day mortality	22 (33.3)	59 (61.5)	< 0.001

Abbreviations: ARDS, acute respiratory distress syndrome; CARDS, COVID-19-related ARDS; n, number; SOFA, sequential organ failure assessment; PaO_2:FiO_2, partial pressure of arterial oxygen to fraction of inspired oxygen ratio; Crs, compliance; MH-LoC, mild-moderate hypoxemia and low compliance.

Outcome

Table 8 presents data on outcomes (i.e., extubated or dead) on day 21 of patients categorized by their oxygenation-compliance combination at baseline in both cohorts.

Table 9 presents data on 60-day mortality of patients categorized by their oxygenation-compliance combination on day 21 in both cohorts. In the ARDSNet cohort, 60-day mortality was 28% in the mild-moderate hypoxemia/low compliance and 20% in the mild-moderate hypoxemia/high compliance combination, 67% in the severe hypoxemia/high compliance combination, and 32% in the severe hypoxemia/low compliance combination. In the CARDS cohort, 60-day mortality was 56% and 50% in the mild-moderate hypoxemia/low compliance and the mild-moderate hypoxemia/high compliance groups, and 82-83% in the severe hypoxemia with low and high compliance, respectively.

Table 8. Outcomes on day 21 of patients categorized by their oxygenation-compliance combination at baseline.

Variable	ARDSNet cohort (n=2909)						CARDS cohort (n=349)					
	MH-LoC (n = 502)	MH-HiC (n = 548)	SH-HiC (n = 561)	SH-LoC (n = 652)	Missing (n = 646)	p value	MH-LoC (n = 10)	MH-HiC (n = 96)	SH-HiC (n = 140)	SH-LoC (n = 74)	Missing (n = 29)	p value
Extubated	359 (71.5)	421 (76.8)	367 (65.4)	382 (58.6)	411 (63.6)	0.001	2 (20.0)	17 (17.7)	31 (22.1)	5 (6.8)	3 (10.3)	0.055
21-day mortality	76 (15.1)	69 (12.6)	110 (19.6)	153 (23.5)	141 (21.8)	0.001	6 (60.0)	32 (33.3)	46 (32.9)	44 (59.5)	16 (55.2)	< 0.001

Abbreviations: ARDS, acute respiratory distress syndrome; CARDS, COVID-19-related ARDS; MH-LoC, mild-moderate hypoxemia and low compliance; MH-HiC, mild-moderate hypoxemia and high compliance; SH-HiC, severe hypoxemia and high compliance; SH-LoC, severe hypoxemia and low compliance; n, number. Baseline was day 0 or, if missing, day 1.

Table 9. Data on 60-day mortality of patients categorized by their oxygenation-compliance combination on day 21.

Variable	ARDSNet cohort (n=124)					CARDS cohort (n=96)				
	MH-LoC (n = 53)	MH-HiC (n = 25)	SH-HiC (n = 15)	SH-LoC (n = 31)	p value	MH-LoC (n = 32)	MH-HiC (n = 36)	SH-HiC (n = 6)	SH-LoC (n = 22)	p value
60-day mortality	15 (28.3)	5 (20.0)	10 (66.7)*	10 (32.3)	0.017	18 (56.3)	18 (50.0)	5 (83.3)	18 (81.8)	0.056

Abbreviations: ARDS, acute respiratory distress syndrome; CARDS, COVID-19-related ARDS; MH-LoC, mild-moderate hypoxemia and low compliance; MH-HiC, mild-moderate hypoxemia and high compliance; SH-HiC, severe hypoxemia and high compliance; SH-LoC, severe hypoxemia and low compliance; n, number. Baseline was day 0 or, if missing, day 1. * SH-HiC vs MH-LoC, MH-HiC, $p<0.05$.

Mechanical Ventilation and AKI

Baseline Characteristics

Of 5367 patients with ARDS initially enrolled in the seven randomized controlled trials, 2960 patients were included in the main analysis (24-27, 29, 30, 32). Reasons for exclusion are depicted in Figure 11. Of the 2960 included patients, late AKI developed in 1000 (33.8%) patients; specifically, 62.4% developed AKI stage I, 21.8% stage II and 15.8% stage III.

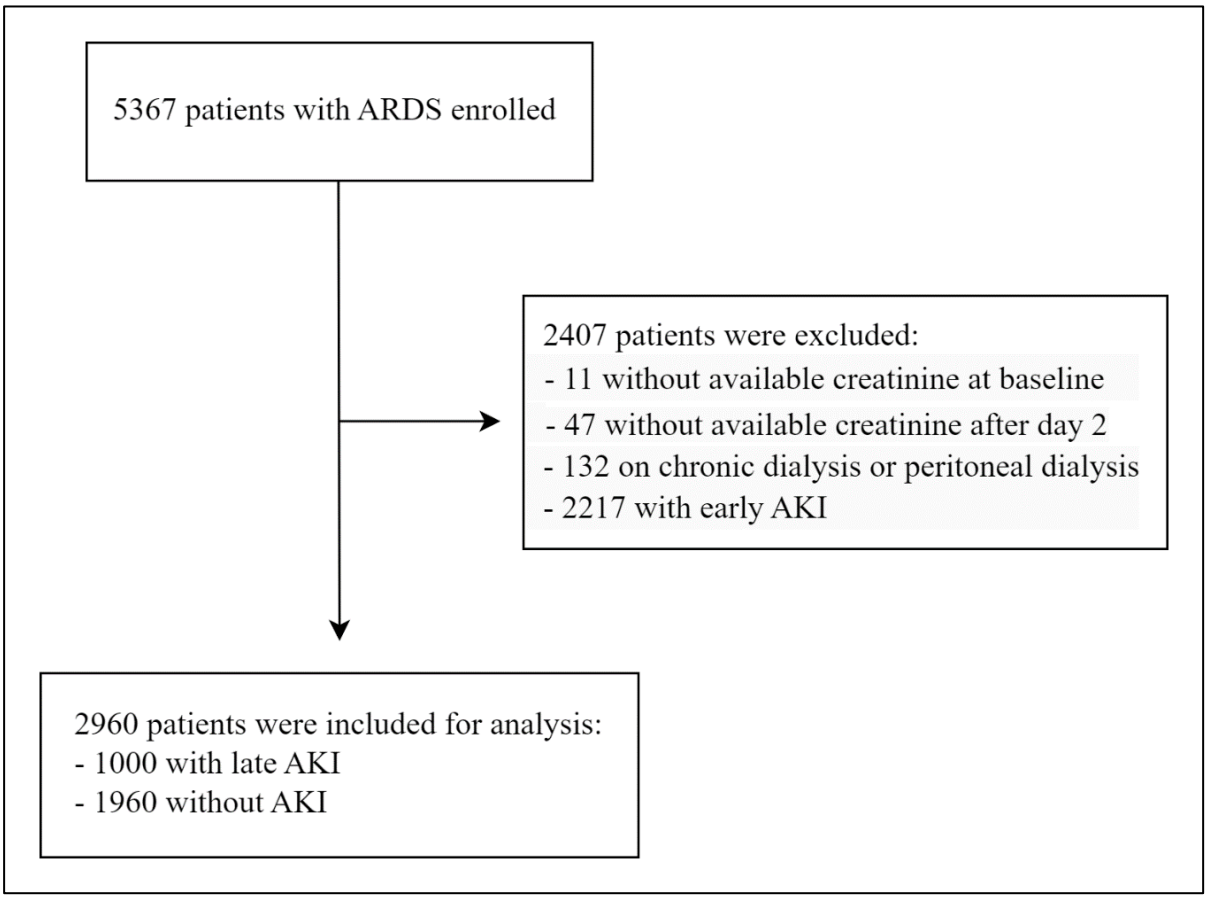


Figure 11. Study flow diagram (AKI, acute kidney injury; ARDS, acute respiratory distress syndrome).

Table 10 presents the baseline characteristics and table 11 the outcomes of patients included in the "late AKI" versus "no AKI" groups. Compared groups differed in terms of age, presence of diabetes mellitus, organ failures (namely, cardiovascular, coagulation, and hepatic), PaO_2:FiO_2, respiratory rate, tidal volume, respiratory system compliance and PEEP,

but not in terms of sex. Driving pressure at baseline was not significantly different between the two groups. Crude 90-day mortality was significantly higher in the “late AKI” compared with the “no AKI” group (39% versus 17%; p<0.001). Consistently, organ failure-free days, ventilator-free days and ICU-free days were significantly lower in the “late AKI” compared with the “no AKI” group (Table 10, Table 11).

Table 10. Baseline characteristics of patients included in the compared groups.

Variable	All patients (n=2960)	No AKI (n=1960)	Late AKI (n=1000)	p value
Age, years	51 (39-63)	50 (39-62)	52 (40-65)	0.001
Female sex, n (%)	1475 (50)	978 (50)	497 (50)	0.919
BMI, kg/m2	27 (23-33)	27 (23-32)	28 (23-34)	0.010
Race, n (%)				< 0.001
White	2118 (72)	1450 (74)	668 (67)	
Black	425 (14)	251 (13)	174 (17)	
Hispanic	164(6)	87 (4)	77 (8)	
Other	212 (7)	141 (7)	71 (7)	
Comorbidities, n (%)				
Hypertension	743 (25)	446 (23)	297 (30)	0.016
Diabetes mellitus	470 (16)	290 (15)	180 (18)	0.030
Cardiovascular disease	217 (7)	138 (7)	79 (8)	0.951
Chronic pulmonary disease	266 (9)	164 (8)	102 (10)	0.524
Malignancies	168 (6)	89 (5)	79 (8)	< 0.001
Risk factors of ARDS, n (%)				
Pneumonia	1609 (54)	1008 (51)	601 (60)	<0.001
Sepsis	459 (16)	328 (17)	131 (13)	0.009
Aspiration	400 (14)	266 (14)	134 (13)	0.893
Trauma	225 (8)	175 (9)	50 (5)	< 0.001
Multiple transfusions	53 (2)	36 (2)	17 (2)	0.788
Organ failure at baseline, n (%)				
Cardiovascular	1729 (58)	1094 (56)	635 (64)	< 0.001

Coagulation	441 (15)	265 (14)	176 (18)	0.003
Hepatic	349 (12)	200 (10)	149 (15)	< 0.001
Creatinine at baseline, mg/dL	0.8 (0.6-1.0)	0.8 (0.6-1.0)	0.8 (0.6-1.1)	< 0.001
Fluid balance on day 1, mL	1350 (90-3063)	1261 (16-3025)	1496 (233-3160)	0.047
Cumulative fluid balance of the first 3 days, mL	2938 (-66-6511)	2618 (-470-5984)	3792 (590-7881)	< 0.001
Respiratory variables at baseline				
PaO_2:FiO_2, mm Hg	134 (100-180)	138 (105-186)	124 (91-173)	< 0.001
RR, breaths/min	24 (18-29)	23 (18-28)	24 (20-30)	< 0.001
VT/PBW, mL/Kg	6.8 (6.0-8.4)	6.9 (6.0-8.5)	6.6 (6.0-8.1)	0.017
Arterial pH	7.39 (7.34-7.44)	7.40 (7.35-7.44)	7.37 (7.32-7.43)	< 0.001
$PaCO_2$, mm Hg	40 (35-45)	39 (34-45)	40 (35-46)	0.257
Plateau pressure, cm H_2O	25 (21-30)	25 (21-30)	26 (22-31)	< 0.001
Crs, mL/cm H_2O	30 (23-40)	31 (24-41)	28 (22-38)	< 0.001
PEEP, cm H_2O	10 (5-12)	10 (5-12)	10 (8-12)	< 0.001
Pdriving, cm H_2O	16 (12-20)	15 (12-20)	16 (12-21)	0.056

Abbreviations: AKI, acute kidney injury; n, number; BMI, body mass index; ARDS, acute respiratory distress syndrome; PaO2:FiO2, partial pressure of arterial oxygen to fraction of inspired oxygen ratio; RR, respiratory rate ; VT, tidal volume; PBW, predicted body weight; Crs, respiratory system compliance; PEEP, positive end-expiratory pressure; Pdriving, driving pressure; ICU, intensive care unit. Data are expressed as median (IQR), unless otherwise indicated.

Table 11. Outcomes of patients included in the compared groups.

Variable	**All patients (n=2960)**	**No AKI (n=1960)**	**Late AKI (n=1000)**	**p value**
90-day mortality, n (%)	728 (25)	338 (17)	390 (39)	<0.001
Organ failure-free days	22 (6-26)	23 (14-27)	12 (0-24)	<0.001
Ventilator-free days	19 (0-24)	21 (4-25)	7 (0-22)	<0.001
ICU-free days	17 (0-23)	19 (7-23)	6 (0-20)	<0.001

Abbreviations: AKI, acute kidney injury; ICU, intensive care unit.

Association Between Baseline Driving Pressure and Development of Late AKI

Table 12 depicts a multivariable logistic regression analysis to isolate the contribution of age, sex, body mass index, diabetes mellitus, organ failures (namely, cardiovascular, coagulation, and hepatic) at baseline, fluid balance, baseline PaO_2:FiO_2 ratio, respiratory rate, tidal volume, respiratory system compliance, PEEP and driving pressure (independent variables) to the development of late AKI (dependent variable). In our multivariable regression model, we did not include plateau pressure due to collinearity with driving pressure. Instead, we included both PEEP and driving pressure because we found no collinearity between them (VIF= 1.049).

Table 12. Multivariable logistic regression analysis to explore the contribution of baseline driving pressure (independent variable) to the development of late AKI (dependent variable).

Variable	Univariable analysis			Multivariable analysis*		
	OR	95% CI	p value	OR	95% CI	p value
Baseline Pdriving (increments of 1 SD)	1.12	1.024-1.23	0.014	1.35	1.15-1.58	< 0.001

Abbreviations: AKI, acute kidney injury; OR, odds ratio; CI, confidence interval; SD, standard deviation (1 SD of driving pressure = 6.6 cm H_2O), Pdriving, driving pressure. *Multivariable model was adjusted for: age, sex, body mass index, diabetes mellitus, circulatory failure, coagulation failure, hepatic failure, fluid balance, partial pressure of arterial oxygen to fraction of inspired oxygen ratio (PaO_2/FiO_2) ratio, respiratory ratio, tidal volume, respiratory system compliance and PEEP.

After controlling for confounders, driving pressure at baseline was independently associated with development of late AKI [odds ratio (OR) 1.046, 95% confidence intervals (CI): 1.021-1.072; p<0.001]. The predicted probabilities of the model were then plotted against driving pressure quintiles. The results indicate that the probability of late AKI increases with higher driving pressure quintiles (p for trend over quintiles=0.011) (Figure 12). We also assessed the linearity of the relationship between baseline driving pressure and late AKI using cubic splines. A likelihood ratio test comparing a linear model to a spline model (4 degrees of freedom) - created by employing a multivariate logistic regression with cubic splines - showed

no significant improvement in fit (p=0.312). This suggests that the association between baseline driving pressure and late AKI is adequately described by a linear term.

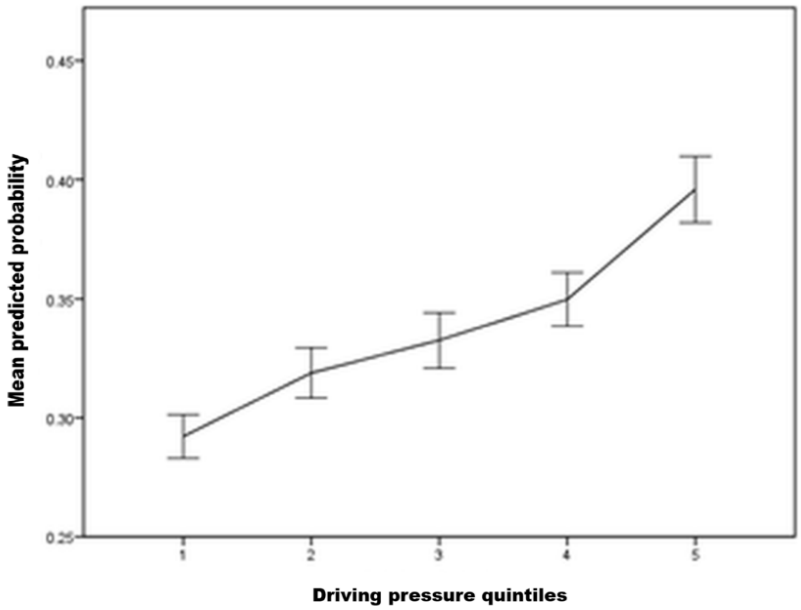


Figure 12. Plot of predicted probabilities for late AKI against driving pressure quintiles. Each bar represents mean value with 95% CI (abbreviations: AKI, acute kidney injury; CI, confidence interval).

Reclassification Tests

Table 13 shows the performance of driving pressure and its components for late AKI prediction. Driving pressure and Ppl, when added to the reference model, resulted in significantly higher ΔAUCs (DeLong p=0.026 and p=0.007, respectively), as well as in better reclassification of patients (Total NRI=0.07, P=0.023, and 0.16, p<0.001), respectively). The model including driving pressure and that including Ppl did not differ significantly (DeLong p=0.09). Figure 13 depicts the ROC curves, as well as the AUCs of the reference and the other three models.

Sensitivity Analyses

We repeated our main analysis by not excluding patients with early AKI. After adjusting for age, sex, body mass index, diabetes mellitus, organ failures (namely, cardiovascular,

coagulation, and hepatic) at baseline, fluid balance, baseline PaO_2:FiO_2 ratio, respiratory rate, tidal volume, respiratory system compliance and PEEP, baseline driving pressure remained independently associated with development of AKI (OR 1.038, 95% CI: 1.020-1.056; p<0.001) (Table 14).

Table 13. Performance of DP and its components for late AKI prediction.

Reference model	Added baseline variable	AUC of the new model	ΔAUC	DeLong test p value*	Total NRI (95% CI)	p value
Age + sex + BMI + DM + circulatory failure + coagulation failure + hepatic failure + FB + PaO_2/FiO_2 ratio + RR + VT + Crs, AUC (95% CI): 0.600 (0.570-0.631)	DP	0.615	0.015	0.026a	0.07 (0.007-0.12)	0.02
	PEEP	0.612	0.012	0.12	0.04 (-0.01-0.10)	0.16
	Ppl	0.625	0.025	0.007	0.16 (0.08-0.22)	0.001

*New model vs reference model. The model including DP and that including Ppl did not differ significantly (DeLong p=0.09). Abbreviations: DP, driving pressure; AUC, area under curve; CI, confidence interval; Δ, difference; NRI, net reclassification improvement; BMI, body mass index; DM, diabetes mellitus; Crs, respiratory system compliance; RR, respiratory rate; VT, tidal volume; PEEP, positive end-expiratory pressure; Ppl, plateau pressure.

Table 14. Multivariable logistic regression analysis to explore the contribution of baseline driving pressure (independent variable) to the development of AKI (dependent variable) in a sensitivity analysis which does not exclude patients with early AKI.

Variable	Univariable analyses			Multivariable analysis		
	OR	95% CI	p value	OR	95% CI	p value
Age (increments of 1 year)	1.012	1.009-1.016	< 0.001	1.013	1.007-1.018	< 0.001
Female sex	0.768	0.686-0.859	< 0.001	0.718	0.604-0.853	< 0.001
BMI (increments of 1 kg/cm^2)	1.022	1.014-1.029	< 0.001	1.013	1.003-1.024	0.015

Diabetes mellitus	1.940	1.673-2.250	< 0.001	1.964	1.579-2.443	< 0.001
Cardiovascular failure	1.760	1.567-1.977	< 0.001	1.466	1.220-1.761	< 0.001
Coagulation failure	1.978	1.698-2.305	< 0.001	2.114	1.666-2.681	< 0.001
Hepatic failure	2.076	1.750-2.462	< 0.001	1.781	1.376-2.305	< 0.001
Fluid balance on day 1 (increment of 100 ml)	1.009	1.007-1.011	< 0.001	1.007	1.005-1.010	< 0.001
Baseline PaO_2:FiO_2 (increments of 10 mmHg)	0.979	0.970-0.987	< 0.001	1.005	0.992-1.020	0.443
Baseline RR (increments of 1 breath/min)	1.033	1.025-1.040	< 0.001	1.028	1.015-1.041	< 0.001
Baseline VT/PBW (increments of 1 ml/Kg)	0.980	0.953-1.008	0.161	0.997	0.979-1.015	0.733
Baseline Crs (increments of 1 ml/cm H_2O)	0.998	0.995-1.001	0.159	1.001	0.997-1.005	0.715
Baseline PEEP (increments of 1 cm H_2O)	1.050	1.036-1.065	< 0.001	1.056	1.029-1.083	< 0.001
Baseline Pdriving (increments of 1 cm H_2O)	1.010	0.999-1.020	0.064	1.038	1.020-1.056	< 0.001

Abbreviations: AKI, acute kidney injury; OR, odds ratio; CI, confidence interval; BMI, body mass index; PaO_2:FiO_2, partial pressure of arterial oxygen to fraction of inspired oxygen ratio; RR, respiratory rate; VT, tidal volume; PBW, predicted body weight; Crs, respiratory system compliance; PEEP, positive end-expiratory pressure; Pdriving, driving pressure. The present sensitivity analysis included a total of 5177 patients; namely, 3217 patients with AKI (both patients with early AKI and patients with late AKI) and 1960 patients with no AKI.

Also, we repeated our main analysis by including patients who developed AKI later than seven days following onset of ARDS; i.e., the “late AKI” group included patients who developed AKI from day 3 to day 28 following onset of ARDS. After adjusting for age, sex, body mass index, diabetes mellitus, organ failures (namely, cardiovascular, coagulation, and hepatic) at baseline, fluid balance, baseline PaO_2:FiO_2 ratio, respiratory rate, tidal volume, respiratory system compliance and PEEP, baseline driving pressure remained independently associated with development of late AKI (OR 1.060, 95% CI: 1.036-1.084; p<0.001) (Table 15).

To explore how the survival status affected the relationship between late AKI and driving pressure, given the close association between AKI and mortality, we performed two

separate multivariate logistic regressions in survivors and non-survivors, respectively. Driving pressure was a predictor of late AKI in survivors only (Table 16).

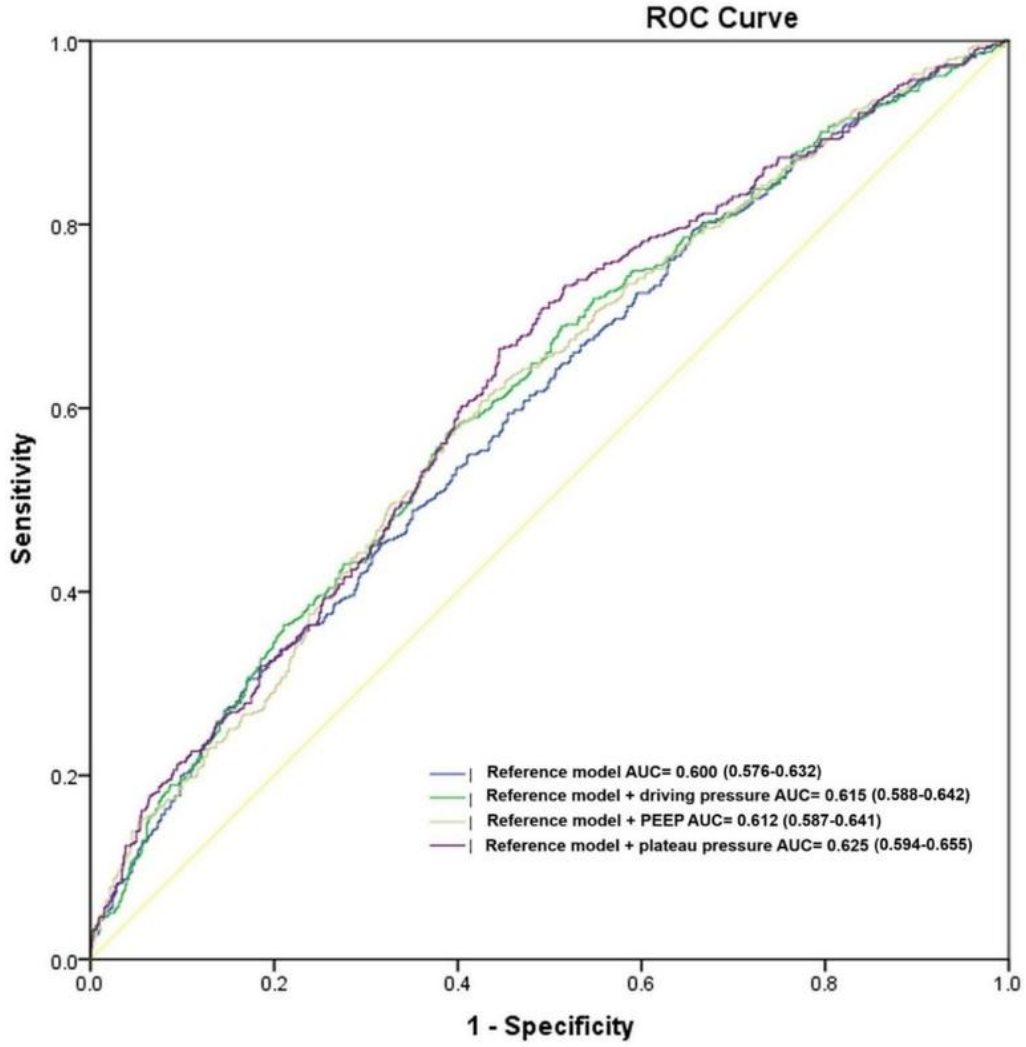


Figure 13. Receiver operating characteristic (ROC) curves and the area under the curves (AUCs) of the four models for late acute kidney injury prediction. The reference model included: age, sex, body mass index, diabetes mellitus, circulatory failure, coagulation failure, hepatic failure, fluid balance, PaO2/FiO2 ratio, respiratory rate, tidal volume, and respiratory system compliance (PEEP, positive end-expiratory pressure).

Table 15. Multivariable logistic regression analysis to explore the contribution of baseline driving pressure (independent variable) to the development of late AKI (dependent variable) in a sensitivity analysis which included patients who developed AKI later than seven days following onset of ARDS.

Variable	Univariable analyses			Multivariable analysis		
	OR	95% CI	p value	OR	95% CI	p value
Age (increments of 1 year)	1.012	1.008-1.017	< 0.001	1.018	1.011-1.025	< 0.001
Female sex	0.859	0.744-0.992	0.039	0.795	0.638-0.991	0.041
BMI (increments of 1 kg/cm^2)	1.007	0.997-1.016	0.163	1.004	0.990-1.018	0.558
Diabetes mellitus	1.199	0.984-1.462	0.071	1.140	0.858-1.516	0.366
Cardiovascular failure	1.340	1.157-1.552	< 0.001	1.273	1.014-1.598	0.038
Coagulation failure	1.233	1.007-1.510	0.043	1.171	0.855-1.603	0.325
Hepatic failure	1.410	1.126-1.766	0.003	1.654	1.179-2.320	0.004
Fluid balance on day 1 (increment of 100 ml)	1.004	1.001-1.006	0.010	1.001	0.998-1.005	0.548
Baseline PaO_2:FiO_2 (increments of 10 mmHg)	0.980	0.969-0.991	< 0.001	1.005	0.988-1.023	0.554
Baseline RR (increments of 1 breath/min)	1.009	1.0-1.019	0.054	1.002	0.986-1.018	0.826
Baseline VT/PBW (increments of 1 ml/Kg)	0.996	0.979-1.014	0.687	0.984	0.940-1.032	0.511
Baseline Crs (increments of 1 ml/cm H_2O)	0.992	0.987-0.997	< 0.001	0.999	0.994-1.004	0.672
Baseline PEEP (increments of 1 cm H_2O O)	1.034	1.015-1.052	< 0.001	1.048	1.015-1.081	0.004
Baseline Pdriving (increments of 1 ml/cm H_2O)	1.033	1.020-1.047	< 0.001	1.060	1.036-1.084	< 0.001

Abbreviations: AKI, acute kidney injury; OR, odds ratio; CI, confidence interval; BMI, body mass index; PaO2:FiO2, partial pressure of arterial oxygen to fraction of inspired oxygen ratio; RR, respiratory rate; VT, tidal volume; PBW, predicted body weight; Crs, respiratory system compliance ; PEEP, positive end-expiratory pressure; Pdriving, driving pressure. The present sensitivity analysis included patients who developed AKI later than seven days following onset of ARDS; i.e., the "late AKI" group included 3217 patients who developed AKI from day 3 to day 28 following onset of ARDS. The "no AKI group" included 1960 patients.

Table 16. Adjusted logistic regressions for late AKI prediction in survivors and non-survivors.

	B	SE	Wald	p value	OR	95% CI
*Driving pressure (non-survivors), SD	0.153	0.138	1.229	0.268	1.166	0.889-1.529
*Driving pressure (survivors), SD	0.269	0.110	5.999	0.014	1.309	1.055-1.624

Abbreviations: AKI, acute kidney injury; OR, odds ratio; CI, confidence interval; SD, standard deviation.*Both analyses were adjusted for: age, sex, body mass index, diabetes mellitus, organ failures (namely, cardiovascular, coagulation, and hepatic) at baseline, fluid balance, baseline PaO2:FiO2 ratio, respiratory rate, tidal volume, respiratory system compliance and PEEP.

We also conducted a sensitivity analysis with baseline creatinine back calculated from the Modification of Diet in Renal Disease (MDRD) equation, assuming an estimated glomerular filtration rate equal to 75 mL/Kg/1.73m^2, as suggested by KDIGO guidelines(61).The results were similar to those of the main analysis. In another sensitivity analysis, a declining course in the driving pressure during the first week of their ICU stay was not associated with less risk of late AKI. We further explored the association of cumulative fluid balance with driving pressure change in late AKI and no AKI patients (Table 17, Table 18, Figure 14). Lastly, we performed sensitivity analyses, which showed that driving pressure was independently associated with both persistent and severe late AKI.

Table 17. Differences in cumulative fluid balance and driving pressure between patients with and without late AKI.

	No AKI	Late AKI
dFB, mL	2475 (-1366 - 6567)	3340 (588 - 6828)*
dDP, cm H_2O	-2 (-6 - 3)	-2 (-6 - 3)
*P<0.001, Mann-Whitney test.		

Abbreviations: AKI, acute kidney injury; dDP, difference in driving pressure; dFB, difference in cumulative fluid balance.

Table 18. Linear regressions, with dDP as dependent and dFB as independent variable.

	B	SE	Beta	T	p value	95% CI	
dFB (late AKI)	0.000077	0.000059	0.069	1.308	0.192	-.000039	0.000194
dFB (no AKI)	0.000173	0.000043	0.170	3.980	0.001	0.000087	0.000258

Abbreviations: AKI, acute kidney injury; CI, confidence interval; dDP, difference in driving pressure; dFB, difference in cumulative fluid balance.

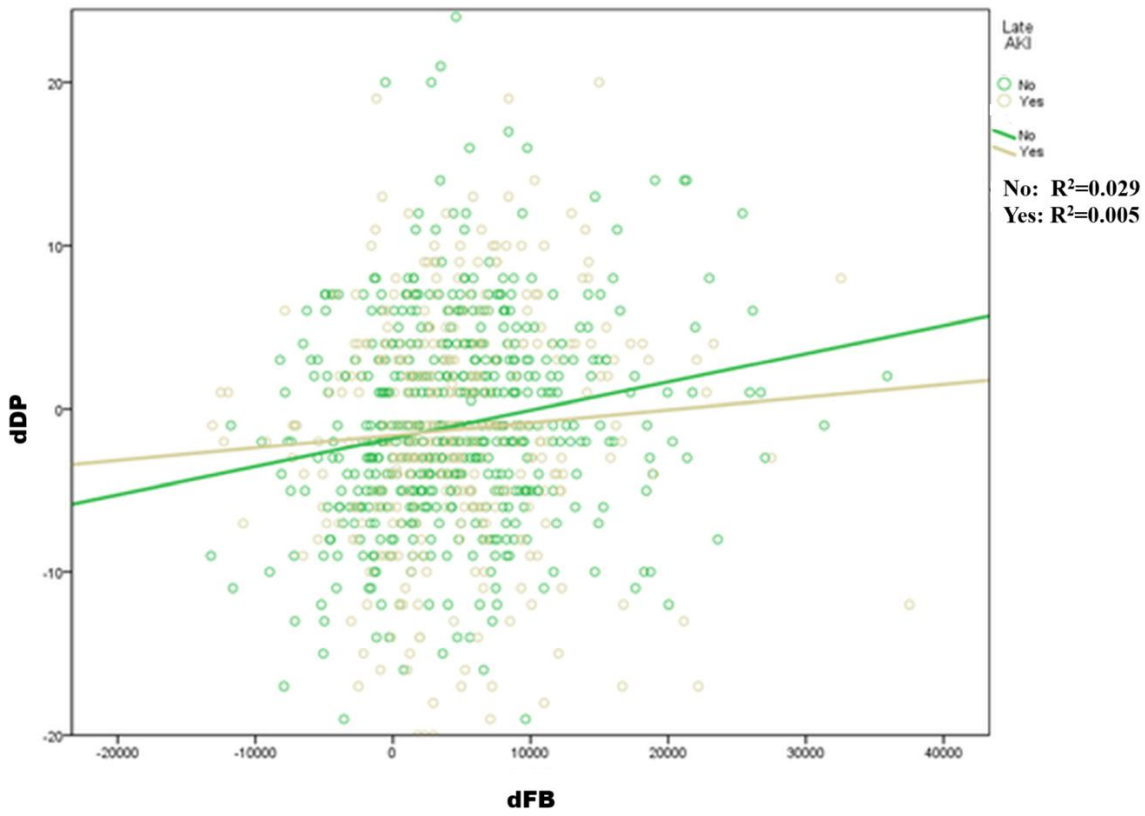


Figure 14. Dot plot between dDP and DFB with regression lines fitted for both groups, late AKI and no AKI (Abbreviations: AKI, acute kidney injury; dDP, difference in driving pressure; dFB, difference in cumulative fluid balance).

Association Between Mean Driving Pressure and Development of Late AKI

In order to ascertain whether the continuing exposure of patients with ARDS to high driving pressure during the first days following onset of ARDS was associated with

development of late AKI, we performed another multivariable analysis, in which baseline driving pressure was replaced by mean driving pressure (i.e., the mean of daily values of driving pressure from onset of ARDS up to day 6 or day of development of AKI, whatever came first). Consistently, mean driving pressure was independently associated with development of late AKI (OR 1.054, 95% CI: 1.030-1.078; p<0.001) (Table 19).

Table 19. Multivariable logistic regression analysis to explore the contribution of mean driving pressure (independent variable) to the development of late AKI (dependent variable).

Variable	Univariable analyses			Multivariable analysis		
	OR	95% CI	p value	OR	95% CI	p value
Age (increments of 1 year)	1.008	1.003-1.013	< 0.001	1.012	1.005-1.018	< 0.001
Female sex	0.992	0.852-1.155	0.919	0.927	0.757-1.135	0.462
BMI (increments of 1 kg/cm^2)	1.013	1.003-1.023	0.010	1.001	0.988-1.013	0.937
Diabetes mellitus	1.254	1.022-1.538	0.030	1.322	1.018-1.717	0.036
Cardiovascular failure	1.377	1.178-1.611	< 0.001	1.181	0.959-1.455	0.118
Coagulation failure	1.366	1.110-1.682	0.003	1.311	0.997-1.723	0.053
Hepatic failure	1.541	1.227-1.934	< 0.001	1.625	1.204-2.193	0.001
Fluid balance on day 1 (increment of 100 mL)	1.003	1.0-1.006	0.041	1.002	0.998-1.005	0.358
Baseline PaO_2:FiO_2 (increments of 10 mm Hg)	0.965	0.953-0.977	<0.001	1.024	1.007-1.042	0.005
Mean RR (increments of 1 breath/min)	1.039	1.026-1.052	< 0.001	1.011	0.993-1.028	0.235
Mean VT/PBW (increments of 1 ml/Kg)	0.964	0.922-1.009	0.119	0.982	0.927-1.039	0.529
Mean Crs (increments of 1 ml/cm H_2O)	0.994	0.989-0.999	0.013	1.0	0.994-1.007	0.878
Mean PEEP (increments of 1 cm H_2O)	1.174	1.148-1.202	< 0.001	1.210	1.170-1.252	< 0.001
Mean Pdriving (increments of 1 cm H_2O)	1.025	1.011-1.040	< 0.001	1.054	1.030-1.078	< 0.001

Abbreviations: AKI, acute kidney injury; OR, odds ratio; CI, confidence interval; BMI, body mass index; PaO2:FiO2, partial pressure of arterial oxygen to fraction of inspired oxygen ratio; RR, respiratory rate; VT, tidal volume; PBW, predicted body weight; Crs, respiratory system compliance; PEEP, positive end-expiratory pressure; Pdriving, driving pressure.

Driving pressure during the first six days following onset of ARDS in both compared groups was significantly higher in the “late AKI” than the “no AKI” group across time (between-

groups repeated measures ANOVA p=0.014) (Figure 15). The association between driving pressure and development of late AKI was consistent across time, i.e., there was no interaction between compared groups and time (p=0.283).

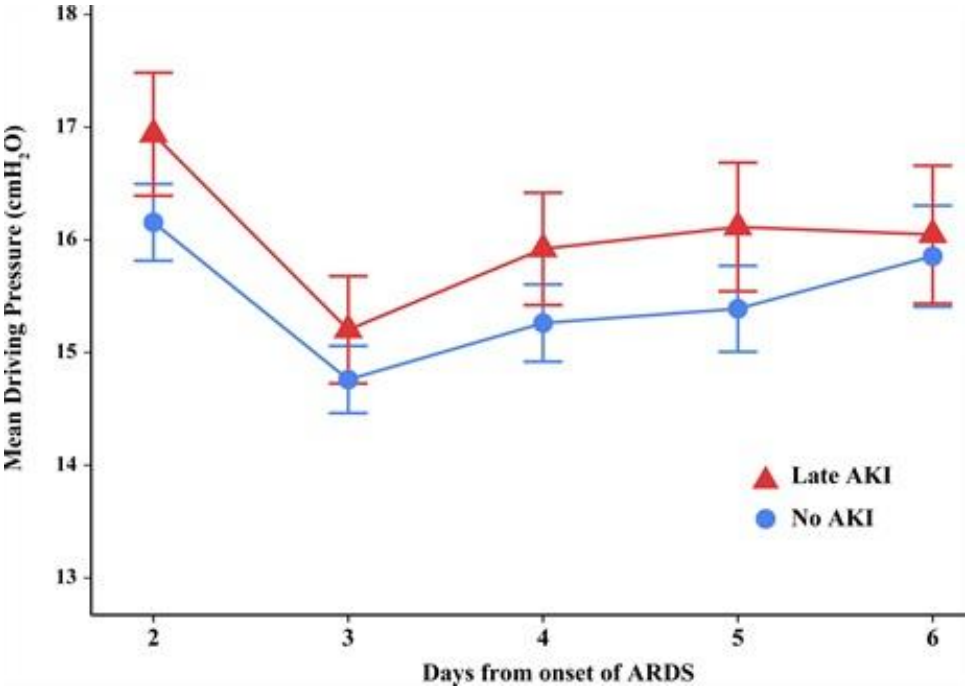


Figure 15. Trajectory of driving pressure during the first 6 days following onset of acute respiratory distress syndrome (ARDS) in both compared groups. Driving pressure was significantly higher in the "late acute kidney injury (AKI)" than the "no AKI" group across time (between-groups repeated measures analysis of variance p=0.014). The association between driving pressure and development of late AKI was consistent across time; that is, there was no interaction between compared groups and time (p = 0.283). The diagram represents mean ± sem of driving pressure values for each group of patients at each time point.

Given that a threshold of driving pressure equal to 15 cm H_2O has been associated with injurious mechanical ventilation (3), we used this threshold to explore the association between driving pressure and development of late AKI. As shown in Figure 16, among patients with a mean driving pressure lower than 15 cm H_2O, mean driving pressure was not associated with development of late AKI in both unadjusted and adjusted analyses [i.e., after again taking into consideration age, sex, body mass index, diabetes mellitus, organ failures (namely, cardiovascular, coagulation, and hepatic) at baseline, fluid balance, baseline PaO_2:FiO_2 ratio, respiratory rate, tidal volume, respiratory system compliance and PEEP]. On the contrary,

among patients with a mean driving pressure of 15 cm H_2O or greater, mean driving pressure was independently associated with the development of late AKI (for adjusted analysis OR 1.049, 95% CI:1.022-1.078; p<0.001).

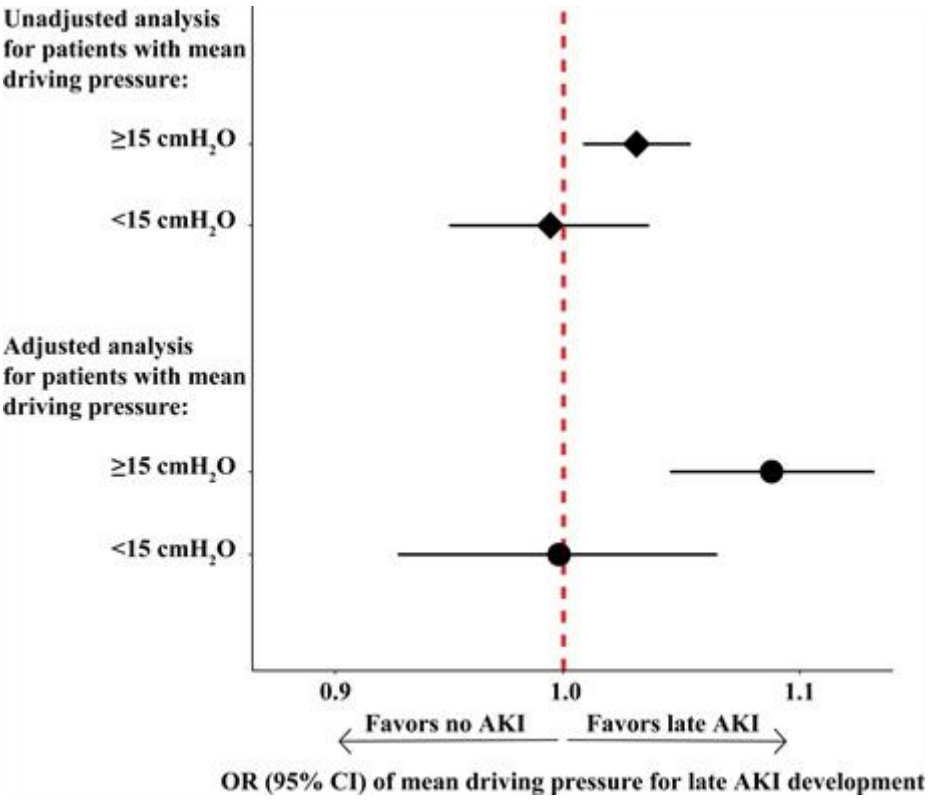


Figure 16. Forest plot exploring the association between driving pressure and development of late acute kidney injury (AKI) by taking into consideration a threshold of 15 cm H2O. Among patients with a mean driving pressure of 15 cm H2O or greater, mean driving pressure was independently associated with the development of late AKI (for adjusted analysis: odds ratio [OR], 1.049; 95% CI, 1.022–1.078; p < 0.001).

B4. Discussion

Our analysis from individual patient data involving more than 4200 patients in total showed that the average prevalence of PMV in ARDS patients has been 15.3% and it has been declining over the last two decades. While the prevalence of PMV appears to be declining, the results of our study showed that mortality has remained unchanged over time and high as 36.8%. Age, malignancy, pneumonia as the cause of ARDS, coagulation dysfunction and hepatic dysfunction during the first 21 days after trial enrollment were identified as risk factors for mortality in ARDS patients that require prolonged mechanical ventilation. In addition, in terms of physiological parameters and their trajectory in ARDS patients requiring PMV we identified a dissociation between oxygenation and compliance during the late stages of ARDS, as a combination of mild-moderate hypoxemia but severely impaired compliance that becomes increasingly prevalent over time, regardless of ARDS etiology. Finally, by focus on AKI in particular, we identified that late AKI is common among ARDS patients and is associated with worse outcome and prolonged mechanical ventilation. Driving pressure was associated with subsequent development of AKI in patients with ARDS, suggesting that injurious mechanical ventilation may lead to AKI. In the subsequent sections, we will provide a more comprehensive analysis of our results.

PMV Study

By incorporating individual patient data from over 4200 subjects with ARDS enrolled in six high-quality randomized controlled trials conducted by the ARDS Network, this secondary analysis showed that prevalence of PMV gradually declined from 18.4% (in 2000) to 10.9% (in 2014). 90-day mortality of patients receiving PMV did not change over the same time period and remained as high as 36.8%. Finally, age, malignancy, pneumonia as the cause of ARDS, coagulation dysfunction and hepatic dysfunction during the first 21 days after trial enrollment were risk factors associated with mortality among patients with ARDS receiving PMV.

We found that prevalence of PMV in trials of ARDS significantly declined over time. This decline in prevalence of PMV was also accompanied by an increase in the percentage of

patients discharged alive without receiving PMV. Indeed, as shown in Figure 3, the percentage of patients with ARDS who were discharged alive without receiving PMV gradually increased from 52.3% in the ARMA trial to 65.6% in the SAILS trial. Taken together, these findings may reflect advances in supportive care of such patients, including lung protective ventilation, conservative fluid management, and protocolized weaning strategies that were required or recommended in later phase ARDS Network trials (24, 29). Interestingly, as shown in our subgroup analyses, improvement in prevalence of PMV mostly involved medical rather than surgical patients with ARDS (Figure 4). This finding may justify ongoing research on ARDS following trauma or elective surgery (64, 65, 67).

Improvement in prevalence of PMV was not found to be accompanied by a decrease in mortality of patients with ARDS receiving PMV. Indeed, as shown in Figure 5, 90-day mortality of patients receiving PMV did not change over time in trials of ARDS, and this was consistent across various subgroups (Figure 6). These findings, taken together, suggest that contemporary management of ARDS may be successfully reducing the number of episodes of PMV, but that work remains to be done to identify practices that lower mortality when recovery is prolonged.

To advance management of patients with PMV, it may be reasonable to first identify risk factors associated with mortality among patients receiving PMV. Considerable relevant research (which identified age and coagulation dysfunction as important risk factors) has been previously done in the general ICU population, not limited to patients with ARDS (68). In the present analysis, we focused on patients with ARDS, and we identified, apart from age and coagulation dysfunction, malignancy, pneumonia as the cause of ARDS, and hepatic dysfunction. This finding may have important implications for clinical trialists as it highlights a challenge. Any intervention to lower mortality in clinical trials of ARDS should target patients with prolonged mechanical ventilation (given that they constitute an increasingly larger proportion of total deaths); yet, mortality of those patients is mostly affected by non-modifiable risk factors.

We found that, among patients with ARDS receiving PMV, non-survivors had higher oxygenation (as assessed by PaO_2:FiO_2) at baseline than survivors by day 90 (Table 3). This seemingly counterintuitive finding might be explained by selection bias. Our study population of 250 patients receiving PMV might include selectively the most vulnerable patients among those with high oxygenation at baseline (as the remaining were discharged alive before day

21) and the most resilient patients among those with low oxygenation at baseline (as the remaining died before day 21). Briefly, in the selected group of patients who are alive but still receive mechanical ventilation on day 21, oxygenation at baseline may not predict long-term survival.

Oxygenation and Compliance Subphenotypes Study

The results of this study highlight the dissociation between oxygenation and compliance during the late stages of ARDS, as a combination of mild-moderate hypoxemia but severely impaired compliance, becomes increasingly prevalent over time, regardless of ARDS etiology.

The dissociation between oxygenation and compliance in ARDS has recently gained attention (20). Impairment of both oxygenation and lung compliance typically characterizes ARDS, and is the result of lung inflammation, impaired hypoxic pulmonary vasoconstriction and alveolar flooding (14, 69, 70). The recently described dissociation between oxygenation and compliance in early ARDS patients is attributed to increased shunt due to vasculopathy, and impaired hypoxic pulmonary vasoconstriction (20-22, 71).

To our knowledge, this is the first systematic examination of an “opposite” dissociation of oxygenation and compliance, observed in persistent ARDS, and characterized by mild-moderate hypoxemia but severely impaired compliance. This dissociation was indicated, but not systematically examined by previous studies, which were mostly limited to the first week from the onset of the syndrome (72-74). Rather, the present analysis took advantage of longitudinal data on oxygenation-compliance for three weeks from the onset of ARDS, for both traditional ARDS and COVID-19-related ARDS. Specifically, our analysis showed that, although the combination of mild-moderate hypoxemia but low compliance was not as rare in early ARDS due to etiologies other than COVID-19 compared to COVID-19 (Table 6), the combination became prominent among patients with persistent ARDS requiring controlled ventilation, regardless of etiology.

It may be worth attempting an explanation why this combination of mild-moderate hypoxemia and low compliance becomes increasingly prevalent over the course of ARDS among patients who remain under controlled mechanical ventilation. In persistent ARDS, the

resolution of pulmonary inflammation may lead to restoration of hypoxic pulmonary vasoconstriction, which in turn may optimize the distribution of perfusion and thus attenuate hypoxemia (70, 75). In spite of the attenuation of hypoxemia, compliance may be reduced due to the progressive development of some degree of fibrosis, known to occur in persistent ARDS (76). Therefore, concurrent improvement in ventilation-perfusion matching and development of fibrosis over time may underlie the pathophysiology of improved oxygenation despite severely impaired compliance in persistent ARDS. The impaired compliance is likely the reason these patients could not be liberated from controlled ventilation, thus resulting in the increased prevalence of the combination of low compliance and mild-moderate hypoxemia among patients requiring prolonged controlled ventilation.

Recognizing this dissociation among patients with persistent ARDS may have important clinical implications. Hypoxemia dominates all diagnostic and management algorithms of ARDS, such as the Berlin definition, indication for prone position or ECMO, and for a good reason: it is a cardinal symptom of ARDS at presentation, and lethal if not managed (2, 57, 77). The impairment in lung compliance is caused by the same underlying pathology and commonly correlates with the severity of hypoxemia. As a result, resolution of hypoxemia over time is considered an adequate indicator of resolution of ARDS, and included in weaning protocols, while improvement in lung mechanics is not (26-29, 78). Indeed, during the first couple of weeks of ARDS, in the majority of patients who improve, both oxygenation and compliance improve. However, as highlighted in this analysis, in a significant fraction of patients requiring prolonged controlled mechanical ventilation, the improvement of hypoxemia is dissociated from that of lung compliance at late stages of ARDS. Weaning attempts when lung compliance is severely impaired might fail and place patients at risk of self-inflicted lung injury (79-81). Indeed, strong inspiratory efforts may promote lung injury in ARDS, and sustained high driving pressures have been shown to occur during assisted ventilation only in patients with low compliance (58, 82). Therefore, acknowledging this common dissociation between oxygenation and compliance in persistent ARDS, rather than relying solely on improvement of oxygenation to characterize a patient's condition as improved, may have implications for patient management. For example, in patients with persistent ARDS, attempts for assisted ventilation could be complemented by close monitoring of effort and driving pressure, to minimize the risk of ventilator or self-inflicted

lung injury (33, 34). Studies on weaning focused on this specific group of patients are lacking and urgently needed.

Mechanical Ventilation and AKI Study

This secondary analysis of individual patient-level data from 2960 participants with ARDS included in seven ARDS Network and PETAL Network randomized controlled trials found that driving pressure was independently associated with subsequent development of AKI. Given that driving pressure may be a marker of injurious mechanical ventilation, our finding renders support to the concept that injurious mechanical ventilation may lead to AKI (83, 84).

In our attempt to comprehensively examine the association between driving pressure and development of late AKI, we took various approaches. In specific, we initially considered the baseline driving pressure (i.e., driving pressure on the day of onset of ARDS) and performed both unadjusted and adjusted analyses (Table 12). Then, we performed a sensitivity analysis which did not exclude patients with early AKI and a sensitivity analysis which included patients who developed AKI later than seven days following ARDS onset. In both sensitivity analyses we found similar results as in the main analysis. Finally, keeping into mind that snapshot measurements may be less informative than repeated measurements, we considered the mean driving pressure (i.e., the mean of daily values of driving pressure from onset of ARDS up to day 6 or day of development of AKI, whatever came first) and again performed both unadjusted and adjusted analyses (Table 19)(85). We found that the association between driving pressure and development of late AKI was consistent across time (Figure 15). To link our findings with previous literature indicating that a threshold of driving pressure equal to 15 cm H_2O is associated with injurious mechanical ventilation, we then used this threshold to explore the association between driving pressure and development of late AKI (3). We found that among patients with a mean driving pressure of 15 cm H_2O or greater, mean driving pressure was independently associated with the development of late AKI (Figure 16); a result with possible implications for clinical practice. Finally, we performed and compared three multivariate logistic regression models in order to delineate which of the following remains a significant factor for late AKI prediction; driving pressure or its components, namely plateau pressure (Ppl) and PEEP. Driving pressure, when added to the

reference model, resulted in significantly higher ΔAUC, as well as in better reclassification of patients, as shown by DeLong test and NRI, respectively, Table 13 and Figure 13. Taken together, the variety of our approaches may indicate the robustness of our main finding (i.e., driving pressure is associated with subsequent development of AKI).

Our analysis may complement the findings of previous meticulous contributions on the association between ARDS and AKI, which focused on early AKI. Indeed, large observational studies involving patients with ARDS focused on AKI which was already present at the time of onset of ARDS (53-56). Similarly, early AKI (specifically, AKI of stage 2 or 3 occurring less than 48 hours since ICU admission) was the focus of a retrospective causal inference study which showed that respiratory variables had a direct causal association with early AKI (86). On top of the above contributions, by focusing on patients who met the AKI criteria more than two (or even three) days following onset of ARDS (i.e., late AKI), our analysis may ensure that injurious mechanical ventilation (as indicated by high driving pressure) could be a contributor to rather than a consequence of AKI (53-56, 86).

Our analysis may also complement the findings of previous meticulous contributions examining the association between invasive mechanical ventilation and AKI in unselected critically ill patients (62, 87, 88). Those contributions did not reveal an association between injurious mechanical ventilation (as indicated by tidal volume) and occurrence of AKI (62, 87, 88). That finding might have two potential explanations. Firstly, there is evidence that tidal volume may not be as reliable a marker of injurious mechanical ventilation as driving pressure (89). Secondly, injurious mechanical ventilation may be more consequential in patients with ARDS compared to those without ARDS and, therefore, studies including exclusively patients with ARDS (such as ours) may have sufficient discriminative power to reveal the association between injurious mechanical ventilation and occurrence of AKI (90).

Our main finding that driving pressure (as a marker of injurious mechanical ventilation) is associated with subsequent development of AKI may have pathophysiological rationale. Indeed, a link between injurious mechanical ventilation (leading to ventilator-induced lung injury) and multi-organ dysfunction has long been established, with mechanisms such as barotrauma, volutrauma, atelectrauma, and biotrauma playing key roles. Among these, biotrauma is particularly relevant, as it extends beyond the lungs: the release of inflammatory cytokines contributes to extrapulmonary organ damage, including kidney injury (46). Experimental models of injurious mechanical ventilation have shown that ventilator-induced

lung injury can trigger renal cell apoptosis and kidney damage (49). Furthermore, subsequent studies have demonstrated that ventilator-induced lung injury is linked to renal endothelial inflammation and microvascular dysfunction (90, 91). Considering these prior observations, our findings align with the expected pathophysiology: in the clinical setting of ARDS, injurious mechanical ventilation, reflected by elevated driving pressure, is associated with the development of AKI. This reinforces the hypothesis that protecting the lungs may also contribute to preserving kidney function in critically ill patients.

Limitations

Limitations of the PMV study

The current analysis has several limitations. First, it is subject to the inherent limitations (such as residual confounding) of retrospective analyses. However, the analysis was based on meticulously collected data from six high-quality randomized controlled trials (24-29).

Second, given that even the most recent three randomized controlled trials (that provided data from the 250 subjects analyzed in Tables 2-4) were published between 2011 and 2014, one may question their relevance with current clinical practice of mechanical ventilation (26-28). However, current clinical practice is based on principles, which were known and widely appreciated by 2011; namely lung protective ventilation, conservative fluid management and personalized weaning strategies (24, 29).

Thirdly, although the principles of mechanical ventilation remain the same, we acknowledge that the pandemic of coronavirus disease (COVID-19) led to changes in care of patients with respiratory failure/ARDS, such as increase in implementation of high-flow nasal oxygen (before intubation) and prone positioning (before and after intubation)(92, 93). We lacked data to examine whether such changes in care of patients triggered by COVID-19 might affected the epidemiology of PMV.

Fourth, not only our clinical practice but also our perception of syndromes, such as ARDS or sepsis, may have been changed since 2014 (i.e., when the most recent ARDSnet trial was published) (28). Indeed, definition of sepsis was modified in 2016 to emphasize the critical

presence of organ failure, while a modification of definition of ARDS was recently proposed (94, 95). Both syndromes are perceived as heterogenous entities with distinct phenotypes (96, 97).

Fifth, while the inclusion criteria were similar across the trials analyzed, exclusion criteria differed such that study cohorts may not be directly comparable. Also, exclusion of a considerable proportion of patients due to very restrictive exclusion criteria of randomized controlled trials might negatively affect both extrapolation of findings in real world and accurate estimations of prevalence of PMV (67). Even so, estimates of trends of prevalence of PMV over time (i.e., the main purpose of this project) should be accurate.

Sixth, although we selected variables to be included in the regression model based on previous contributions and our own clinical expertise, we still acknowledge that other variables (such as pre-ICU comorbidities other than malignancy) could also have been used (33, 38, 64, 65).

Seventh, we lacked data to explore whether outcomes of patients with ARDS receiving PMV might have been influenced by nosocomial infections and patient/surrogate decision making. The latter has been found to be often characterized by unreasonably optimistic expectations (68). Finally, we acknowledge that prolonged mechanical ventilation is just a feature (albeit the cardinal one) of the broad syndrome of chronic critical illness (98).

Limitations of the Oxygenation and Compliance Subphenotypes Study

The findings of this study should be interpreted in the context of the limitations imposed by its retrospective nature. First, although the ARDSNet cohort consisted of patients enrolled in multiple ICUs from one continent (North America), the CARDS cohort consisted of patients enrolled in only two ICUs from one European country. Second, the sample size is limited by missing data on compliance from patients who remained on mechanical ventilation on day 21, mainly because mechanics were not monitored on assisted modes. However, an exploratory analysis of CARDS patients indicated that both compliance and oxygenation had improved prior to assisted ventilation (data not shown). Third, to facilitate the analysis, we had to use thresholds for oxygenation and compliance, acknowledging the inherent limitations of using thresholds to create classes in the continuum of a disease spectrum. We

also had to use the PaO_2:FiO_2 ratio at different levels of FiO_2 as an index of oxygenation, despite its nonlinear behavior, as this is what is currently used in clinical practice. Finally, we cannot provide information on the underlying cause of impaired compliance, to what extent it contributed to the need for prolonged ventilation, or its management in the surviving patients.

Limitations of the Mechanical Ventilation and AKI Study

Our analysis has certain limitations. First, given that it is an observational study, it could not establish causality. However, our approach to focus on development of late AKI may ensure that high driving pressure could only be a potential contributor to rather than a consequence of AKI. Second, AKI definition was based only on the serum creatinine criterion. However, this reliance on creatinine criterion (due to unavailability of hourly urine output data) seems not uncommon in the literature (45, 53, 54, 56, 62). Third, it was based on data from randomized controlled with strict exclusion criteria (24-30). However, such data have already been valuable to reveal both the importance of driving pressure and the attributive mortality of AKI (83, 85, 99). Finally, it represented a North American population and, therefore, it may lack generalizability. However, our analysis included a large sample size, provided by multiple centers, and focused on late AKI, which seems, so far, an underestimated subgroup of the AKI population.

B5. Conclusions

Our analysis has reached the following 3 conclusions:

First, the analysis of 4216 patients enrolled in six ARDS Network trials showed that prevalence of PMV among patients with ARDS gradually declined, while their mortality did not change. Risk factors associated with mortality were mostly non-modifiable.

Second, in persistent ARDS regardless of etiology, a combination of mild-moderate hypoxemia but low compliance becomes prevalent among patients who require PMV under controlled modes of mechanical ventilation.

Third, late AKI is prevalent in ARDS patients and associated with PMV, while driving pressure was associated with subsequent development of AKI in patients with ARDS.

The above findings may have important implications for clinical trialists to design and undertake clinical trials focusing on ARDS patients that require PMV. In addition, acknowledging that improvement in oxygenation is not always associated with restoration of lung integrity in persistent ARDS, adds to the increasingly recognized importance of monitoring lung mechanics in mechanically ventilated patients, throughout the course of ARDS in order to provide protective ventilation. Finally, our study suggests that injurious mechanical ventilation may lead to AKI and, therefore, approaches used to reduce driving pressure could potentially have protective renal effects.

B6. Scientific Impact and International Recognition

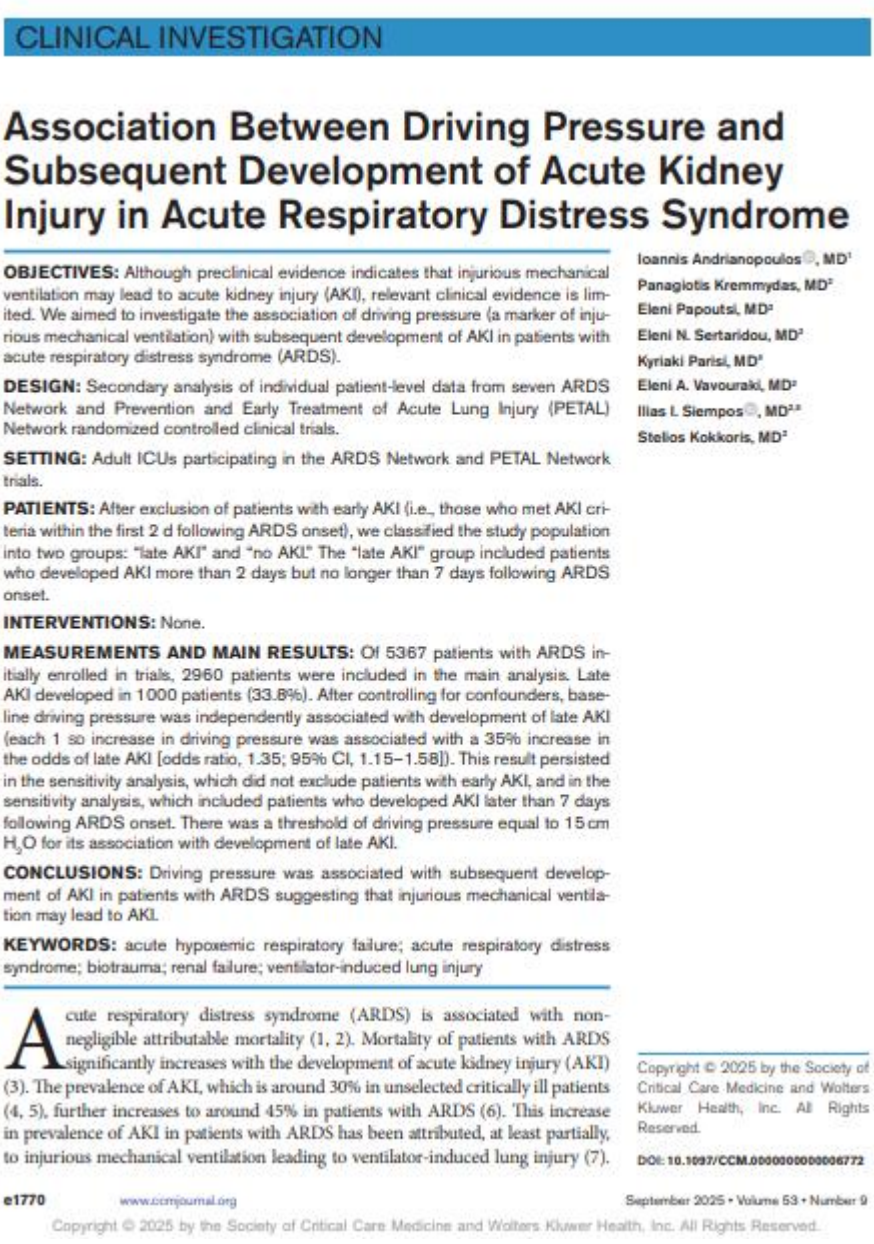
Results of our research have been published in three internationally recognized peer reviewed journals:

1. Andrianopoulos I, Kremmydas P, Papoutsi E, Sertaridou EN, Parisi K, Vavouraki EA, Siempos II, Kokkoris S. Association Between Driving Pressure and Subsequent Development of Acute Kidney Injury in Acute Respiratory Distress Syndrome. Crit Care Med. 2025 Sep 1;53(9):e1770-e1780. doi: 10.1097/CCM.0000000000006772. Epub 2025 Jul 2. PMID: 40601361.
2. Andrianopoulos I, Giannakoulis VG, Papoutsi E, Papathanakos G, Koulouras V, Thompson BT, Siempos II. PROLONGED MECHANICAL VENTILATION IN ACUTE RESPIRATORY DISTRESS SYNDROME. Shock. 2024 Feb 1;61(2):240-245. doi: 10.1097/SHK.0000000000002248. Epub 2023 Nov 15. PMID: 38010051.
3. [Papoutsi E*, Andrianopoulos I]*, Mavrikaki V, Bolaki M, Stamatopoulou V, Toli E, Papathanakos G, Koulouras V, Kondili E, Siempos II, Vaporidi K. A combination of mild-moderate hypoxemia and low compliance is highly prevalent in persistent ARDS: a retrospective study. Respir Res. 2024 Jan 3;25(1):1. doi: 10.1186/s12931-023-02626-9. PMID: 38173002; PMCID: PMC10765810. *co-first author with equal contribution.

In addition, part of the findings has been presented in two international Critical Care congresses (American Thoracic Society's 2023 International Conference, ATS and 44th International Symposium on Intensive Care on Emergency Medicine 2025, ISICEM 2025).

Publications in Peer-Reviewed Journals Resulting from PhD Thesis

Association Between Driving Pressure and Subsequent Development of Acute Kidney Injury in Acute Respiratory Distress Syndrome. Crit Care Med. 2025.



CLINICAL INVESTIGATION

Association Between Driving Pressure and Subsequent Development of Acute Kidney Injury in Acute Respiratory Distress Syndrome

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OBJECTIVES: Although preclinical evidence indicates that injurious mechanical ventilation may lead to acute kidney injury (AKI), relevant clinical evidence is limited. We aimed to investigate the association of driving pressure (a marker of injurious mechanical ventilation) with subsequent development of AKI in patients with acute respiratory distress syndrome (ARDS).

DESIGN: Secondary analysis of individual patient-level data from seven ARDS Network and Prevention and Early Treatment of Acute Lung Injury (PETAL) Network randomized controlled clinical trials.

SETTING: Adult ICUs participating in the ARDS Network and PETAL Network trials.

PATIENTS: After exclusion of patients with early AKI (i.e., those who met AKI criteria within the first 2 d following ARDS onset), we classified the study population into two groups: "late AKI" and "no AKI." The "late AKI" group included patients who developed AKI more than 2 days but no longer than 7 days following ARDS onset.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Of 5367 patients with ARDS initially enrolled in trials, 2960 patients were included in the main analysis. Late AKI developed in 1000 patients (33.8%). After controlling for confounders, baseline driving pressure was independently associated with development of late AKI (each 1 SD increase in driving pressure was associated with a 35% increase in the odds of late AKI [odds ratio, 1.35; 95% CI, 1.15–1.58]). This result persisted in the sensitivity analysis, which did not exclude patients with early AKI, and in the sensitivity analysis, which included patients who developed AKI later than 7 days following ARDS onset. There was a threshold of driving pressure equal to 15 cm H_2O for its association with development of late AKI.

CONCLUSIONS: Driving pressure was associated with subsequent development of AKI in patients with ARDS suggesting that injurious mechanical ventilation may lead to AKI.

KEYWORDS: acute hypoxemic respiratory failure; acute respiratory distress syndrome; biotrauma; renal failure; ventilator-induced lung injury

Acute respiratory distress syndrome (ARDS) is associated with non-negligible attributable mortality (1, 2). Mortality of patients with ARDS significantly increases with the development of acute kidney injury (AKI) (3). The prevalence of AKI, which is around 30% in unselected critically ill patients (4, 5), further increases to around 45% in patients with ARDS (6). This increase in prevalence of AKI in patients with ARDS has been attributed, at least partially, to injurious mechanical ventilation leading to ventilator-induced lung injury (7).

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Association between driving pressure and subsequent development of acute kidney injury in ARDS

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Author Contributions: IA and SK conceived of the study. IA, PK, EP, IIS and SK contributed to study design. All authors were responsible for interpretation of the data. EP and PK undertook statistical analyses. IA and SK drafted the manuscript. PK, EP, ENS, KP, EAV and IIS critically revised the manuscript for important intellectual content. EP and IIS had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript.
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Keywords: biotrauma; ventilator-induced lung injury; acute respiratory distress syndrome; acute hypoxemic respiratory failure; renal failure

ABSTRACT

Objective: Although preclinical evidence indicates that injurious mechanical ventilation may lead to acute kidney injury (AKI), relevant clinical evidence is limited. We aimed to investigate the association of driving pressure (a marker of injurious mechanical ventilation) with subsequent development of AKI in patients with acute respiratory distress syndrome (ARDS).
Design: Secondary analysis of individual patient-level data from seven ARDS Network and PETAL Network randomized controlled clinical trials.
Setting: Adult intensive care units participating in the ARDS Network and PETAL Network trials.
Patients: After exclusion of patients with early AKI (i.e., those who met AKI criteria within the first two days following ARDS onset), we classified the study population into two groups: "late AKI" and "no AKI". The "late AKI" group included patients who developed AKI more than two days but no longer than seven days following ARDS onset.
Interventions: None.
Measurements and Main Results: Of 5367 patients with ARDS initially enrolled in trials, 2960 patients were included in the main analysis. Late AKI developed in 1000 (33.8%) patients. After controlling for confounders, baseline driving pressure was independently associated with development of late AKI [each 1 standard deviation increase in driving pressure was associated with a 35% increase in the odds of late AKI (OR=1.35, 95% CI: 1.15–1.58)]. This result persisted in the sensitivity analysis which did not exclude patients with early AKI and in the sensitivity analysis which included patients who developed AKI later than seven days following ARDS onset. There was a threshold of driving pressure equal to 15 cmH_2O for its association with development of late AKI.
Conclusions: Driving pressure was associated with subsequent development of AKI in patients with ARDS, suggesting that injurious mechanical ventilation may lead to AKI.

Key points

Question: Is high driving pressure associated with subsequent development of acute kidney injury (AKI)?
Findings: This secondary analysis of individual patient-level data from seven ARDS Network and PETAL Network randomized controlled clinical trials showed that driving pressure was independently associated with the development of subsequent AKI. There was a threshold of driving pressure equal to 15 cmH_2O for its association with the development of AKI.
Meaning: Injurious mechanical ventilation may lead to AKI and, therefore, approaches used to reduce driving pressure could potentially have protective renal effects.

INTRODUCTION

Acute respiratory distress syndrome (ARDS) is associated with non-negligible attributable mortality[1,2]. Mortality of patients with ARDS significantly increases with the development of acute kidney injury (AKI)[3]. The prevalence of AKI, which is around 30% in unselected critically ill patients[4,5], further increases to around 45% in patients with ARDS[6]. This increase in prevalence of AKI in patients with ARDS has been attributed, at least partially, to injurious mechanical ventilation leading to ventilator-induced lung injury[7]. According to the concept of biotrauma, ventilator-induced lung injury may propagate an inflammatory response, which in turn may mediate injury of multiple organs, including kidney[8–11].

Preclinical and limited clinical data suggest that acute lung injury mediates AKI through multiple pathophysiological pathways that involve not only release of inflammatory mediators (as noted above), but also vasoconstriction of renal vessels, activation of the renin-angiotensin-aldosterone system and reduction in the renal blood flow by reduction of the cardiac output[12,13]. In addition, an increase in the afterload of right ventricle, as it is often the case in patients with ARDS, is associated with higher central venous pressure and therefore a higher risk for AKI[9].

Conversely, AKI may lead to increased fluid accumulation in the lung, which in turn worsens lung compliance and increases driving pressure[9]. In other words, high driving pressure may not be a contributor (as a marker of ventilator-induced lung injury) to but rather a consequence of AKI in patients with ARDS. The latter nuance (was high driving pressure a contributor to or a consequence of AKI?) could not be assessed in previous meticulous large observational studies involving patients with ARDS, because they focused on AKI which was already present at the time of onset of ARDS[14–16].

Having the above considerations in mind, we endeavored to study patients with ARDS who did not meet the AKI criteria within the first two days following onset of ARDS. Specifically, we examined whether high driving pressure was associated with subsequent development of AKI. By focusing on patients who met the AKI criteria more than two days following onset of ARDS (i.e., late AKI), we ensured that high driving pressure could be a contributor (as a marker of injurious mechanical ventilation) to rather than a consequence of AKI.

METHODS

Study design and patient population

We performed a secondary analysis of individual patient-level data from seven ARDS Network and Prevention and Early Treatment of Acute Lung Injury (PETAL) Network randomized controlled clinical trials; namely, ARMA[17], ALVEOLI[18], FACTT[19], ALTA[20], EDEN[21], SAILS[22] and ROSE[23] trials. In all those trials, patients received positive-pressure mechanical ventilation through an endotracheal tube, had a partial pressure of arterial oxygen to fraction

of inspired oxygen ratio (PaO_2:FiO_2) ≤ 300 mmHg and had bilateral infiltrates on chest radiography not fully explained by cardiac failure. As previously[24–26], we were granted access to data through the Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC) of the National Heart, Lung, and Blood Institute (NHLBI). Because data would be received in de-identified form, the Institutional Review Board of Evangelismos Hospital waived the need of informed consent and approved the study (protocol number 536; approval date 29-11-2023; study title "Association between driving pressure and development of late acute kidney injury in patients with acute respiratory distress syndrome"). Procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation (institutional) and with the Helsinki Declaration of 1975.

Study groups and definitions

We defined AKI according to the Kidney Disease Improving Global Outcome (KDIGO) criteria[27,28]. Because of unavailability of hourly urine output data, we only used the serum creatinine criterion as per previous similar studies[14]. We defined baseline creatinine as the lowest value of creatinine on the day of onset of ARDS (day 1). After exclusion of patients with early AKI (i.e., those who met the AKI criteria within the first two days following onset of ARDS), we classified the study population into two groups: "late AKI" and "no AKI". The "late AKI" group included patients who developed AKI more than two days but no longer than seven days following onset of ARDS. This threshold of two days to define late AKI has been previously used in the literature[29]. The "no AKI" category included patients who did not develop AKI during index stay in the intensive care unit (ICU). We provide details on study groups and definitions in Online Data Supplement.

Data collection and outcomes

We provide details on data collection in Online Data Supplement. With regard to respiratory system mechanics, we collected data on plateau pressure, positive end-expiratory pressure (PEEP) and driving pressure (defined as plateau pressure minus PEEP). Data on driving pressure were available for consecutive days up to day 6 following onset of ARDS.

The primary outcome of the present analysis was development of late AKI. Secondary outcomes were 90-day mortality, organ failure-free days, ventilator-free days, and ICU-free days; the latter were defined as previously in the literature[30,31].

Statistical analysis

We presented continuous variables as median with interquartile range (IQR) and compared them using the Mann-Whitney test. We presented categorical variables as percentages and compared them using the chi-squared or Fisher's exact test, as appropriate. We estimated the association between driving pressure and development of late AKI via

binary logistic regression analyses, with driving pressure as the independent variable and the development of late AKI as the dependent variable. We used multivariable logistic regression analyses to adjust for confounding factors known to be associated with development of AKI, such as age, sex, body mass index, presence of diabetes mellitus, organ failures (namely, cardiovascular, coagulation, and hepatic) and fluid balance[14]. We also adjusted for respiratory variables other than driving pressure, such as PaO_2:FiO_2, respiratory rate, tidal volume, respiratory system compliance and PEEP. We tested for collinearity between variables by calculating variance inflation factor (VIF); a VIF< 5 was considered to rule out collinearity[32]. We also assessed the linearity of the relationship between baseline driving pressure and late AKI using cubic splines. We performed repeated measurements using two-way repeated measures ANOVA. We performed and compared three multivariate regressions in order to delineate which of the following remains a significant factor for late AKI prediction; plateau pressure (Ppl), PEEP or both, expressed as a difference, namely driving pressure. Firstly, we defined a reference clinical model including the same baseline variables used in the previous logistic regressions. Then, three separate multivariate logistic regression analyses were conducted to assess the performance of the predictive models, after adding the individual risk factors to the reference model individually. Improvements in the model were evaluated by difference in the area under the curves (AUCs) (ΔAUC) and DeLong test. We also quantified the improvement of each factor on late AKI risk prediction with the net reclassification improvement (NRI), which measures how much a new model improves the classification of individuals compared to a reference model. It assesses whether the new model more accurately reclassifies individuals into appropriate risk categories. A positive NRI indicates that the new model improves classification compared to the reference model. We considered statistical significance at an α level of 0.05; all P values were two-sided. We conducted all statistical analyses using SPSS software version 28.0 (SPSS, Inc., Chicago, IL) and R software version 4.2.1 (R Foundation for Statistical Computing).

RESULTS

Baseline characteristics

Of 5367 patients with ARDS initially enrolled in the seven randomized controlled trials[17-23], 2960 patients were included in the main analysis. Reasons for exclusion are depicted in **eFigure 1** (Online Data Supplement). Of the 2960 included patients, late AKI developed in 1000 (33.8%) patients; specifically, 62.4% developed AKI stage I, 21.8% stage II and 15.8% stage III.

Table 1 presents the baseline characteristics and **eTable 1** (Online Data Supplement) the outcomes of patients included in the “late AKI” versus “no AKI” groups. Compared groups differed in terms of age, presence of diabetes mellitus, organ failures (namely, cardiovascular, coagulation, and hepatic), PaO_2:FiO_2, respiratory rate, tidal volume, respiratory system

compliance and PEEP, but not in terms of sex. Driving pressure at baseline was not significantly different between the two groups. Crude 90-day mortality was significantly higher in the "late AKI" compared with the "no AKI" group (39% versus 17%; p<0.001). Consistently, organ failure-free days, ventilator-free days and ICU-free days were significantly lower in the "late AKI" compared with the "no AKI" group (**Table 1)**.

Association between baseline driving pressure and development of late AKI

Table 2 depicts a multivariable logistic regression analysis to isolate the contribution of age, sex, body mass index, diabetes mellitus, organ failures (namely, cardiovascular, coagulation, and hepatic) at baseline, fluid balance, baseline PaO_2:FiO_2 ratio, respiratory rate, tidal volume, respiratory system compliance, PEEP and driving pressure (independent variables) to the development of late AKI (dependent variable). In our multivariable regression model, we did not include plateau pressure due to collinearity with driving pressure. Instead, we included both PEEP and driving pressure because we found no collinearity between them (VIF= 1.049). After controlling for confounders, driving pressure at baseline was independently associated with development of late AKI [odds ratio (OR) 1.046, 95% confidence intervals (CI): 1.021-1.072; p<0.001]. The predicted probabilities of the model were then plotted against driving pressure quintiles. The results indicate that the probability of late AKI increases with higher driving pressure quintiles (p for trend over quintiles=0.011) (**eFigure 2,** Online Data Supplement). We also assessed the linearity of the relationship between baseline driving pressure and late AKI using cubic splines. A likelihood ratio test comparing a linear model to a spline model (4 degrees of freedom) – created by employing a multivariate logistic regression with cubic splines - showed no significant improvement in fit (p=0.312). This suggests that the association between baseline driving pressure and late AKI is adequately described by a linear term.

Reclassification tests

Table 3 shows the performance of driving pressure and its components for late AKI prediction. Driving pressure and Ppl, when added to the reference model, resulted in significantly higher ΔAUCs (DeLong p=0.026 and p=0.007, respectively), as well as in better reclassification of patients (Total NRI=0.07, P=0.023, and 0.16, p<0.001), respectively). The model including driving pressure and that including Ppl did not differ significantly (DeLong p=0.09). **Figure 1** depicts the ROC curves, as well as the AUCs of the reference and the other three models.

Sensitivity analyses

We repeated our main analysis by not excluding patients with early AKI. After adjusting for age, sex, body mass index, diabetes mellitus, organ failures (namely, cardiovascular, coagulation, and hepatic) at baseline, fluid balance, baseline PaO_2:FiO_2 ratio, respiratory rate, tidal volume, respiratory system compliance and PEEP, baseline driving pressure remained independently associated with development of AKI (OR 1.038, 95% CI: 1.020-1.056; p<0.001) (**eTable 2,** Online Data Supplement).

Also, we repeated our main analysis by including patients who developed AKI later than seven days following onset of ARDS; i.e., the "late AKI" group included patients who developed AKI from day 3 to day 28 following onset of ARDS. After adjusting for age, sex, body mass index, diabetes mellitus, organ failures (namely, cardiovascular, coagulation, and hepatic) at baseline, fluid balance, baseline PaO_2:FiO_2 ratio, respiratory rate, tidal volume, respiratory system compliance and PEEP, baseline driving pressure remained independently associated with development of late AKI (OR 1.060, 95% CI: 1.036-1.084; p<0.001) (**eTable 3,** Online Data Supplement).

To explore how the survival status affected the relationship between late AKI and driving pressure, given the close association between AKI and mortality, we performed two separate multivariate logistic regressions in survivors and non-survivors, respectively. Driving pressure was a predictor of late AKI in survivors only (**eTable 4,** Online Data Supplement).

We also conducted a sensitivity analysis with baseline creatinine back calculated from the Modification of Diet in Renal Disease (MDRD) equation, assuming an estimated glomerular filtration rate equal to 75mL/Kg/1.73m^2, as suggested by KDIGO guidelines.[27] The results were similar to those of the main analysis (Online Data Supplement). In another sensitivity analysis, a declining course in the driving pressure during the first week of their ICU stay was not associated with less risk of late AKI (Online Data Supplement). We further explored the association of cumulative fluid balance with driving pressure change in late AKI and no AKI patients (**eTable 5, eTable 6, eFigure 3,** Online Data Supplement). Lastly, we performed sensitivity analyses, which showed that driving pressure was independently associated with both persistent and severe late AKI (Online Data Supplement).

Association between mean driving pressure and development of late AKI

In order to ascertain whether the continuing exposure of patients with ARDS to high driving pressure during the first days following onset of ARDS was associated with development of late AKI, we performed another multivariable analysis, in which baseline driving pressure was replaced by mean driving pressure (i.e., the mean of daily values of driving pressure from onset of ARDS up to day 6 or day of development of AKI, whatever came first). Consistently, mean driving pressure was independently associated with development of late AKI (OR 1.054, 95% CI: 1.030-1.078; p<0.001) (**eTable 7,** Online Data Supplement)).

Driving pressure during the first six days following onset of ARDS in both compared groups was significantly higher in the "late AKI" than the "no AKI" group across time (between-groups repeated measures ANOVA p=0.014) (**Figure 2**). The association between driving

pressure and development of late AKI was consistent across time; i.e., there was no interaction between compared groups and time (p=0.283).

Given that a threshold of driving pressure equal to 15 cmH_2O has been associated with injurious mechanical ventilation[33], we used this threshold to explore the association between driving pressure and development of late AKI. As shown in **Figure 3**, among patients with a mean driving pressure lower than 15 cmH_2O, mean driving pressure was not associated with development of late AKI in both unadjusted and adjusted analyses [i.e., after again taking into consideration age, sex, body mass index, diabetes mellitus, organ failures (namely, cardiovascular, coagulation, and hepatic) at baseline, fluid balance, baseline PaO_2:FiO_2 ratio, respiratory rate, tidal volume, respiratory system compliance and PEEP]. On the contrary, among patients with a mean driving pressure of 15 cmH_2O or greater, mean driving pressure was independently associated with the development of late AKI (for adjusted analysis OR 1.049, 95% CI:1.022-1.078; p<0.001).

DISCUSSION

This secondary analysis of individual patient-level data from 2960 participants with ARDS included in seven ARDS Network and PETAL Network randomized controlled trials found that driving pressure was independently associated with subsequent development of AKI. Given that driving pressure may be a marker of injurious mechanical ventilation[34,35], our finding renders support to the concept that injurious mechanical ventilation may lead to AKI.

In our attempt to comprehensively examine the association between driving pressure and development of late AKI, we took various approaches. In specific, we initially considered the baseline driving pressure (i.e., driving pressure on the day of onset of ARDS) and performed both unadjusted and adjusted analyses (**Table 2**). Then, we performed a sensitivity analysis which did not exclude patients with early AKI and a sensitivity analysis which included patients who developed AKI later than seven days following ARDS onset. In both sensitivity analyses we found similar results as in the main analysis. Finally, keeping into mind that snapshot measurements may be less informative than repeated measurements[36], we considered the mean driving pressure (i.e., the mean of daily values of driving pressure from onset of ARDS up to day 6 or day of development of AKI, whatever came first) and again performed both unadjusted and adjusted analyses (**eTable 7,** Online data supplement). We found that the association between driving pressure and development of late AKI was consistent across time (**Figure 2**). To link our findings with previous literature indicating that a threshold of driving pressure equal to 15 cmH_2O is associated with injurious mechanical ventilation[33], we then used this threshold to explore the association between driving pressure and development of late AKI. We found that among patients with a mean driving pressure of 15 cmH_2O or greater, mean driving pressure was independently associated with the development of late AKI (**Figure 3**); a result with possible implications for clinical practice. Finally, we performed and compared three multivariate logistic regression models in order to delineate which of the following remains a significant factor for late AKI prediction; driving

pressure or its components, namely plateau pressure (Ppl) and PEEP. Driving pressure, when added to the reference model, resulted in significantly higher ΔAUC, as well as in better reclassification of patients, as shown by DeLong test and NRI, respectively, **Table 3** and **Figure 1**. Taken together, the variety of our approaches may indicate the robustness of our main finding (i.e., driving pressure is associated with subsequent development of AKI).

Our analysis may complement the findings of previous meticulous contributions on the association between ARDS and AKI, which focused on early AKI. Indeed, large observational studies involving patients with ARDS focused on AKI which was already present at the time of onset of ARDS[14–16]. Similarly, early AKI (specifically, AKI of stage 2 or 3 occurring less than 48 hours since ICU admission) was the focus of a retrospective causal inference study which showed that respiratory variables had a direct causal association with early AKI[37]. On top of the above contributions[14–16,37], by focusing on patients who met the AKI criteria more than two (or even three) days following onset of ARDS (i.e., late AKI), our analysis may ensure that injurious mechanical ventilation (as indicated by high driving pressure) could be a contributor to rather than a consequence of AKI.

Our analysis may also complement the findings of previous meticulous contributions examining the association between invasive mechanical ventilation and AKI in unselected critically ill patients[29,38,39]. Those contributions did not reveal an association between injurious mechanical ventilation (as indicated by tidal volume) and occurrence of AKI[29,38,39]. That finding might have two potential explanations. Firstly, there is evidence that tidal volume may not be as reliable a marker of injurious mechanical ventilation as driving pressure[40]. Secondly, injurious mechanical ventilation may be more consequential in patients with ARDS compared to those without ARDS and, therefore, studies including exclusively patients with ARDS (such as ours) may have sufficient discriminative power to reveal the association between injurious mechanical ventilation and occurrence of AKI[41].

Our main finding that driving pressure (as a marker of injurious mechanical ventilation) is associated with subsequent development of AKI may have pathophysiological rationale. Indeed, a link between injurious mechanical ventilation (leading to ventilator-induced lung injury) **and multi-organ dysfunction** has long been established, with mechanisms such as **barotrauma, volutrauma, atelectrauma, and biotrauma** playing key roles. Among these, **biotrauma** is particularly relevant, as it extends beyond the lungs: the release of inflammatory cytokines contributes to **extrapulmonary organ damage**, including **kidney injury.[7]** Experimental models of injurious mechanical ventilation have shown that ventilator-induced lung injury **can trigger renal cell apoptosis and kidney damage.[10]** Furthermore, subsequent studies have demonstrated that ventilator-induced lung injury **is linked to renal endothelial inflammation and microvascular dysfunction.[41,42]** Considering these prior observations, our findings **align with the expected pathophysiology**: in the **clinical setting of ARDS**, **injurious mechanical ventilation, reflected by elevated driving pressure, is associated with the development of AKI**. This reinforces the hypothesis that protecting the lungs may also contribute to **preserving kidney function** in critically ill patients.

Our analysis has certain limitations. First, given that it is an observational study, it could not establish causality. However, our approach to focus on development of late AKI may ensure that high driving pressure could only be a potential contributor to rather than a consequence of AKI. Second, AKI definition was based only on the serum creatinine criterion. However, this reliance on creatinine criterion (due to unavailability of hourly urine output data) seems not uncommon in the literature[6,14,16,29]. Third, it was based on data from randomized controlled with strict exclusion criteria[17-23]. However, such data have already been valuable to reveal both the importance of driving pressure and the attributive mortality of AKI[34,43,44]. Finally, it represented a North American population and, therefore, it may lack generalizability. However, our analysis included a large sample size, provided by multiple centers, and focused on late AKI, which seems, so far, an underestimated subgroup of the AKI population.

CONCLUSIONS

In conclusion, the present secondary analysis found that driving pressure was associated with subsequent development of AKI in patients with ARDS. This finding suggests that injurious mechanical ventilation may lead to AKI and, therefore, approaches used to reduce driving pressure could potentially have protective renal effects.

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Table 1. Baseline characteristics of patients included in the compared groups.

Variable	**All patients (n=2960)**	**No AKI (n=1960)**	**Late AKI (n=1000)**	**p value**
Age, years	51 (39-63)	50 (39-62)	52 (40-65)	0.001
Female sex, n (%)	1475 (50)	978 (50)	497 (50)	0.919
BMI, kg/m^2	27 (23-33)	27 (23-32)	28 (23-34)	0.010
Race, n (%)				<0.001
White	2118 (72)	1450 (74)	668 (67)	
Black	425 (14)	251 (13)	174 (17)	
Hispanic	164(6)	87 (4)	77 (8)	
Other	212 (7)	141 (7)	71 (7)	
Comorbidities, n (%)				
Hypertension	743 (25)	446 (23)	297 (30)	0.016
Diabetes mellitus	470 (16)	290 (15)	180 (18)	0.030
Cardiovascular disease	217 (7)	138 (7)	79 (8)	0.951
Chronic pulmonary disease	266 (9)	164 (8)	102 (10)	0.524
Malignancies	168 (6)	89 (5)	79 (8)	<0.001
Risk factors of ARDS, n (%)				
Pneumonia	1609 (54)	1008 (51)	601 (60)	<0.001
Sepsis	459 (16)	328 (17)	131 (13)	0.009
Aspiration	400 (14)	266 (14)	134 (13)	0.893
Trauma	225 (8)	175 (9)	50 (5)	<0.001
Multiple transfusions	53 (2)	36 (2)	17 (2)	0.788
Organ failure at baseline, n (%)				
Cardiovascular	1729 (58)	1094 (56)	635 (64)	<0.001
Coagulation	441 (15)	265 (14)	176 (18)	0.003
Hepatic	349 (12)	200 (10)	149 (15)	<0.001

Creatinine at baseline, mg/dL	0.8 (0.6-1.0)	0.8 (0.6-1.0)	0.8 (0.6-1.1)	<0.001
Fluid balance on day 1, mL	1350 (90-3063)	1261 (16-3025)	1496 (233-3160)	0.047
Cumulative fluid balance of the first 3 days, mL	2938 (-66-6511)	2618 (-470-5984)	3792 (590-7881)	<0.001
Respiratory variables at baseline				
PaO_2:FiO_2, mmHg	134 (100-180)	138 (105-186)	124 (91-173)	<0.001
Respiratory rate, breaths/min	24 (18-29)	23 (18-28)	24 (20-30)	<0.001
VT/PBW, mL/Kg	6.8 (6.0-8.4)	6.9 (6.0-8.5)	6.6 (6.0-8.1)	0.017
Arterial pH	7.39 (7.34-7.44)	7.40 (7.35-7.44)	7.37 (7.32-7.43)	<0.001
$PaCO_2$, mmHg	40 (35-45)	39 (34-45)	40 (35-46)	0.257
Plateau pressure, cmH_2O	25 (21-30)	25 (21-30)	26 (22-31)	<0.001
Respiratory system compliance, mL/ cmH_2O	30 (23-40)	31 (24-41)	28 (22-38)	<0.001
PEEP, cmH_2O	10 (5-12)	10 (5-12)	10 (8-12)	<0.001
Driving pressure, cmH_2O	16 (12-20)	15 (12-20)	16 (12-21)	0.056

Abbreviations: AKI, acute kidney injury; n, number; BMI, body mass index; ARDS, acute respiratory distress syndrome; PaO_2:FiO_2, partial pressure of arterial oxygen to fraction of inspired oxygen ratio; VT, tidal volume; PBW, predicted body weight; PEEP, positive end-expiratory pressure; ICU, intensive care unit.

Data are expressed as median (IQR), unless otherwise indicated.

Table 2. Multivariable logistic regression analysis to explore the contribution of baseline driving pressure (independent variable) to the development of late AKI (dependent variable).

Variable	**Univariable analysis**			**Multivariable analysis***		
	OR	**95%CI**	**p value**	**OR**	**95%CI**	**p value**
Baseline driving pressure (increments of 1 SD)	1.12	1.024- 1.23	0.014	1.35	1.15 - 1.58	<0.001

Abbreviations: AKI, acute kidney injury; OR, odds ratio; CI, confidence interval; SD, standard deviation (1 SD of driving pressure=6.6 cmH_2O). *Multivariable model was adjusted for: age, sex, body mass index, diabetes mellitus, circulatory failure, coagulation failure, hepatic failure, fluid balance, partial pressure of arterial oxygen to fraction of inspired oxygen ratio (PaO2/FiO2) ratio, respiratory ratio, tidal volume, respiratory system compliance and PEEP.

Table 3. Performance of DP and its components for late AKI prediction.

Reference model	Added baseline variable	AUC of the new model	ΔAUC	DeLong test p value*	Total NRI (95% CI)	p value
Age+sex+BMI+DM+ circulatory failure+coagulation failure+hepatic failure+FB+ PaO2/FiO2 ratio+RR+VT+Crs AUC (95% CI): 0.600 (0.570-0.631)	DP	0.615	0.015	0.026[a]	0.07 (0.007-0.12)	0.02
	PEEP	0.612	0.012	0.12	0.04 (-0.01-0.10)	0.16
	Ppl	0.625	0.025	0.007	0.16 (0.08-0.22)	0.001

*New model vs reference model. [a]The model including DP and that including Ppl did not differ significantly (DeLong p=0.09). *Abbreviations*: DP, driving pressure; AUC, area under curve; CI, confidence interval; Δ, difference; NRI, net reclassification improvement; BMI, body mass index; DM, diabetes mellitus; RR, respiratory rate; VT, tidal volume; PEEP, positive end-expiratory pressure; Ppl, plateau pressure.

FIGURES

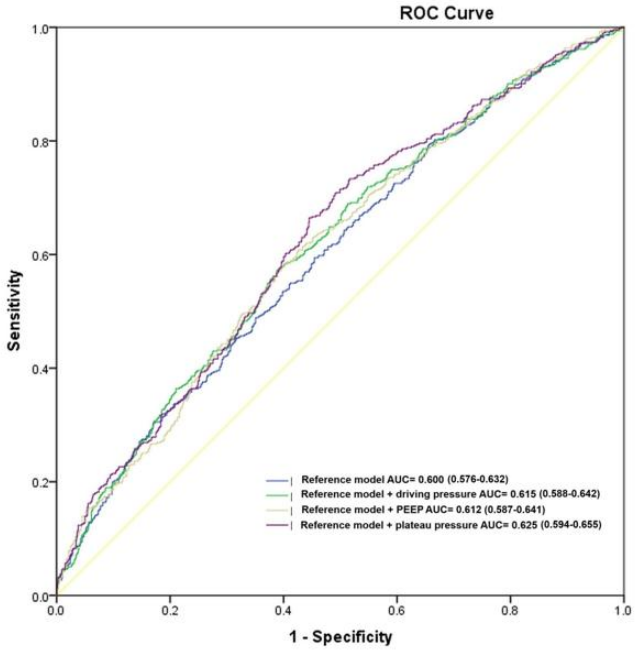

Figure 1. ROC curves and the AUCs of the four models for late AKI prediction. Abbreviations: ROC, receiver operating characteristics; AUC, area under the curve; PEEP, positive end-expiratory pressure. The reference model included: age, sex, body mass index, diabetes mellitus, circulatory failure, coagulation failure, hepatic failure, fluid balance, partial pressure of arterial oxygen to fraction of inspired oxygen ratio (PaO_2/FiO_2) ratio, respiratory rate, tidal volume and respiratory system compliance.

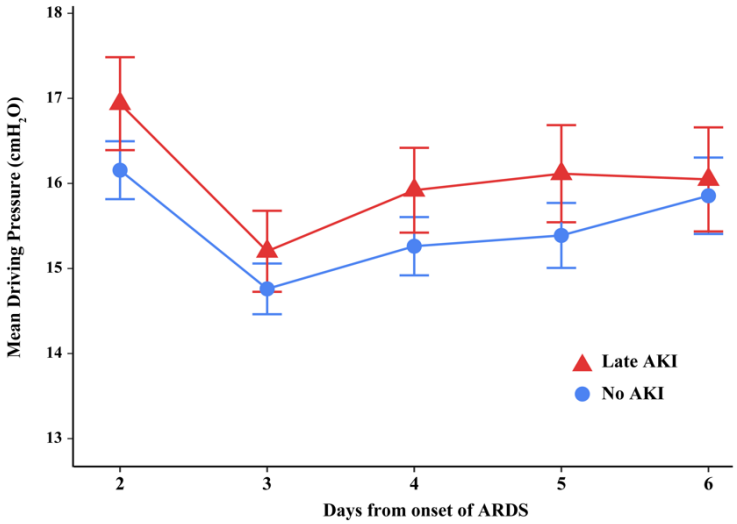

Figure 2. Trajectory of driving pressure during the first six days following onset of ARDS in both compared groups. Driving pressure was significantly higher in the "late AKI" than the "no AKI" group across time (between-groups repeated measures ANOVA p=0.014). The association between driving pressure and development of late AKI was consistent across time; i.e., there was no interaction between compared groups and time (p=0.283). The diagram represents mean ± standard error of the mean of driving pressure values for each group of patients at each time point.

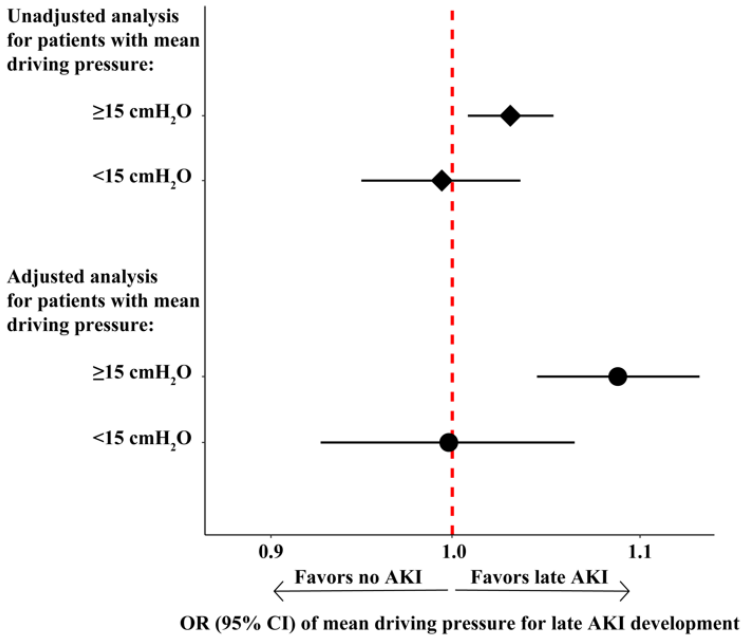

Figure 3. Forest plot exploring the association between driving pressure and development of late AKI by taking into consideration a threshold of 15 cmH_2O. Among patients with a mean driving pressure of 15 cmH_2O or greater, mean driving pressure was independently associated with the development of late AKI (for adjusted analysis OR 1.049, 95% CI:1.022-1.078; p<0.001).

Online Data Supplement

Association between driving pressure and subsequent development of acute kidney injury in ARDS

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Contents

20	**eReferences**	

Details on study groups and definitions

With the exemption of the "traditional (i.e., higher) tidal volume" group of the ARMA randomized controlled trial, all patients included in the ARDS Network and PETAL Network trials received lung protective ventilation. We excluded patients with chronic kidney disease (defined as requirement for chronic dialysis or peritoneal dialysis). We also excluded patients without available data on creatinine on day 1 [i.e., on the day of onset of acute respiratory distress syndrome (ARDS)] or afterwards. We excluded patients who had a serum creatinine on day 1 greater than 1.5 mg/dl, a difference between the highest and lowest value of creatinine on days 1 or 2 equal or greater than 0.3 mg/dl, and a ratio of highest value of creatinine on days 1 or 2 to baseline creatinine equal or higher than 1.5, because they might have already developed acute kidney injury (AKI) during the first two days following onset of ARDS (i.e., early AKI). For the late AKI group, we divided creatinine of each day (from day 3 to day 7) with the baseline creatinine value; if the result of the division was equal or greater than 1.5, then, we considered the patient as late AKI. Moreover, if there was an increase in creatinine of ≥ 0.3 mg/dL within any two-days interval from day 3 to day 7, we also considered the patient as late AKI.

Details on data collection

From the seven included ARDS Network and PETAL Network randomized controlled trials, we extracted data on demographics (age, sex, body mass index and race), comorbidities (data on hypertension, chronic pulmonary disease and cardiovascular disease were not available for ARMA and ALVEOLI trials), risk factors of ARDS, organ failure (namely cardiovascular, coagulation and hepatic) at baseline, fluid balance, creatinine (up to day 7 after ARDS onset) and respiratory variables. We collected data on 90-day mortality, organ failure-free days, ventilator-free days and intensive care unit (ICU)-free days. Organ failures were defined according to the various components of Sequential Organ Failure Assessment (SOFA) score. Specifically, cardiovascular failure was defined as a systolic blood pressure ≤ 90 mmHg or the requirement for vasopressors, coagulation failure as platelet concentration ≤ 80,000/μL, and hepatic failure as the concentration of bilirubin ≥ 2 mg/dL.

With regard to respiratory system mechanics, we retrieved data on positive end-expiratory pressure (PEEP), plateau pressure, tidal volume per predicted body weight (VT/PBW) and driving pressure (defined as plateau pressure minus PEEP). Data on driving pressure were available for consecutive days 2 to 6 following onset of ARDS. As baseline values for these parameters, we used the data of day 2, due to their unavailability on day 1. Their mean values were estimated by dividing the sum of values (up to day 6 or day of development of AKI

whatever came first) with the total number of measurements. The mean value was used as a surrogate of the trajectory of each parameter across time.

Sensitivity analyses

Late AKI definition based on estimated baseline creatinine by MDRD equation

We conducted a sensitivity analysis with baseline creatinine back calculated from the Modification of Diet in Renal Disease (MDRD) equation, assuming an estimated estimated glomerular filtration rate equal to 75mL/Kg/1.73m^2, as suggested by KDIGO guidelines (reference 27 of the main manuscript). Late AKI according to the initial definition was identified in 33.3% of patients, whereas with the new definition in 34%. The Cohen Kappa measure of agreement showed excellent agreement (Kappa=0.86, p<0.001) between the two definitions. Moreover, the multivariate logistic regression model with the new definition of late AKI gave quite similar results with the initial model for driving pressure (SD): OR=1.290, 95% CI: 1.107-1.518. It seems that there was no misclassification of late AKI cases.

Late AKI risk for patients with declining driving pressure during the first week of ICU stay

Data regarding driving pressure after recruitment maneuvers or prone position were not available. Nevertheless, we tried to identify patients who had a declining course in the driving pressure during the first week of their ICU stay, and explore whether they had different risk for late AKI. Specifically, for no AKI patients we calculated the difference in driving pressure (dDP) as that between the driving pressure of day 6 post-admission (the last available in the data base) and the baseline driving pressure. Similarly, for the AKI patients we calculated dDP as the difference between the driving pressure of the first day of late AKI development and the baseline value. Forty percent of patients were found to have an increase in driving pressure (dDP>0) and 60% a decrease (dDP<0). Then, dDP was inserted in the multivariate model (instead of baseline DP) as a binary variable (1, 0, for dDP values > or < 0, respectively), and was not found to be associated with late AKI (p=0.57).

In addition to that, as it was shown in the repeated measures ANOVA in the original manuscript (**Figure 2, original manuscript**), the within-subjects effect in the no AKI group was non-significant, meaning that in patients with no AKI, driving pressure did not drop significantly over time. Therefore, we can conclude that there was not an association between decreasing driving pressure over time and less risk of late AKI.

Association of cumulative fluid balance with driving pressure change in late AKI and no AKI patients

Only data on cumulative fluid balance up to day 4 post-admission were available and, thus, longitudinal analyses beyond that day could not be carried out. We performed linear regressions, with the difference of driving pressure (dDP) as dependent variable and the difference in cumulative fluid balance (dFB) (up to day 4 post-admission) as independent

variable, in the late AKI and the no AKI group, separately. Specifically, dFB in late AKI group was defined as that between the FB on the first day of late AKI occurrence (up to day 4 post-admission) and the baseline FB; in no AKI group it was defined as the difference between the FB on day 4 (last available) and the baseline FB. Moreover, dDP was defined as follows: in late AKI, as the difference between the driving pressure on the first day of late AKI occurrence (up to day 5 post-admission) and the baseline driving pressure. In no AKI group, it was defined as the difference between the driving pressure on day 5 post-admission and the baseline driving pressure. Day 5 was chosen, because we wanted to keep a meaningful time sequence, i.e. for a patient with available data for FB on day 4 (the last available), we would select the driving pressure of the following day (day 5) for the analysis, assuming that dFB was the 'risk factor' and dDP the 'outcome'. The same logic was followed in all patients, i.e., dFB always preceded dDP by one day. Interestingly, although dFB was significantly lower in patients with no AKI (**eTable 5**), its rise was significantly associated with dDP only in patients with no AKI, **eTable 6**.

We also plotted both regression lines (for late AKI and no AKI groups), **eFigure 3**. As the slope of the no AKI group regression line is greater compared to that of the late AKI group, we could assume that a similarly high dFB in no AKI patients have a greater impact on dDP than in late AKI patients.

Association between driving pressure and persistent late AKI

Persistent late AKI was defined as the late AKI which lasted for more than 48 hours, while transient AKI as that lasted less than 48 hours (*Chawla 2017*). Persistent late AKI was developed in 13.4% of the participants (40.4% of the late AKI patients). The multivariate logistic model revealed that driving pressure (SD) was independently associated with persistent late AKI: OR 1.667, 95% CI: 1.352-2.045.

Association between driving pressure and late AKI stages

AKI stages were defined according to KDIGO guidelines (*References 27 and 28 of the original manuscript*). We then divided patients into two groups, those with severe late AKI (stage 2 and 3), and those without (no AKI and mild late AKI of stage 1). Severe late AKI was present in 12.5% of the cohort (37.6% of the late AKI patients). We performed another multivariate logistic model, which revealed that driving pressure (SD) was independently associated with severe late AKI: OR 1.495, 95% CI: 1.201-1.832.

eTable 1. Baseline characteristics and outcomes of patients included in the compared groups.

Variable	All patients (n=2960)	No AKI (n=1960)	Late AKI (n=1000)	p value
Age, years	51 (39-63)	50 (39-62)	52 (40-65)	0.001
Female sex, n (%)	1475 (50)	978 (50)	497 (50)	0.919
BMI, kg/m^2	27 (23-33)	27 (23-32)	28 (23-34)	0.010
Race, n (%)				<0.001
White	2118 (72)	1450 (74)	668 (67)	
Black	425 (14)	251 (13)	174 (17)	
Hispanic	164(6)	87 (4)	77 (8)	
Other	212 (7)	141 (7)	71 (7)	
Comorbidities, n (%)				
Hypertension	743 (25)	446 (23)	297 (30)	0.016
Diabetes mellitus	470 (16)	290 (15)	180 (18)	0.030
Cardiovascular disease	217 (7)	138 (7)	79 (8)	0.951
Chronic pulmonary disease	266 (9)	164 (8)	102 (10)	0.524
Malignancies	168 (6)	89 (5)	79 (8)	<0.001
Risk factors of ARDS, n (%)				
Pneumonia	1609 (54)	1008 (51)	601 (60)	<0.001
Sepsis	459 (16)	328 (17)	131 (13)	0.009
Aspiration	400 (14)	266 (14)	134 (13)	0.893
Trauma	225 (8)	175 (9)	50 (5)	<0.001
Multiple transfusions	53 (2)	36 (2)	17 (2)	0.788

Organ failure at baseline, n (%)				
Cardiovascular	1729 (58)	1094 (56)	635 (64)	<0.001
Coagulation	441 (15)	265 (14)	176 (18)	0.003
Hepatic	349 (12)	200 (10)	149 (15)	<0.001
Creatinine at baseline, mg/dL	0.8 (0.6-1.0)	0.8 (0.6-1.0)	0.8 (0.6-1.1)	<0.001
Fluid balance on day 1, mL	1350 (90-3063)	1261 (16-3025)	1496 (233-3160)	0.047
Cumulative fluid balance of the first 3 days, mL	2938 (-66-6511)	2618 (-470-5984)	3792 (590-7881)	<0.001
Respiratory variables at baseline				
PaO_2:FiO_2, mmHg	134 (100-180)	138 (105-186)	124 (91-173)	<0.001
Respiratory rate, breaths/min	24 (18-29)	23 (18-28)	24 (20-30)	<0.001
VT/PBW, mL/Kg	6.8 (6.0-8.4)	6.9 (6.0-8.5)	6.6 (6.0-8.1)	0.017
Arterial pH	7.39 (7.34-7.44)	7.40 (7.35-7.44)	7.37 (7.32-7.43)	<0.001
$PaCO_2$, mmHg	40 (35-45)	39 (34-45)	40 (35-46)	0.257
Plateau pressure, cmH_2O	25 (21-30)	25 (21-30)	26 (22-31)	<0.001
Respiratory system compliance, mL/ cmH_2O	30 (23-40)	31 (24-41)	28 (22-38)	<0.001
PEEP, cmH_2O	10 (5-12)	10 (5-12)	10 (8-12)	<0.001
Driving pressure, cmH_2O	16 (12-20)	15 (12-20)	16 (12-21)	0.056
Outcomes				
90-day mortality, n (%)	728 (25)	338 (17)	390 (39)	<0.001
Organ failure-free days, days	22 (6-26)	23 (14-27)	12 (0-24)	<0.001

Ventilator-free days, days	19 (0-24)	21 (4-25)	7 (0-22)	<0.001
ICU-free days, days	17 (0-23)	19 (7-23)	6 (0-20)	<0.001

Abbreviations: AKI, acute kidney injury; n, number; BMI, body mass index; ARDS, acute respiratory distress syndrome; PaO_2:FiO_2, partial pressure of arterial oxygen to fraction of inspired oxygen ratio; VT, tidal volume; PBW, predicted body weight; PEEP, positive end-expiratory pressure; ICU, intensive care unit.

Data are expressed as median (IQR), unless otherwise indicated.

eTable 2. Multivariable logistic regression analysis to explore the contribution of baseline driving pressure (independent variable) to the development of AKI (dependent variable) in a sensitivity analysis which does not exclude patients with early AKI.

Variable	Univariable analyses			Multivariable analysis		
	OR	95%CI	p value	OR	95%CI	p value
Age (increments of 1 year)	1.012	1.009-1.016	<0.001	1.013	1.007-1.018	<0.001
Female sex	0.768	0.686-0.859	<0.001	0.718	0.604-0.853	<0.001
BMI (increments of 1 kg/cm^2)	1.022	1.014-1.029	<0.001	1.013	1.003-1.024	0.015
Diabetes mellitus	1.940	1.673-2.250	<0.001	1.964	1.579-2.443	<0.001
Cardiovascular failure	1.760	1.567-1.977	<0.001	1.466	1.220-1.761	<0.001
Coagulation failure	1.978	1.698-2.305	<0.001	2.114	1.666-2.681	<0.001
Hepatic failure	2.076	1.750-2.462	<0.001	1.781	1.376-2.305	<0.001
Fluid balance on day 1 (increment of 100 ml)	1.009	1.007-1.011	<0.001	1.007	1.005-1.010	<0.001
Baseline PaO_2:FiO_2 (increments of 10 mmHg)	0.979	0.970-0.987	<0.001	1.005	0.992-1.020	0.443
Baseline respiratory rate (increments of 1 breath/min)	1.033	1.025-1.040	<0.001	1.028	1.015-1.041	<0.001
Baseline VT/PBW (increments of 1 ml/Kg)	0.980	0.953-1.008	0.161	0.997	0.979-1.015	0.733
Baseline respiratory system compliance (increments of 1 ml/cmH_2O)	0.998	0.995-1.001	0.159	1.001	0.997-1.005	0.715
Baseline PEEP (increments of 1 cmH_2O)	1.050	1.036-1.065	<0.001	1.056	1.029-1.083	<0.001
Baseline driving pressure	1.010	0.999-1.020	0.064	1.038	1.020-1.056	<0.001

(increments of 1 cmH_2O)

Abbreviations: AKI, acute kidney injury; OR, odds ratio; CI, confidence interval; BMI, body mass index; PaO_2:FiO_2, partial pressure of arterial oxygen to fraction of inspired oxygen ratio; VT, tidal volume; PBW, predicted body weight; PEEP, positive end-expiratory pressure.
The present sensitivity analysis included a total of 5177 patients; namely, 3217 patients with AKI (both patients with early AKI and patients with late AKI) and 1960 patients with no AKI.

eTable 3. Multivariable logistic regression analysis to explore the contribution of baseline driving pressure (independent variable) to the development of late AKI (dependent variable) in a sensitivity analysis which included patients who developed AKI later than seven days following onset of ARDS.

Variable	Univariable analyses			Multivariable analysis		
	OR	95%CI	p value	OR	95%CI	p value
Age (increments of 1 year)	1.012	1.008-1.017	<0.001	1.018	1.011-1.025	<0.001
Female sex	0.859	0.744-0.992	0.039	0.795	0.638-0.991	0.041
BMI (increments of 1 kg/cm^2)	1.007	0.997-1.016	0.163	1.004	0.990-1.018	0.558
Diabetes mellitus	1.199	0.984-1.462	0.071	1.140	0.858-1.516	0.366
Cardiovascular failure	1.340	1.157-1.552	<0.001	1.273	1.014-1.598	0.038
Coagulation failure	1.233	1.007-1.510	0.043	1.171	0.855-1.603	0.325
Hepatic failure	1.410	1.126-1.766	0.003	1.654	1.179-2.320	0.004
Fluid balance on day 1 (increment of 100 ml)	1.004	1.001-1.006	0.010	1.001	0.998-1.005	0.548
Baseline PaO_2:FiO_2 (increments of 10 mmHg)	0.980	0.969-0.991	<0.001	1.005	0.988-1.023	0.554
Baseline respiratory rate (increments of 1 breath/min)	1.009	1.0-1.019	0.054	1.002	0.986-1.018	0.826
Baseline VT/PBW (increments of 1 ml/Kg)	0.996	0.979-1.014	0.687	0.984	0.940-1.032	0.511
Baseline respiratory system compliance (increments of 1 ml/cmH_2O)	0.992	0.987-0.997	<0.001	0.999	0.994-1.004	0.672
Baseline PEEP (increments of 1 cmH_2O)	1.034	1.015-1.052	<0.001	1.048	1.015-1.081	0.004
Baseline driving pressure	1.033	1.020-1.047	<0.001	1.060	1.036-1.084	<0.001

(increments of 1 ml/cmH_2O)

Abbreviations: AKI, acute kidney injury; OR, odds ratio; CI, confidence interval; BMI, body mass index; PaO_2:FiO_2, partial pressure of arterial oxygen to fraction of inspired oxygen ratio; VT, tidal volume; PBW, predicted body weight; PEEP, positive end-expiratory pressure.

The present sensitivity analysis included patients who developed AKI later than seven days following onset of ARDS; i.e., the “late AKI” group included 3217 patients who developed AKI from day 3 to day 28 following onset of ARDS. The “no AKI group” included 1960 patients.

eTable 4. Adjusted logistic regressions for late AKI prediction in survivors and non-survivors.

	B	SE	Wald	p value	OR	95% CI
*Driving pressure (non-survivors), SD	.153	.138	1.229	.268	1.166	.889-1.529
*Driving pressure (survivors), SD	.269	.110	5.999	.014	1.309	1.055-1.624

Abbreviations: AKI, acute kidney injury; OR, odds ratio; CI, confidence interval; SD, standard deviation.

*Both analyses were adjusted for: age, sex, body mass index, diabetes mellitus, organ failures (namely, cardiovascular, coagulation, and hepatic) at baseline, fluid balance, baseline PaO_2:FiO_2 ratio, respiratory rate, tidal volume, respiratory system compliance and PEEP.

eTable 5. Differences in cumulative fluid balance and driving pressure between patients with and without late AKI.

	No AKI	Late AKI
dFB, mL	2475 (-1366 - 6567)	3340 (588 - 6828)*
dDP, cmH_2O	-2 (-6 - 3)	-2 (-6 - 3)

*P<0.001, Mann-Whitney test.

Abbreviations: AKI, acute kidney injury; dDP, difference in driving pressure; dFB, difference in cumulative fluid balance.

eTable 6. Linear regressions, with dDP as dependent and dFB as independent variable.

	B	SE	Beta	t	p value	95% CI	
dFB (late AKI)	.000077	.000059	.069	1.308	.192	-.000039	.000194
dFB (no AKI)	.000173	.000043	.170	3.980	**.001**	.000087	.000258

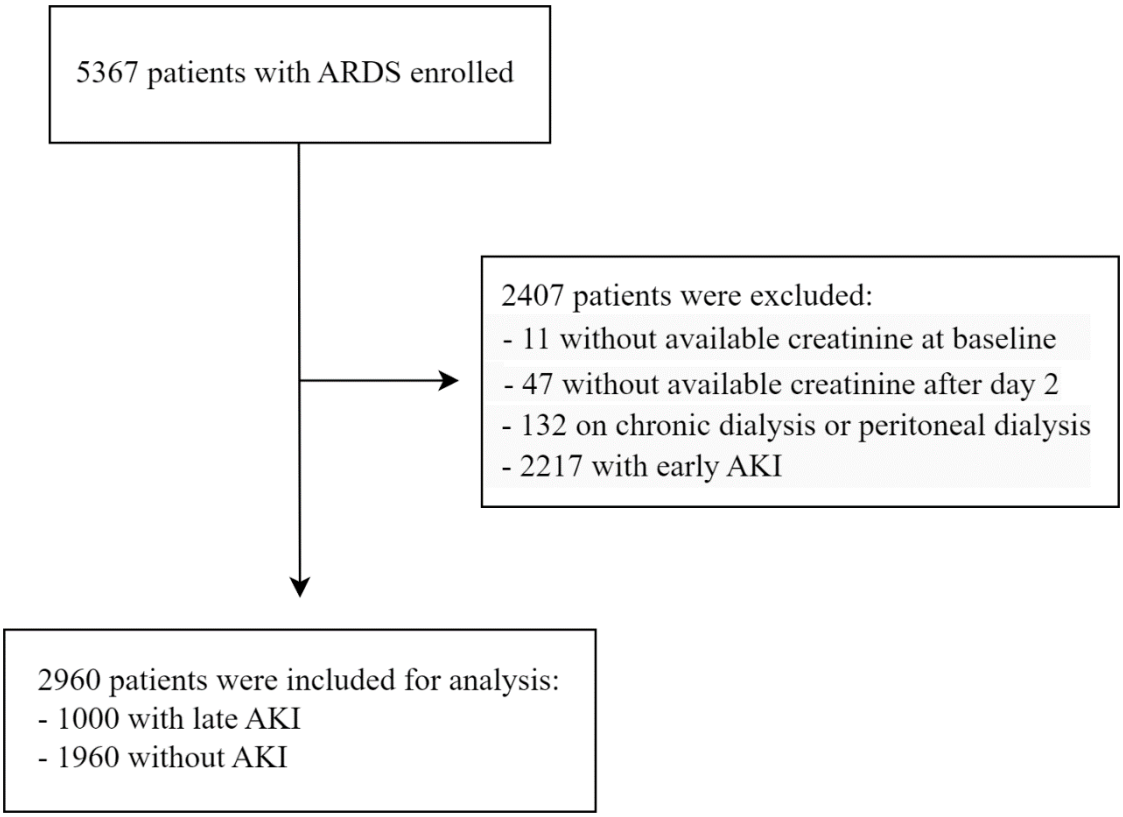
Abbreviations: AKI, acute kidney injury; CI, confidence interval; dDP, difference in driving pressure; dFB, difference in cumulative fluid balance.

eTable 7. Multivariable logistic regression analysis to explore the contribution of mean driving pressure (independent variable) to the development of late AKI (dependent variable).

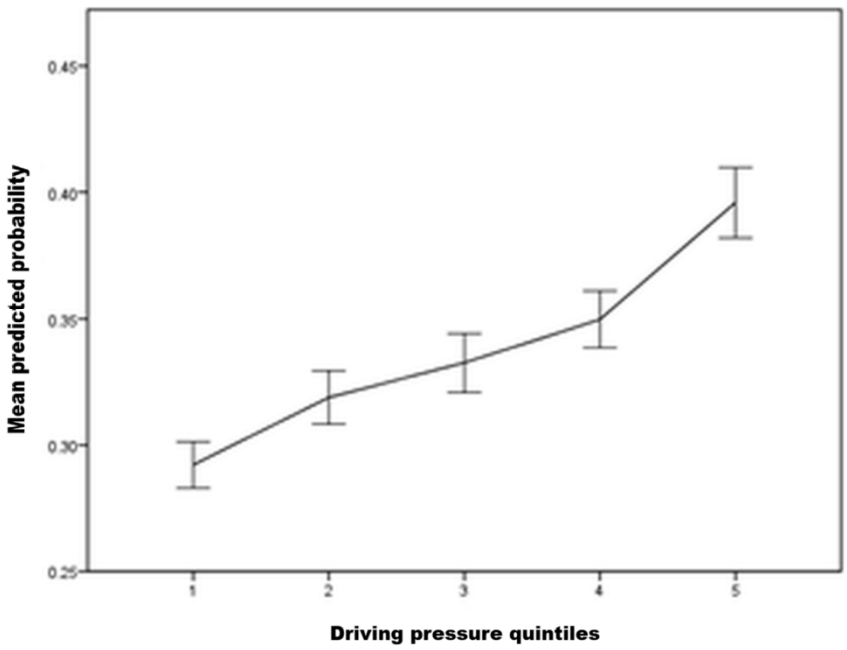
Variable	Univariable analyses			Multivariable analysis		
	OR	**95%CI**	**p value**	**OR**	**95%CI**	**p value**
Age (increments of 1 year)	1.008	1.003 - 1.013	<0.001	1.012	1.005-1.018	<0.001
Female sex	0.992	0.852 - 1.155	0.919	0.927	0.757-1.135	0.462
BMI (increments of 1 kg/cm^2)	1.013	1.003-1.023	0.010	1.001	0.988-1.013	0.937
Diabetes mellitus	1.254	1.022 - 1.538	0.030	1.322	1.018-1.717	0.036
Cardiovascular failure	1.377	1.178 - 1.611	<0.001	1.181	0.959-1.455	0.118
Coagulation failure	1.366	1.110 - 1.682	0.003	1.311	0.997-1.723	0.053
Hepatic failure	1.541	1.227 - 1.934	<0.001	1.625	1.204-2.193	0.001
Fluid balance on day 1 (increment of 100mL)	1.003	1.0 - 1.006	0.041	1.002	0.998-1.005	0.358
Baseline PaO_2:FiO_2 (increments of 10 mmHg)	0.965	0.953 - 0.977	<0.001	1.024	1.007-1.042	0.005
Mean respiratory rate (increments of 1 breath/min)	1.039	1.026-1.052	<0.001	1.011	0.993-1.028	0.235
Mean VT/PBW (increments of 1 ml/Kg)	0.964	0.922-1.009	0.119	0.982	0.927-1.039	0.529
Mean respiratory system compliance (increments of 1 ml/cmH_2O)	0.994	0.989-0.999	0.013	1.0	0.994-1.007	0.878
Mean PEEP (increments of 1 cmH_2O)	1.174	1.148-1.202	<0.001	1.210	1.170-1.252	<0.001
Mean driving pressure (increments of 1 cmH_2O)	1.025	1.011-1.040	<0.001	1.054	1.030-1.078	<0.001

Abbreviations: AKI, acute kidney injury; OR, odds ratio; CI, confidence interval; BMI, body mass index; PaO_2:FiO_2, partial pressure of arterial oxygen to fraction of inspired oxygen ratio; VT, tidal volume; PBW, predicted body weight; PEEP, positive end-expiratory pressure.

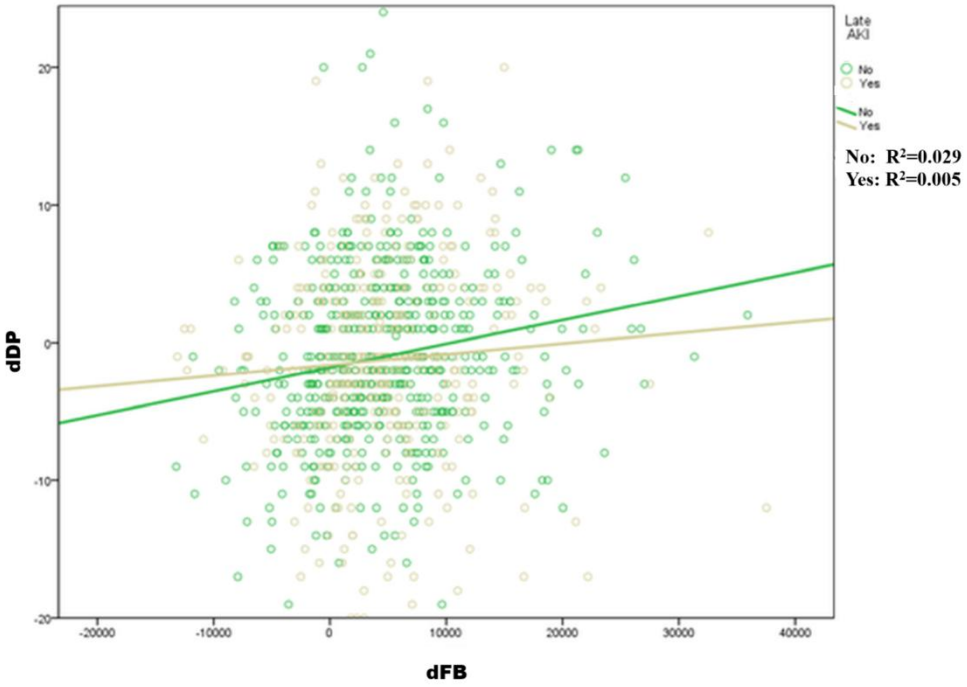
eFigure 1. Study flow diagram. *Abbreviations*: AKI, acute kidney injury; ARDS, acute respiratory distress syndrome.



eFigure 2. Plot of predicted probabilities for late AKI against driving pressure quintiles. Each bar represents mean value with 95% CI. *Abbreviations*: AKI, acute kidney injury; CI, confidence interval.



eFigure 3. Dot plot between dDP and DFB with regression lines fitted for both groups, late AKI and no AKI. *Abbreviations*: AKI, acute kidney injury; dDP, difference in driving pressure; dFB, difference in cumulative fluid balance.



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PROLONGED MECHANICAL VENTILATION IN ACUTE RESPIRATORY DISTRESS SYNDROME

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ABSTRACT—**Purpose:** Trajectory of acute respiratory distress syndrome (ARDS) spans from rapidly improving cases to cases receiving prolonged mechanical ventilation (PMV). We attempted to estimate temporal trends of prevalence and mortality of PMV and to identify risk factors associated with mortality of patients with ARDS receiving PMV. **Methods:** We performed a secondary analysis of individual patient data from six randomized controlled clinical trials conducted by the ARDS Network. Prolonged mechanical ventilation was defined as the need for mechanical ventilation for >21 consecutive days. **Results:** Of 4,216 patients with ARDS, 646 (15.3%) received PMV. Prevalence of PMV gradually declined from 18.4% in the ARDS Network: Low-Tidal-Volume Trial (published in 2000) trial to 10.9% in the SAILS (2014) trial ($R^2 = 0.728$, $P = 0.031$). Ninety-day mortality of patients receiving PMV did not change over time ($R^2 = 0.271$, $P = 0.290$) and remained as high as 36.8%. In the three most recent trials, risk factors associated with mortality among the 250 patients with ARDS receiving PMV included age, malignancy, pneumonia as the cause of ARDS, coagulation dysfunction, and hepatic dysfunction during the first 21 days after trial enrollment. **Conclusion:** Although prevalence of PMV among patients enrolled in ARDS Network trials gradually declined, mortality did not change. Risk factors associated with mortality were mostly nonmodifiable.

KEYWORDS—Acute hypoxemic respiratory failure; intensive care unit; epidemiology; chronic critical illness

INTRODUCTION

Acute respiratory distress syndrome (ARDS), an entity with considerable attributable mortality (1), is heterogeneous (2). As an indication of the heterogeneity of ARDS, there are patients whose hypoxemia improves rapidly (i.e., within 24 h) (3,4), others whose severe hypoxemia persists for several days (5), and still others who receive prolonged mechanical ventilation (PMV). Patients with ARDS, as opposed to those without ARDS, are indeed four times more likely to receive PMV (6).

Based on studies involving unselected critically ill patients (i.e., not specifically patients with ARDS), PMV poses a constant challenge for the treating clinicians as it is associated with poor outcomes (7,8). In addition, it is very costly as, for example, patients with PMV occupy 30% of general intensive care unit (ICU) beds (6,9). Given its immense clinical and financial burden on healthcare systems, PMV has emerged as an important research priority (10). Prolonged mechanical ventilation was indeed recognized as an important research priority as early as 2005 at a National Association for Medical Direction of Respiratory Care Consensus Conference. That Consensus Conference report stated that "the number of patients meeting the definition of PMV will likely continue to increase" over time and that "predicting mortality outcomes is vital" (11). Nevertheless, subsequent relevant evidence specifically involving patients with ARDS is limited.

Having the above considerations into mind, we endeavored to take advantage of the large high-quality databases of randomized controlled trials conducted by the ARDS Network to estimate temporal trends of prevalence and mortality of PMV and to identify risk factors associated with mortality of patients with ARDS receiving PMV.

METHODS

Study design and patient population

We performed a secondary analysis by obtaining individual patient data from subjects enrolled in the following 6 randomized controlled trials conducted by the ARDS Network: Low-Tidal-Volume Trial (ARMA) (12), Assessment of Low Tidal Volume and Elevated End-expiratory Volume to Obviate Lung Injury Trial (ALVEOLI) (13), Fluid and Catheter Treatment Trial (FACTT) (14), Albuterol for the Treatment of Acute Lung Injury Trial (ALTA) (15), Early versus Delayed Enteral Nutrition Trial (EDEN) (16), and Statins for Acutely Injured Lungs from Sepsis Trial (SAILS) (17). All included subjects were endotracheally intubated and had ARDS. As previously (18–20), we were granted access to data after submitting a prospective protocol to the Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC) of the National Heart, Lung, and Blood Institute (NHLBI). Because the data would be received in deidentified form (nonhuman subjects research), the institutional review board of Evangelismos Hospital waived the need of informed consent and approved the study (protocol number 140/5-5-2022).

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Prolonged mechanical ventilation in acute respiratory distress syndrome

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Purpose: Trajectory of acute respiratory distress syndrome (ARDS) spans from rapidly improving cases to cases receiving prolonged mechanical ventilation (PMV). We attempted to estimate temporal trends of prevalence and mortality of PMV and to identify risk factors associated with mortality of patients with ARDS receiving PMV.

Methods: We performed a secondary analysis of individual patient data from six randomized controlled clinical trials conducted by the ARDS Network. PMV was defined as the need for mechanical ventilation for >21 consecutive days.

Results: Of 4216 patients with ARDS, 646 (15.3%) received PMV. Prevalence of PMV gradually declined from 18.4% in the ARMA (published in 2000) trial to 10.9% in the SAILS (2014) trial (R^2=0.728, p=0.031). 90-day mortality of patients receiving PMV did not change over time (R^2=0.271, p=0.290) and remained as high as 36.8%. In the three most recent trials, risk factors associated with mortality among the 250 patients with ARDS receiving PMV included age, malignancy, pneumonia as the cause of ARDS, coagulation dysfunction and hepatic dysfunction during the first 21 days after trial enrollment.

Conclusion: Although prevalence of PMV among patients enrolled in ARDS Network trials gradually declined, mortality did not change. Risk factors associated with mortality were mostly non-modifiable.

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Having the above considerations into mind, we endeavored to take advantage of the large high-quality databases of randomized controlled trials conducted by the ARDS Network in order to estimate temporal trends of prevalence and mortality of PMV and to identify risk factors associated with mortality of patients with ARDS receiving PMV.

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Evangelismos Hospital waived the need of informed consent and approved the study (protocol number 140/5-5-2022).

Study Objectives and Definitions

The present secondary analysis had three objectives. The first objective was to estimate temporal trends of prevalence of PMV in clinical trials of ARDS. The second objective was to estimate temporal trends of mortality of patients with ARDS receiving PMV. Finally, the third objective was to identify risk factors associated with mortality of patients with ARDS receiving PMV.

With regard to the definition of PMV, periods of ventilator dependence ranging from 2 days to 28 days have been used in the literature (21, 22). However, most papers, including the abovementioned NAMDRC Consensus Conference report (11), used a threshold of 21 days (10). Accordingly, in this secondary analysis, PMV was defined as the requirement for invasive mechanical ventilation for more than 21 consecutive days after trial enrollment.

Statistical Analysis

We presented continuous variables as median with interquartile range (IQR) and compared them using the non-parametric Mann-Whitney U test or Kruskal-Wallis H test, as appropriate. We presented categorical variables as percentages and compared them using the Chi-squared or Fisher's exact test, as appropriate. We estimated the prevalence and mortality of PMV across time via a simple linear regression model, with time as the independent variable and within-study prevalence of PMV (or, respectively, mortality of patients with PMV) as the dependent variable. We carried out four subgroup analyses involving only medical patients (i.e., after exclusion of patients with ARDS following trauma or elective surgery); involving only surgical patients (i.e., patients with ARDS following trauma or elective surgery); involving only patients with pulmonary causes (namely, pneumonia and aspiration) of ARDS; and involving only patients with extrapulmonary causes of ARDS.

In order to identify risk factors associated with mortality of patients with ARDS receiving PMV, we utilized a multivariate binary logistic regression model with 90-day mortality (i.e., the primary outcome of the present analysis) as the dependent variable, using all available information on mortality and risk factors. In the light of previous contributions involving the general ICU population (8, 9), we considered the following risk factors for inclusion in the model: age, baseline severity of illness [as assessed by the Acute Physiology and Chronic Health Evaluation (APACHE III) score], malignancy, pneumonia as the cause of ARDS, persistent severe ARDS (defined as previously) (5), coagulation dysfunction and hepatic dysfunction during the first 21 days after trial enrollment. We presented relevant results as odds ratio (OR) and 95% confidence intervals (CI). All p values were two-sided and thought to

denote statistical significance if equal to or less than 0.05. We performed statistical analyses using SPSS software version 28.0 (SPSS, Inc., Chicago, IL) and GraphPad Prism version 9.0.0, (GraphPad Software, La Jolla, California, USA).

RESULTS

Temporal trends of prevalence and mortality of PMV

Out of 4216 patients with ARDS enrolled in six ARDS Network trials (12-17), 646 (15.3%) patients received PMV. **Figure 1** presents temporal trends of prevalence of PMV in clinical trials of ARDS. Prevalence of PMV gradually declined from 18.4% in the ARMA (published in 2000) trial to 10.9% in the SAILS (2014) trial (R^2=0.728, p=0.031). During the same time period, percentage of patients with ARDS who were discharged alive without receiving PMV gradually increased from 52.3% in the ARMA trial to 65.6% in the SAILS trial (R^2=0.780, p=0.020; **Figure 1**). This was also the case (i.e., prevalence of PMV gradually declined, while percentage of patients with ARDS who were discharged alive without receiving PMV gradually increased) in the subgroup analyses involving only medical patients or only patients with pulmonary causes of ARDS, but not in the subgroup analyses involving only surgical patients or only patients with extrapulmonary causes of ARDS (**Supplemental Figure 1**).

Figure 2 presents temporal trends of 90-day mortality of patients with ARDS receiving PMV. Mortality of patients receiving PMV did not change over time in clinical trials of ARDS (R^2=0.271, p=0.290) and remained as high as 36.8%. This was also the case (i.e., mortality of patients receiving PMV did not change over time) in the subgroup analyses involving only medical patients or only surgical patients or only patients with pulmonary causes of ARDS or only patients with extrapulmonary causes of ARDS (**Supplemental Figure 2**).

Baseline characteristics and clinical course of patients with PMV

To better reflect modern clinical practice, the remainder of our analyses considered only data from the three most recently published ARDS Network trials; namely, ALTA, EDEN, and SAILS (all published after 2010) (15-17). Of the 1853 patients with ARDS enrolled in these trials (15-17), 250 (13.5%) patients received PMV.

Table 1 presents baseline characteristics and initial management of the 250 patients with ARDS receiving PMV. Out of those 250 patients, 92 (36.8%) died by day 90. Non-survivors, as opposed to survivors, were older [59.0 (44.3-69.0) vs 51.5 (42.0-63.0) years; p=0.012], had higher APACHE III score [102.0 (83.5-123.3) vs 93.0 (78.0-106.0); p=0.006], were more likely to have malignancy [12 (13.0%) vs 3 (1.9%); p<0.001], were more likely to have pneumonia as a cause of ARDS [65 (70.7%) vs 91 (57.6%); p=0.040] and had higher baseline partial pressure of arterial oxygen to fraction of inspired oxygen ratio (PaO_2:FiO_2) [157.8 (106.5-192.4) vs 118.1

(89.7-160.0); p<0.001]. There was no difference between non-survivors and survivors in terms of initial management, such as ventilator settings and cumulative fluid balance (**Table 1**).

Table 2 presents the clinical course of the 250 patients with ARDS receiving PMV. Non-survivors, as opposed to survivors, were more likely to experience coagulation dysfunction [64 (69.6%) vs 60 (38.0%); p<0.001] and hepatic dysfunction [35 (38.0%) vs 39 (24.7%); p=0.026] during the first 21 days after trial enrollment (**Table 2)**.

Risk factors associated with mortality of patients with ARDS receiving PMV

Table 3 presents a multivariable binary logistic regression analysis to identify risk factors associated with 90-day mortality of patients with ARDS receiving PMV. Risk factors independently associated with mortality were age (OR 1.03, 95% CI 1.01-1.05), malignancy (OR 5.77, 95% CI 1.45-22.95), pneumonia as the cause of ARDS (OR 2.56, 95% CI 1.32- 4.97), coagulation dysfunction (OR 4.17, 95% CI 2.17-8.01) and hepatic dysfunction (OR 2.07, 95% CI 1.07-4.00) during the first 21 days after trial enrollment (**Table 3**).

DISCUSSION

By incorporating individual patient data from over 4200 subjects with ARDS enrolled in six high-quality randomized controlled trials conducted by the ARDS Network, this secondary analysis showed that prevalence of PMV gradually declined from 18.4% (in 2000) to 10.9% (in 2014). 90-day mortality of patients receiving PMV did not change over the same time period and remained as high as 36.8%. Finally, age, malignancy, pneumonia as the cause of ARDS, coagulation dysfunction and hepatic dysfunction during the first 21 days after trial enrollment were risk factors associated with mortality among patients with ARDS receiving PMV.

We found that prevalence of PMV in trials of ARDS significantly declined over time. This decline in prevalence of PMV was also accompanied by an increase in the percentage of patients discharged alive without receiving PMV. Indeed, as shown in **Figure 1**, the percentage of patients with ARDS who were discharged alive without receiving PMV gradually increased from 52.3% in the ARMA trial to 65.6% in the SAILS trial. Taken together, these findings may reflect advances in supportive care of such patients, including lung protective ventilation (12), conservative fluid management (14), and protocolized weaning strategies that were required or recommended in later phase ARDS Network trials. Interestingly, as shown in our subgroup analyses (**Supplemental Figure 1**), improvement in prevalence of PMV mostly involved medical rather than surgical patients with ARDS. This finding may justify ongoing research on ARDS following trauma or elective surgery (23**-25**).

Improvement in prevalence of PMV was not found to be accompanied by a decrease in mortality of patients with ARDS receiving PMV. Indeed, as shown in **Figure 2**, 90-day mortality of patients receiving PMV did not change over time in trials of ARDS and this was consistent across various subgroups **(Supplemental Figure 2)**. These findings, taken together, suggest that contemporary management of ARDS may be successfully reducing the number of episodes of PMV but that work remains to be done to identify practices that lower mortality when recovery is prolonged.

To advance management of patients with PMV, it may be reasonable to first identify risk factors associated with mortality among patients receiving PMV. Considerable relevant research (which identified age and coagulation dysfunction as important risk factors) has been previously done in the general ICU population, not limited to patients with ARDS (26, 27). In the present analysis, we focused on patients with ARDS and we identified, apart from age and coagulation dysfunction, malignancy, pneumonia as the cause of ARDS, and hepatic dysfunction. This finding may have important implications for clinical trialists as it highlights a challenge. Any intervention to lower mortality in clinical trials of ARDS should target patients with prolonged mechanical ventilation (given that they constitute an increasingly larger proportion of total deaths); yet, mortality of those patients is mostly affected by non-modifiable risk factors.

We found that, among patients with ARDS receiving PMV, non-survivors had higher oxygenation (as assessed by PaO_2:FiO_2) at baseline than survivors by day 90 (**Table 2**). This seemingly counterintuitive finding might be explained by selection bias. Our study population of 250 patients receiving PMV might include selectively the most vulnerable patients among those with high oxygenation at baseline (as the remaining were discharged alive before day 21) and the most resilient patients among those with low oxygenation at baseline (as the remaining died before day 21). Briefly, in the selected group of patients who are alive but still receive mechanical ventilation at day 21, oxygenation at baseline may not predict long-term survival.

The current analysis has several limitations. First, it is subject to the inherent limitations (such as residual confounding) of retrospective analyses. However, the analysis was based on meticulously collected data from six high-quality randomized controlled trials (12-17). Second, given that even the most recent three randomized controlled trials (that provided data from the 250 subjects analyzed in **Tables 1-3**) were published between 2011 and 2014 (15-17), one may question their relevance with current clinical practice of mechanical ventilation. However, current clinical practice is based on principles, which were known and widely appreciated by 2011; namely lung protective ventilation, conservative fluid management and personalized weaning strategies (12, 14). Thirdly, although the principles of mechanical ventilation remain the same (28), we acknowledge that the pandemic of coronavirus disease (COVID-19) led to changes in care of patients with respiratory

failure/ARDS, such as increase in implementation of high-flow nasal oxygen (before intubation) and prone positioning (before and after intubation) (29). We lacked data to examine whether such changes in care of patients triggered by COVID-19 might affected the epidemiology of PMV. Fourth, not only our clinical practice but also our perception of syndromes, such as ARDS or sepsis, may have been changed since 2014 (i.e., when the most recent ARDSNet trial was published) (17). Indeed, definition of sepsis was modified in 2016 to emphasize the critical presence of organ failure (30), while a modification of definition of ARDS was recently proposed (31). Both syndromes are perceived as heterogenous entities with distinct phenotypes (32, 33).

Fifth, while the inclusion criteria were similar across the trials analyzed, exclusion criteria differed such that study cohorts may not be directly comparable. Also, exclusion of a considerable proportion of patients due to very restrictive exclusion criteria of randomized controlled trials might negatively affect both extrapolation of findings in real world and accurate estimations of prevalence of PMV (34). Even so, estimates of trends of prevalence of PMV over time (i.e., the main purpose of this project) should be accurate. Sixth, although we selected variables to be included in the regression model based on previous contributions (8, 9, 26, 27) and our own clinical expertise, we still acknowledge that other variables (such as pre-ICU comorbidities other than malignancy) could also have been used. Seventh, we lacked data to explore whether outcomes of patients with ARDS receiving PMV might have been influenced by nosocomial infections and patient/surrogate decision making. The latter has been found to be often characterized by unreasonably optimistic expectations (35). Finally, we acknowledge that prolonged mechanical ventilation is just a feature (albeit the cardinal one) of the broad syndrome of chronic critical illness (21).

CONCLUSIONS

This analysis of 4216 patients enrolled in six ARDS Network trials showed that prevalence of PMV among patients with ARDS gradually declined, while their mortality did not change. Risk factors associated with mortality were mostly non-modifiable. These findings may have important implications for clinical trialists.

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Authors' Contributions

IA designed the study, contributed to data interpretation and wrote the first draft of the manuscript. VGG contributed to study design, undertook statistical analyses, contributed to data interpretation and critically revised the manuscript for important intellectual content. EP contributed to data cleaning, data interpretation and critically revised the manuscript for important intellectual content. GP and VK contributed to data interpretation, critically revised the manuscript for important intellectual content and provided administrative support. BTT conceived of the study, contributed to data interpretation and critically revised the manuscript for important intellectual content. IIS contributed to study design and data interpretation, critically revised the manuscript for important intellectual content, supervised the study and is the guarantor. All authors read and approved the final manuscript.

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FIGURES

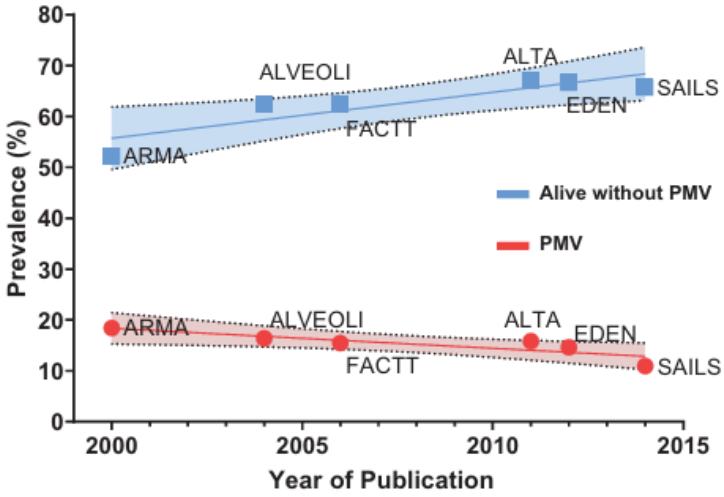


Figure 1. Temporal trends of prevalence of prolonged mechanical ventilation in clinical trials of acute respiratory distress syndrome. Prevalence of prolonged mechanical ventilation (PMV) gradually declined from 18.4% in the ARMA (published in 2000) trial to 10.9% in the SAILS (2014) trial (R^2=0.728, p=0.031). During the same time period, percentage of patients with acute respiratory distress syndrome (ARDS) who were discharged alive without receiving PMV gradually increased from 52.3% in the ARMA trial to 65.6% in the SAILS trial (R^2=0.780, p=0.020).

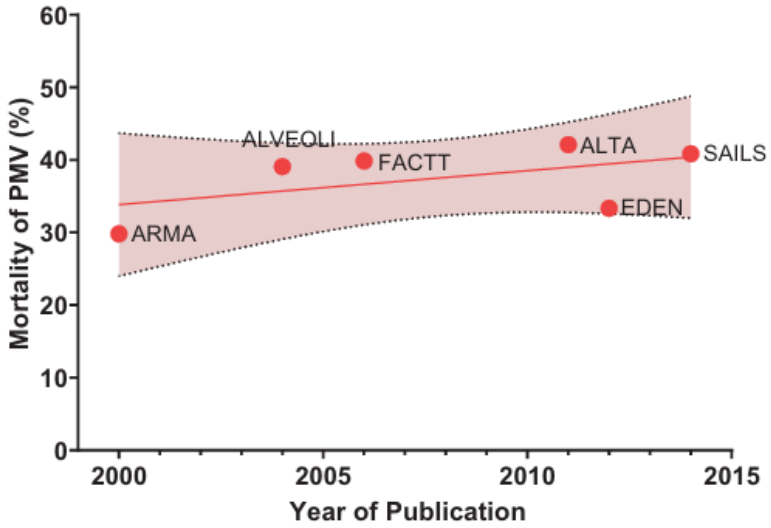


Figure 2. Temporal trends of 90-day mortality of patients with acute respiratory distress syndrome receiving prolonged mechanical ventilation. Mortality of patients with acute respiratory distress syndrome (ARDS) receiving prolonged mechanical ventilation (PMV) did not change over time in clinical trials conducted by the ARDS Network (R^2=0.271, p=0.290).

Table 1. Baseline characteristics and initial management of 250 patients with ARDS receiving PMV.				
Variable[a]	**Total (n=250)**	**Non-survivors (n=92)**	**Survivors (n=158)**	**p value**
Age (years)	55.0 [42.0-65.0]	59.0 [44.3-69.0]	51.5 [42.0-63.0]	0.012
Female sex	119 (47.6%)	46 (50.0%)	73 (46.2%)	0.562
Race				0.613
White	161 (64.4%)	61 (66.3%)	100 (63.3%)	
Black	42 (16.8%)	17 (18.5%)	25 (15.8%)	
Hispanic or Latino	38 (15.2%)	11 (12.0%)	27 (17.1%)	
Other	8 (3.2%)	2 (2.2%)	6 (3.8%)	
Body Mass Index (kg/m^2)	29.2 [23.3-35.6]	28.0 [22.9-34.6]	30.2 [23.7-36.3]	0.149
APACHE III score	96.0 [79.0-114.0]	102.0 [83.5-123.3]	93.0 [78.0-106.0]	0.006
Usage of vasopressors within 24 hours prior to trial enrollment	154 (61.6%)	60 (65.2%)	94 (59.5%)	0.370
Comorbidity				
Any comorbidity	162 (64.8%)	67 (72.8%)	95 (60.1%)	0.043
Malignancy[b]	15 (6.0%)	12 (13.0%)	3 (1.9%)	<0.001
Cardiovascular disease[c]	120 (48.0%)	46 (50.0%)	74 (46.8%)	0.629
Liver disease[d]	16 (6.4%)	8 (8.7%)	8 (5.1%)	0.258
Chronic pulmonary disease	36 (14.4%)	17 (18.5%)	19 (12.0%)	0.161
Immunosuppression[e]	37 (14.8%)	23 (25.0%)	14 (8.9%)	<0.001
Cause of ARDS				
Pneumonia	156 (62.4%)	65 (70.7%)	91 (57.6%)	0.040
Sepsis	48 (19.2%)	15 (16.3%)	33 (20.9%)	0.375
Trauma	13 (5.2%)	4 (4.3%)	9 (5.7%)	0.773
Aspiration	19 (7.6%)	4 (4.3%)	15 (9.5%)	0.139
Physiological parameters on the day of trial enrollment[f]				
Tidal volume (ml/kg)	6.2 [6.0-7.4]	6.4 [6.0-7.8]	6.1 [5.9-7.1]	0.220
Respiratory rate (breaths/minute)	26.0 [20.0-31.0]	26.0 [20.0-31.0]	26.0 [21.0-32.0]	0.474
PEEP (cmH_2O)	10.0 [5.0-12.0]	10.0 [5.0-12.0]	10.0 [5.3-14.0]	0.143
Pdriving (cmH_2O)	15.0 [12.0-20.0]	15.0 [12.0-18.0]	16.0 [12.0-20.0]	0.310
PaO_2:FiO_2	129.5 [94.7-176.0]	157.8 [106.5-192.4]	118.1 [89.7-160.0]	<0.001

Cumulative fluid balance (ml, days 0-2)	3659 [503-7290]	3934.0 [503.0-7652.0]	3581.5 [395.5-7123.5]	0.359

Abbreviations: ARDS, acute respiratory distress syndrome; PMV, prolonged mechanical ventilation; APACHE, Acute Physiology and Chronic Health Evaluation; PEEP, positive end-expiratory pressure; Pdriving, driving pressure; PaO_2: FiO_2, partial pressure of arterial oxygen to fraction of inspired oxygen ratio.

[a] Data are presented as number (percentage) or median [interquartile range].

[b] Malignancy includes solid tumor with metastasis, leukemia and lymphoma.

[c] Cardiovascular disease includes prior myocardial infarction, hypertension, congestive heart failure, peripheral vascular disease and prior stroke with sequelae.

[d] Liver disease includes cirrhosis and hepatic failure with coma or encephalopathy.

[e] Immunosuppression refers to radiation, chemotherapy or administration of systemic steroids (greater than or equal to 0.3 mg/kg/day prednisone or equivalent) within the past six months.

[f] Trial enrollment (specifically, randomization) occurred a median of 1.0 day [1.0-2.0] after intubation and a median of 1.0 day [0.0-1.0] after diagnosis of ARDS. There were no statistically significant differences regarding the median time from intubation to trial enrollment (p=0.772) or regarding the median time from diagnosis of ARDS to trial enrollment (p=0.860) between the three randomized controlled trials (15-17).

Table 2. Clinical course during the first 21 days after trial enrollment of the 250 patients with ARDS receiving PMV.

Variable[a]	**Total (n=250)**	**Non-survivors (n=92)**	**Survivors (n=158)**	**p value**
Persistent severe ARDS[b]	50 (20.0%)	18 (19.6%)	32 (20.3%)	0.982
Non-pulmonary organ dysfunction[c]	231 (92.4%)	91 (98.9%)	140 (88.6%)	0.003
Coagulation dysfunction	124 (49.6%)	64 (69.6%)	60 (38.0%)	<0.001
Renal dysfunction	139 (55.6%)	56 (60.9%)	83 (52.5%)	0.201
Cardiovascular dysfunction	207 (82.8%)	82 (89.1%)	125 (79.1%)	0.043
Hepatic dysfunction	74 (29.6%)	35 (38.0%)	39 (24.7%)	0.026

Abbreviations: ARDS, acute respiratory distress syndrome; PMV, prolonged mechanical ventilation.

[a] Data are presented as number (percentage).

[b] Persistent severe ARDS was defined as partial pressure of arterial oxygen to fraction of inspired oxygen ratio ≤100 mmHg on the second day after trial enrollment. If that value was not available, then the next available value up to day 7 after trial enrollment was considered.

[c] Non-pulmonary organ dysfunctions were defined as follows: coagulation dysfunction as platelets <100 10^3/mm^3; hepatic dysfunction as bilirubin ≥2 mg/dL; cardiovascular

dysfunction as usage of vasopressors, and renal dysfunction as creatinine ≥2 mg/dL at any time up to day 21 after trial enrollment.

Table 3. Multivariable binary logistic regression analysis to identify risk factors associated with 90-day mortality of patients with ARDS receiving PMV.

Risk factor	OR	95% CI	p value
Age (increments of 1 year)	1.03	1.01-1.05	0.005
APACHE III (increments of 1)	1.00	0.99-1.01	0.708
Malignancy	5.77	1.45-22.95	0.013
Pneumonia as the cause of ARDS	2.56	1.32-4.97	0.005
Persistent severe ARDS[a]	1.19	0.56-2.53	0.656
Coagulation dysfunction[b]	4.17	2.17-8.01	<0.001
Hepatic dysfunction[c]	2.07	1.07-4.00	0.030

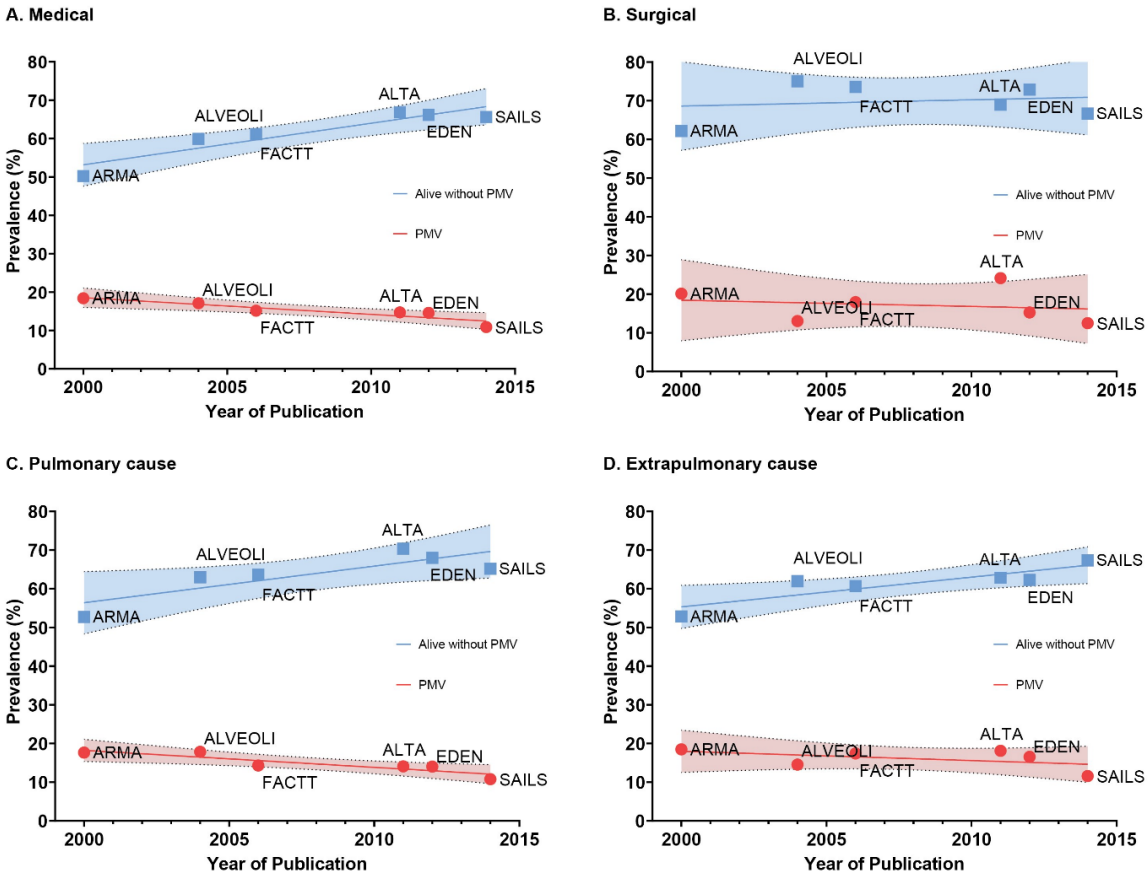
Abbreviations: ARDS, acute respiratory distress syndrome; PMV, prolonged mechanical ventilation; OR, odds ratio; CI, confidence intervals; APACHE, Acute Physiology and Chronic Health Evaluation.

[a] Persistent severe ARDS was defined as partial pressure of arterial oxygen to fraction of inspired oxygen ratio ≤100 mmHg on the second day after trial enrollment. If that value was not available, then the next available value up to day 7 after trial enrollment was considered.
[b] Coagulation dysfunction was defined as platelets <100 10^3/mm^3 at any time up to day 21 after trial enrollment.
[c] Hepatic dysfunction was defined as bilirubin ≥2 mg/dL at any time up to day 21 after trial enrollment.

Data Supplement

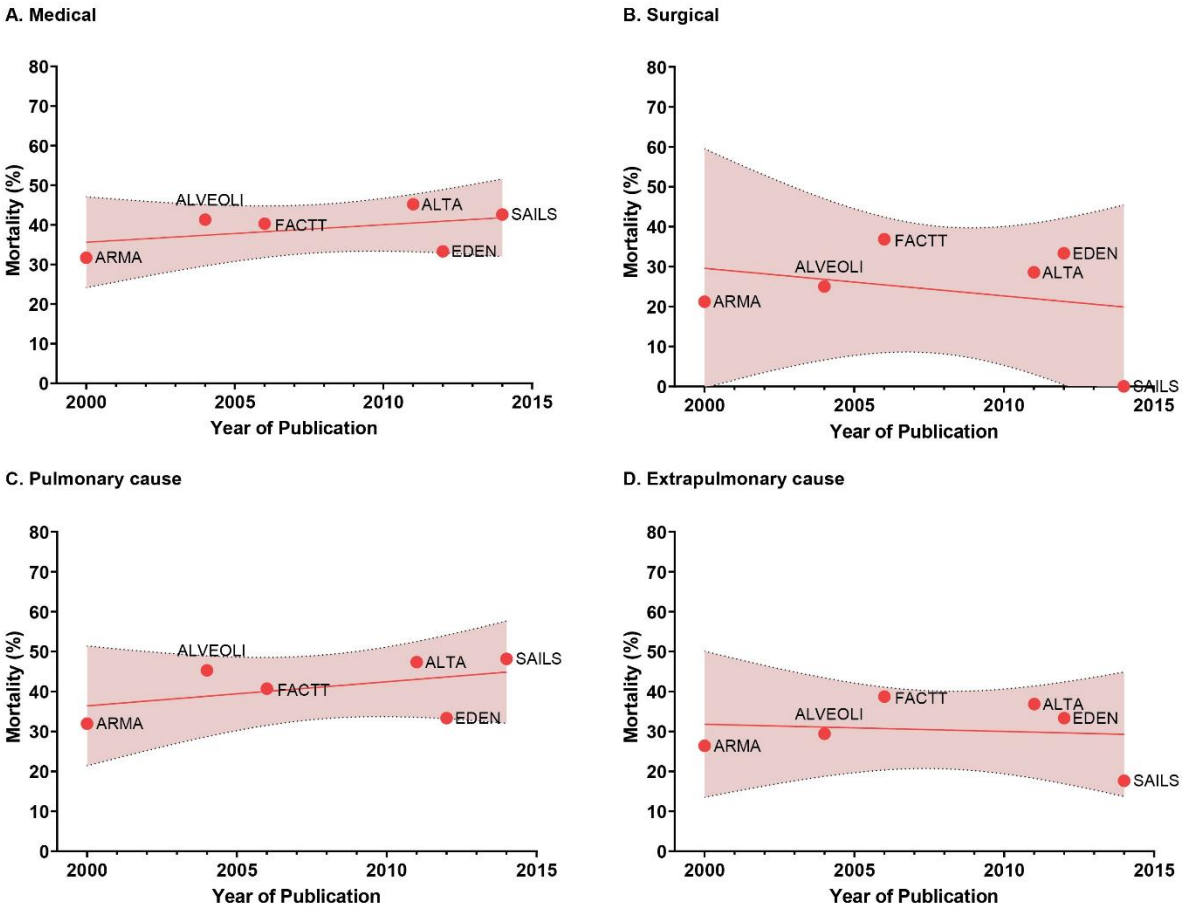
Title: Prolonged mechanical ventilation in acute respiratory distress syndrome

Authors: Ioannis Andrianopoulos, Vassilis G. Giannakoulis, Eleni Papoutsi, Georgios Papathanakos, Vasilios Koulouras, B. Taylor Thompson, Ilias I. Siempos



Supplemental Figure 1. Temporal trends of prevalence of prolonged mechanical ventilation (PMV) in subgroup analyses involving (A) only medical patients; (B) only surgical patients; (C) only patients with pulmonary causes of acute respiratory distress syndrome (ARDS); and (D) only patients with extrapulmonary causes of ARDS.

(A) In the subgroup analysis involving only medical patients (i.e., after exclusion of patients with ARDS following trauma or elective surgery), prevalence of PMV gradually declined (R^2=0.828, p=0.012), while percentage of patients with ARDS who were discharged alive without receiving PMV gradually increased (R^2=0.862, p=0.008). **(B)** In the subgroup analysis involving only surgical patients (i.e., patients with ARDS following trauma or elective surgery), neither prevalence of PMV declined (R^2=0.038, p=0.713) nor percentage of patients with ARDS who were discharged alive without receiving PMV increased (R^2=0.032, p=0.734). **(C)** In the subgroup analysis involving only patients with pulmonary causes (namely, pneumonia and aspiration) of ARDS, prevalence of PMV gradually declined (R^2=0.794, p=0.017), while percentage of patients with ARDS who were discharged alive without receiving PMV gradually increased (R^2=0.695, p=0.039). **(D)** In the subgroup analysis involving only patients with extrapulmonary causes of ARDS, prevalence of PMV did not decline (R^2=0.241, p=0.322), while percentage of patients with ARDS who were discharged alive without receiving PMV gradually increased (R^2=0.760, p=0.024).



Supplemental Figure 2. Temporal trends of 90-day mortality of patients with acute respiratory distress syndrome (ARDS) receiving prolonged mechanical ventilation (PMV) in subgroup analyses involving (A) only medical patients; (B) only surgical patients; (C) only patients with pulmonary causes of ARDS; and (D) only patients with extrapulmonary causes of ARDS.

Mortality of patients receiving PMV did not change over time in the subgroup analyses involving **(A)** only medical patients (i.e., after exclusion of patients with ARDS following trauma or elective surgery) (R^2=0.197, p=0.379) or **(B)** only surgical patients (i.e., patients with ARDS following trauma or elective surgery) (R^2=0.081, p=0.585) or **(C)** only patients with pulmonary causes (namely, pneumonia and aspiration) of ARDS (R^2=0.210, p=0.360) or **(D)** only patients with extrapulmonary causes of ARDS (R^2=0.016, p=0.813).

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A combination of mild-moderate hypoxemia and low compliance is highly prevalent in persistent ARDS: a retrospective study

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Abstract

Background The Acute Respiratory Distress Syndrome (ARDS) is characterized by lung inflammation and edema, impairing both oxygenation and lung compliance. Recent studies reported a dissociation between oxygenation and compliance (severe hypoxemia with preserved compliance) in early ARDS and COVID-19-related-ARDS (CARDS). During the pandemic, in patients requiring prolonged mechanical ventilation, we observed the opposite combination (mild-moderate hypoxemia but significantly impaired compliance). The purpose of our study was to investigate the prevalence of this combination of mild-moderate hypoxemia and impaired compliance in persistent ARDS and CARDS.

Methods For this retrospective study, we used individual patient-level data from two independent cohorts of ARDS patients. The ARDSNet cohort included patients from four ARDS Network randomized controlled trials. The CARDS cohort included patients with ARDS due to COVID-19 hospitalized in two intensive care units in Greece. We used a threshold of 150 for PaO_2/FiO_2 and 30 ml/cmH_2O for compliance, estimated the prevalence of each of the four combinations of oxygenation and compliance at baseline, and examined the change in its prevalence from baseline to day 21 in the ARDSNet and CARDS cohorts.

Results The ARDSNet cohort included 2909 patients and the CARDS cohort included 349 patients. The prevalence of the combination of mild-moderate hypoxemia and low compliance increased from baseline to day 21 both in the ARDSNet cohort (from 22.2 to 42.7%) and in the CARDS cohort (from 3.1 to 33.3%). Among surviving patients with low compliance, oxygenation improved over time. The 60-day mortality rate was higher for patients who had mild-moderate hypoxemia and low compliance on day 21 (28% and 56% in ARDSNet and CARDS), compared to those who had mild-moderate hypoxemia and high compliance (20% and 50%, respectively).

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Conclusions Among patients with ARDS who require prolonged controlled mechanical ventilation, regardless of ARDS etiology, a dissociation between oxygenation and compliance characterized by mild-moderate hypoxemia but low compliance becomes increasingly prevalent. The findings of this study highlight the importance of monitoring mechanics in patients with persistent ARDS.

Keywords Acute respiratory failure, Acute respiratory distress syndrome, COVID-19, Prolonged mechanical ventilation

Introduction

Acute respiratory distress syndrome (ARDS) is defined as non-cardiogenic pulmonary edema causing hypoxemia [1]. Filling of the injured alveoli with protein-rich edema fluid [2], causes both an impairment in gas exchange and a reduction in lung compliance. Impairments in oxygenation and mechanics are thought to coincide and reflect the severity of ARDS [1]. However, it was observed that several patients with ARDS due to the coronavirus disease-19 (COVID-19) presented a dissociation between severe hypoxemia and relatively well-preserved compliance [3, 4]. A subsequent secondary analysis of the LUNG SAFE study revealed that approximately one in eight patients meeting the hypoxemia criterion of ARDS exhibited preserved compliance [5], confirming this dissociation between oxygenation and compliance in patients presenting with ARDS regardless of etiology. The above observations were limited to the first days after the onset of ARDS, i.e., at early stages.

The number of ARDS patients dramatically increased during the COVID-19 pandemic, as did patients who required prolonged mechanical ventilation [6]. During the pandemic, we observed that many patients after several days of mechanical ventilation exhibited an 'opposite' dissociation between oxygenation and compliance, characterized by mild-moderate hypoxemia but significantly reduced compliance.

Whether such a dissociation between oxygenation and compliance becomes prevalent in persistent ARDS regardless of etiology, or rather it is a particular feature of COVID-19 related ARDS is not known. This knowledge may be important given that a nonnegligible proportion of patients with ARDS require prolonged mechanical ventilation; i.e., they remain under ventilation more than 21 days after intubation [7]. Based on our observation, we endeavored to systematically examine the presence of this combination of mild-moderate hypoxemia and significantly impaired compliance, focusing specifically on patients with ARDS requiring prolonged mechanical ventilation.

Methods

For this retrospective study, we used individual patient-level data from two independent cohorts of patients with ARDS.

The first cohort of our study ("ARDSNet" cohort) consisted of patients with ARDS enrolled in four prospective therapeutic clinical trials conducted by the ARDS Network, namely FACTT [8], ALTA [9], EDEN [10], and SAILS [11]. As previously [12, 13], we were granted access to data through the Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC) of the National Heart, Lung, and Blood Institute (NHLBI). Because data would be received in de-identified form, the Institutional Review Board of Evangelismos Hospital waived the need for informed consent and approved the study.

The second cohort of our study ("CARDS" cohort) consisted of patients with ARDS related to COVID-19 admitted between October 2020 and January 2022 (i.e., when the alpha and delta Sars-Cov-2 variants were prominent) in two academic intensive care units (ICU) at tertiary hospitals in Crete and Ioannina, Greece. Part of data from those patients have been included in previously published observational studies [14, 15]. The Institutional Review Board at each participating study site (Ioannina: University Hospital of Ioannina, and Crete: University Hospital of Heraklion) approved of the data collection and waived the need for informed consent owing to the observational study design and the collection of de-identified data.

For both independent cohorts, we collected data on age, sex, Sequential Organ Failure Assessment (SOFA) score (both total SOFA score and non-respiratory SOFA score) at baseline, partial pressure of arterial oxygen to fraction of inspired oxygen ratio (PaO_2:FiO_2) and respiratory system compliance at baseline (day 0 or, if missing, day 1) and on days 7, 12 or 14 and 21. Day 0 was the day of enrollment for the ARDSNet cohort, and the day of intubation for the CARDS cohort. Data on day 12 were available from the ALTA, EDEN, and SAILS studies, while data on day 14 were available from the FACTT trial and the CARDS cohort. None of the patients were treated with extracorporeal oxygenation or carbon dioxide removal.

We used a threshold for low PaO_2:FiO_2 a value below 150, which has been used to identify patients with significant hypoxemia likely to benefit from prone position [16], and for low compliance a value below 30 mL/cmH_2O, which has been shown to be associated with sustained high driving pressure and weaning failure [17, 18]. Accordingly, we considered four combinations of oxygenation and compliance in our study: mild-moderate hypoxemia/low compliance, mild-moderate hypoxemia/

high compliance, severe hypoxemia/high compliance, and severe hypoxemia/low compliance.

We first analyzed all patients at baseline, and evaluated the prevalence of each of the four combinations. Data from all patients were included in this analysis (no exclusion criteria). In the ARDSNet cohort, we also conducted a sensitivity analysis by including only those patients who were randomized to the control group in the trials. We subsequently focused on patients who were on mechanical ventilation and had available data on oxygenation (as assessed by PaO_2:FiO_2) and respiratory system compliance on day 21. The primary endpoint of the study was the change in prevalence of the combination of mild-moderate hypoxemia/low compliance over time from baseline to day 21 among these patients. Secondary endpoints included: the difference in the prevalence of the combination of mild-moderate hypoxemia and low compliance between the ARDSNet cohort and the CARDS cohort; the trajectory of oxygenation among patients with either low or high compliance (using the abovementioned threshold of 30 mL/cmH_2O) from baseline to day 21; the mortality at day 21 based on the oxygenation-compliance combination at baseline, and the 60-day mortality based on the oxygenation-compliance combination on day 21.

We presented continuous variables as medians with interquartile range (IQR) and compared them using the Mann-Whitney test (for 2 groups) or the Kruskal-Wallis test (for multiple groups). We presented categorical variables as percentages and compared them using the chi-squared or Fisher's exact test, and corrected for multiple comparisons as appropriate. No formal sample size calculation prior to this purely observational study was performed. All p values were two-sided, and we considered statistical significance at an α level of 0.05. Statistical analyses were conducted using SPSS software version 28.0 (SPSS, Inc., Chicago, IL), and alluvial plots using R software version 4.2.1 (R Foundation for Statistical Computing).

Results

Characteristics of included patients in the two cohorts

Figure 1 and Supplemental Fig. 1 present the patient flow diagram for both cohorts (ARDSNet and CARDS). In the ARDSNet cohort, out of the 2909 patients with ARDS, the majority of patients (67%) were liberated from mechanical ventilation ("extubated" group) by day 21, 19% of patients had died ("deceased" group) by day 21, 10% remained on mechanical ventilation but did not have data on compliance, mostly because they were ventilated on assisted or partially assisted modes ("ventilated in assisted modes" group) by day 21, and 4% of patients were on mechanical ventilation and had available data on oxygenation and compliance ("ventilated in control modes" group) on day 21. In the CARDS cohort, out of the 349 patients, 17% were in the "extubated" group, 41% in the "deceased", 15% in the "ventilated in assisted modes" and 28% were in the "ventilated in control modes" group.

Table 1 presents the baseline characteristics of patients categorized based on their status on day 21 (i.e., ventilated in control or assisted modes, extubated, or deceased) in the ARDSNet and CARDS cohorts. The combination of mild-moderate hypoxemia and low compliance at baseline was less common among patients ventilated in control modes compared to other groups in the ARDSNet cohort but not in the CARDS cohort.

Supplemental Table 1 presents the comparison of baseline characteristics of patients included in the ARDSNet versus the CARDS cohort. Regardless of their status on day 21, patients in the ARDSNet cohort were younger, had higher total SOFA score, higher non-respiratory SOFA score and lower respiratory system compliance at baseline compared to patients in the CARDS cohort. The combination of mild-moderate hypoxemia but low compliance at baseline was more common in the ARDSNet cohort than in the CARDS cohort.

Trajectory of oxygenation and compliance from baseline to day 21

In the ARDSNet cohort, the combination of mild-moderate hypoxemia but low compliance increased among patients ventilated in control mode from a prevalence of 22.2% at baseline to 42.7% on day 21 ($p<0.001$). A sensitivity analysis including only patients who were randomized to the control group showed similar results, specifically the combination of mild-moderate hypoxemia but low compliance increased from a prevalence of 23.1% at baseline to 47.8% on day 21 ($p<0.001$). Likewise, in the CARDS cohort, the combination of mild-moderate hypoxemia but low compliance increased from a prevalence of 3.1% at baseline to 33.3% on day 21 ($p<0.001$). The prevalence of the combination of mild-moderate hypoxemia but low compliance on day 21 was similar in both the ARDSNet and CARDS cohorts ($p=0.155$).

After limiting our analysis to only those patients ventilated in control modes on day 21, the combination of mild-moderate hypoxemia but low compliance increased from a prevalence of 7.4% (12.0% and 2.1% in the ARDSNet and CARDS cohort, respectively) at baseline to 38.6% (42.7% and 33.3% in the ARDSNet and CARDS cohort, respectively) on day 21 ($p<0.001$ for all comparisons). Alluvial plots to depict the change in prevalence of the different combinations over time from baseline to day 21 are shown in Fig. 2. In the sensitivity analysis including only patients from the ARDSNet cohort with pneumonia as the primary risk factor of ARDS (Supplemental Table 2), the combination of mild-moderate hypoxemia

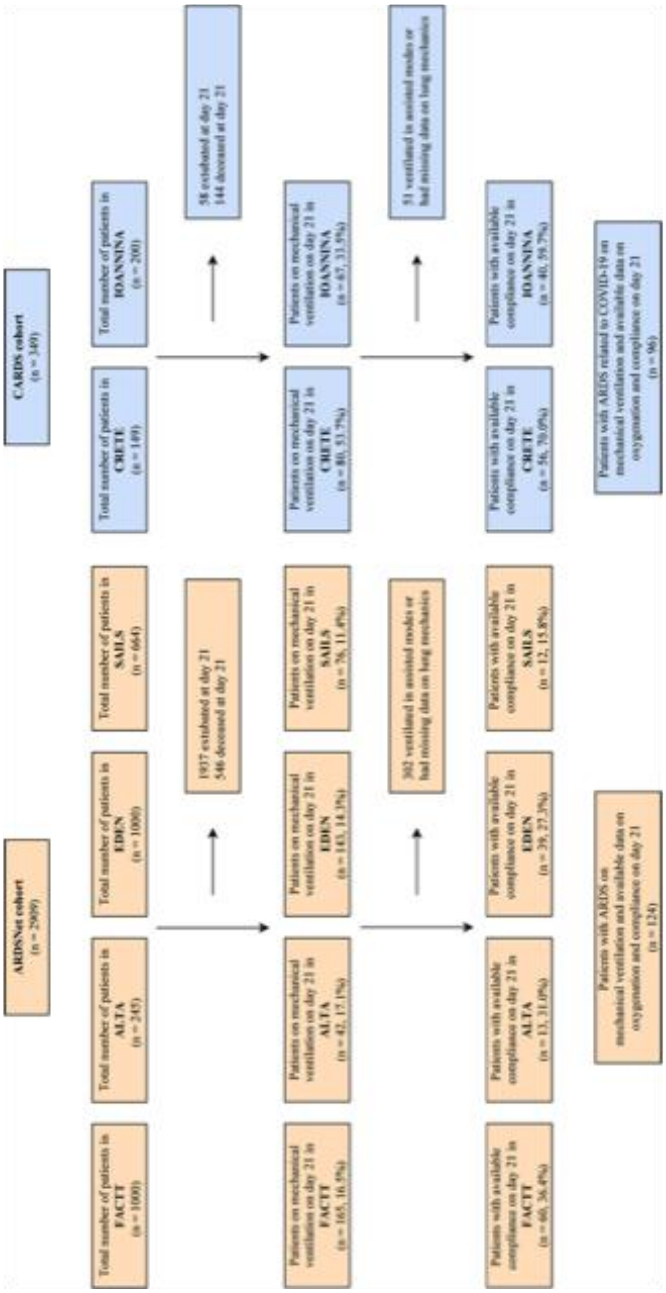

Fig. 1 Patient flow diagram

Table 1 Baseline characteristics of patients according to status on day 21 of ARDSNet and CARDS cohort

	ARDSNet cohort				CARDS cohort			
	Ventilated in Control modes[1] (n = 124)	Ventilated in Assisted modes[1] (n = 302)	Extubated (n = 1937)	Deceased (n = 546)	Ventilated in Control modes[1] (n = 96)	Ventilated in Assisted modes[1] (n = 51)	Extubated (n = 58)	Deceased (n = 144)
Age	52.5 (41.0–65.8)	54.0 (42.0–65.0)	50.0 (39.0–60.0)*	58.0 (45.0–71.0)*	71.0 (61.0–75.8)	69.0 (61.0–74.0)	63.5 (53.0–75.0)**	72.0 (64.0–77.0)
Female sex n (%)	50 (40.3)	138 (45.7)	975 (50.3)	246 (45.1)	32 (33.3)	20 (39.2)	23 (39.7)	45 (31.5)
Baseline SOFA score	7 (5–9)	7 (5–9)	6 (4–8)#	8 (6–10)#	4 (4–6)	4 (4–8)	4 (4–6)##	5 (4–7)##
Non-respiratory SOFA	3 (1–6)	4 (2–6)§	3 (1–5)	5 (3–7)§	1 (0–3)	1 (0–4)	1 (0–2)	1 (0–3)
PaO_2:FiO_2 at baseline	103 (81–147)*	146 (107–195)	150 (106–200)	127 (89–177)*	120 (88–153)	131 (110–181)	118 (101–158)	101 (76–147)**
Crs at baseline	27 (22–35)	28 (21–36)	30 (23–40)	28 (21–38)	36 (30–45)	40 (35–48)	38 (33–45)	32 (26–39)¨
MH-LoC at baseline[2]	13/108 (12.0)'	56/223 (25.1)	357/1527 (23.4)	76/405 (18.8)	2/94 (2.1)	0/43 (0.0)	2/55 (3.6)	6/128 (4.7)

Abbreviations: ARDS, acute respiratory distress syndrome; CARDS, COVID-19-related acute respiratory distress syndrome; n, number; SOFA, sequential organ failure assessment; PaO_2:FiO_2, partial pressure of arterial oxygen to fraction of inspired oxygen ratio; Crs, compliance; MH-LoC, mild-moderate hypoxemia and low compliance

Age, baseline SOFA, non-respiratory SOFA and lung mechanics at baseline are presented as median with interquartile range (IQR) and compared using the Kruskal-Wallis test. Sex is presented as percentage and compared using the chi-squared test. Pairwise comparisons were corrected using the Bonferroni method, and statistical significance was considered at an α level of 0.05

[1]The "ventilated in control modes" group consisted of patients who were on mechanical ventilation and had available data on oxygenation and compliance on day 21; the "ventilated in assisted modes" group consisted of patients who remained on mechanical ventilation but did not have data on compliance, mostly because they were ventilated on assisted or partially assisted modes by day 21; the "extubated" group consisted of patients who were liberated from mechanical ventilation by day 21; and the "deceased" group consisted of patients who died by day 21

[2]Due to missing data on respiratory system compliance at baseline, the total number of patients is less for this variable (shown as denominator)

*Deceased vs. all other groups $p < 0.05$, and extubated vs. ventilated in assisted modes $p < 0.001$; # Deceased vs. all other groups, and extubated vs. ventilated in control, assisted modes $p < 0.05$; § Deceased vs. extubated, ventilated in control modes, and ventilated in assisted modes vs. extubated $p < 0.001$; ' Deceased vs. all other groups $p < 0.05$, and ventilated in control modes vs. ventilated in assisted modes, extubated $p < 0.001$; ¨ Extubated vs. deceased, ventilated in assisted modes $p < 0.05$; 'Ventilated in control modes vs. ventilated in assisted modes, extubated $p < 0.05$

**Extubated vs. ventilated in control modes, deceased $p < 0.05$; ##Deceased vs. extubated $p < 0.05$; ¨¨Deceased vs. ventilated in assisted modes $p < 0.01$; ¯ Deceased vs. all other groups $p < 0.01$

but low compliance increased from a prevalence of 5.4% at baseline to 34.6% on day 21 ($p < 0.001$).

Among patients who had low compliance, in whom the underlying pathophysiology, edema or atelectasis causing the impairment in mechanics, would be expected to affect oxygenation, oxygenation appeared to improve over time (Fig. 3A-B). This was also the case for patients who had high compliance (Fig. 3C-D).

Outcome

Supplemental Table 3 presents data on outcomes (i.e., extubated or dead) on day 21 of patients categorized by their oxygenation-compliance combination at baseline in both cohorts. The corresponding Kaplan-Meier curves are presented as Supplemental Fig. 2.

Supplemental Table 4 presents data on 60-day mortality of patients categorized by their oxygenation-compliance combination on day 21 in both cohorts. In the ARDSNet cohort, 60-day mortality was 28% in the mild-moderate hypoxemia/low compliance and 20% in the mild-moderate hypoxemia/high compliance combination, 67% in the severe hypoxemia/high compliance combination, and 32% in the severe hypoxemia/low compliance combination. In the CARDS cohort, 60-day mortality was 56% and 50% in the mild-moderate hypoxemia/low compliance and the mild-moderate hypoxemia/high compliance groups, and 82–83% in the severe hypoxemia with low and high compliance, respectively.

Discussion

The results of this study highlight the dissociation between oxygenation and compliance during the late stages of ARDS, as a combination of mild-moderate hypoxemia but severely impaired compliance, becomes increasingly prevalent over time, regardless of ARDS etiology.

The dissociation between oxygenation and compliance in ARDS has recently gained attention [4]. Impairment of both oxygenation and lung compliance typically characterizes ARDS, and is the result of lung inflammation, impaired hypoxic pulmonary vasoconstriction and alveolar flooding

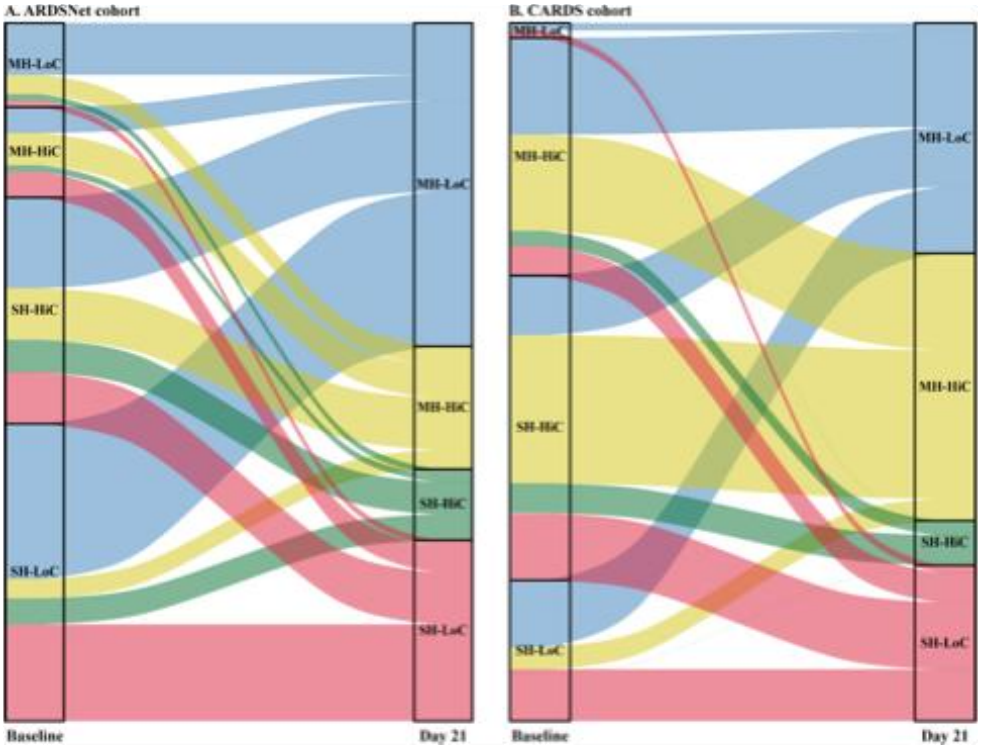

Fig. 2 Alluvial plot of changes in prevalence of different combinations of oxygenation and compliance over time from baseline to day 21, among patients who remained on controlled ventilation and had available data on oxygenation and compliance, in (**A**) the ARDSNet cohort, and (**B**) the CARDS cohort. Each block represents a different combination, and the height of a block represents the number of patients in this combination. Combinations at baseline are illustrated with different colors. Each stream field between two blocks represents the change in the number of patients in the respective combinations from baseline to day 21, and the height of a stream field is proportionate to this number of patients. A total of 108 and 94 patients with available data on oxygenation and compliance on both baseline and day 21 are included in the alluvial plot of the ARDSNet and CARDS cohort, respectively. MH-HiC: mild-moderate hypoxemia/high compliance; MH-LoC: mild-moderate hypoxemia/low compliance; SH-HiC: severe hypoxemia/high compliance; and SH-LoC: severe hypoxemia/low compliance

[19–21]. The recently described dissociation between oxygenation and compliance in early ARDS patients [3, 4] is attributed to increased shunt due to vasculopathy, and impaired hypoxic pulmonary vasoconstriction [4, 5, 22].

To our knowledge, this is the first systematic examination of an "opposite" dissociation of oxygenation and compliance, observed in persistent ARDS, and characterized by mild-moderate hypoxemia but severely impaired compliance. This dissociation was indicated, but not systematically examined by previous studies [23, 24], which were mostly limited to the first week from the onset of the syndrome [25]. Rather, the present analysis took advantage of longitudinal data on oxygenation-compliance for three weeks from the onset of ARDS, for both traditional ARDS and COVID-19-related ARDS. Specifically, our analysis showed that, although the combination of mild-moderate hypoxemia but low compliance was not as rare in early ARDS due to etiologies other than COVID-19 compared to COVID-19 (Supplemental Table 1), the combination became prominent among patients with persistent ARDS requiring controlled ventilation, regardless of etiology.

It may be worth attempting an explanation why this combination of mild-moderate hypoxemia and low compliance becomes increasingly prevalent over the course of ARDS among patients who remain under controlled mechanical ventilation. In persistent ARDS, the resolution of pulmonary inflammation may lead to restoration of hypoxic pulmonary vasoconstriction, which in turn may optimize the distribution of perfusion and thus attenuate hypoxemia [20, 26]. In spite of the attenuation of hypoxemia, compliance

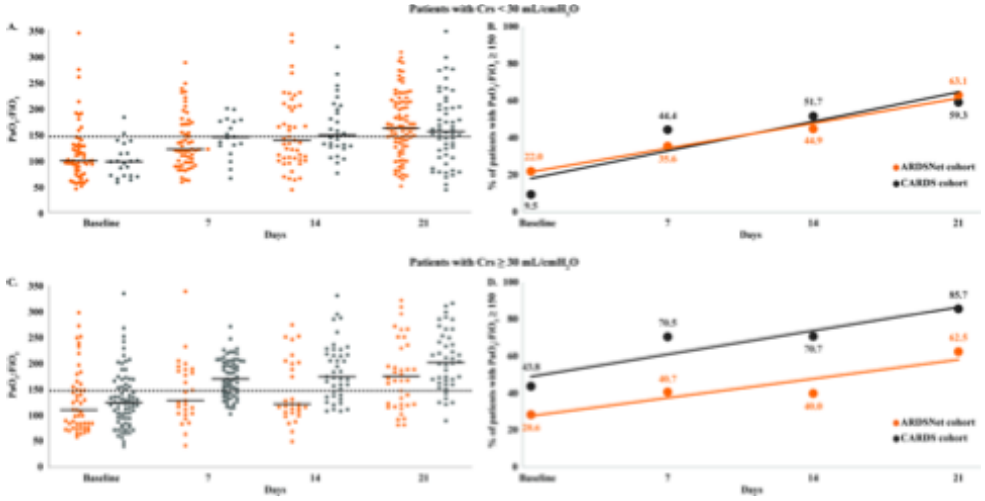

Fig. 3 (**A**) Trajectory of oxygenation, as assessed by the partial pressure of arterial oxygen to fraction of inspired oxygen ratio (PaO_2:FIO_2), (line at median), and (**B**) percent of patients with mild-moderate hypoxemia, among patients with low compliance at baseline and on days 7, 14 and 21 in the two independent cohorts (ARDSNet and CARDS). (**C**) Trajectory of oxygenation, as assessed by the partial pressure of arterial oxygen to fraction of inspired oxygen ratio (PaO_2:FIO_2), and (**D**) percent of patients with mild-moderate hypoxemia, among patients with high compliance at baseline and on days 7, 14 and 21 in the two independent cohorts

may be reduced due to the progressive development of some degree of fibrosis, known to occur in persistent ARDS [27]. Therefore, concurrent improvement in ventilation-perfusion matching and development of fibrosis over time may underlie the pathophysiology of improved oxygenation despite severely impaired compliance in persistent ARDS. The impaired compliance is likely the reason these patients could not be liberated from controlled ventilation, thus resulting in the increased prevalence of the combination of low compliance and mild-moderate hypoxemia among patients requiring prolonged controlled ventilation.

Recognizing this dissociation among patients with persistent ARDS may have important clinical implications. Hypoxemia dominates all diagnostic and management algorithms of ARDS, such as the Berlin definition [1], indication for prone position [16] or ECMO [28], and for a good reason: it is a cardinal symptom of ARDS at presentation, and lethal if not managed. The impairment in lung compliance is caused by the same underlying pathology, and commonly correlates with the severity of hypoxemia. As a result, resolution of hypoxemia over time is considered an adequate indicator of resolution of ARDS, and included in weaning protocols [8–11, 29], while improvement in lung mechanics is not. Indeed, during the first couple of weeks of ARDS, in the majority of patients who improve, both oxygenation and compliance improve. However, as highlighted in this analysis, in a significant fraction of patients requiring prolonged controlled mechanical ventilation, the improvement of hypoxemia is dissociated from that of lung compliance at late stages of ARDS. Weaning attempts when lung compliance is severely impaired might fail and place patients at risk of self-inflicted lung injury [30–32]. Indeed, strong inspiratory efforts may promote lung injury in ARDS, and sustained high driving pressures have been shown to occur during assisted ventilation only in patients with low compliance [17, 33]. Therefore, acknowledging this common dissociation between oxygenation and compliance in persistent ARDS, rather than relying solely on improvement of oxygenation to characterize a patient's condition as improved, may have implications for patient management. For example, in patients with persistent ARDS, attempts for assisted ventilation could be complemented by close monitoring of effort and driving pressure, to minimize the risk of ventilator or self-inflicted lung injury [34, 35]. Studies on weaning focused on this specific group of patients are lacking and urgently needed.

The findings of this study should be interpreted in the context of the limitations imposed by its retrospective nature. First, although the ARDSNet cohort consisted of patients enrolled in multiple ICUs from one continent (North America), the CARDS cohort consisted of patients enrolled in only two ICUs from one European country. Second, the sample size is limited by missing data on compliance from patients who remained on mechanical ventilation on day 21, mainly because mechanics were not monitored on assisted modes. However, an exploratory analysis of

CARDS patients indicated that both compliance and oxygenation had improved prior to assisted ventilation (data not shown). Third, to facilitate the analysis, we had to use thresholds for oxygenation and compliance, acknowledging the inherent limitations of using thresholds to create classes in the continuum of a disease spectrum. We also had to use the PaO_2:FiO_2 ratio at different levels of FiO_2 as an index of oxygenation, despite its nonlinear behavior, as this is what is currently used in clinical practice. Finally, we cannot provide information on the underlying cause of impaired compliance, to what extent it contributed to the need for prolonged ventilation, or its management in the surviving patients.

Conclusions

In conclusion, in persistent ARDS regardless of the etiology, a combination of mild-moderate hypoxemia but low compliance becomes prevalent among patients who remain under controlled ventilation. Acknowledging that improvement in oxygenation is not always associated with restoration of lung integrity in persistent ARDS, adds to the increasingly recognized importance of monitoring lung mechanics in mechanically ventilated patients, throughout the course of ARDS in order to provide protective ventilation.

List of abbreviations

ARDS	Acute respiratory distress syndrome
COVID-19	Coronavirus disease 2019
CARDS	COVID-19-related ARDS
ICU	Intensive care unit
BioLINCC	Biologic Specimen and Data Repository Information Coordinating Center
NHLBI	National Heart, Lung, and Blood Institute
PaO_2:FiO_2	Partial pressure of arterial oxygen to fraction of inspired oxygen ratio
Crs	Respiratory system compliance
SOFA	Sequential Organ Failure Assessment
VT	Tidal volume
PEEP	Positive end expiratory pressure
Ppl	Plateau pressure
MH-LoC	mild-moderate hypoxemia/low compliance
MH-HiC	mild-moderate hypoxemia /high compliance
SH-HiC	severe hypoxemia /high compliance
SH-LoC	severe hypoxemia /low compliance

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12931-023-02626-9.

Supplementary Material 1: Supplemental Table 1. Baseline characteristics of patients according to status on day 21. **Supplemental Table 2.** Baseline characteristics and lung mechanics of the patients with pneumonia as primary risk factor for ARDS. **Supplemental Table 3.** Outcomes on day 21 of patients categorized by their oxygenation-compliance combination at baseline. **Supplemental Table 4.** Data on 60-day mortality of patients categorized by their oxygenation-compliance combination on day 21. **Supplemental Figure 1.** Detailed patient flow diagram for both study cohorts. **Supplemental Figure 2.** Kaplan-Meier curves of mortality up to day 21 of patients categorized by their oxygenation-compliance combination at baseline

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Author contributions

EP contributed to study design, undertook statistical analyses, contributed to data interpretation and wrote the first draft of the manuscript. IA contributed to study design, data collection, data interpretation and critically revised the manuscript for important intellectual content. VM, MB and VS contributed to data collection, data interpretation and critically revised the manuscript for important intellectual content. ET, GP, VK and EK contributed to data collection, data interpretation, offered administrative support and critically revised the manuscript for important intellectual content. IIS contributed to study design, data interpretation and critically revised the manuscript for important intellectual content. IKV conceived of and designed the study, supervised the study, wrote the first draft of the manuscript and is the guarantor. All authors read and approved the final manuscript.

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Data availability

Data of patients from the ARDSNet cohort are available through the Biologic Specimen and Data Repository Information Coordinating Center of the National Heart, Lung, and Blood Institute (https://biolincc.nhlbi.nih.gov/home/). Data of patients from the CARDS cohort are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This research was conducted in accordance with the Declaration of Helsinki. With regard to the ARDSNet cohort, because data would be received in de-identified form, the Institutional Review Board of Evangelismos Hospital waived the need for informed consent and approved the study. With regard to the CARDS cohort, the Institutional Review Board at each participating study site (Ioannina: University Hospital of Ioannina, and Crete: University Hospital of Heraklion) approved of the data collection and waived the need for informed consent owing to the observational study design and the collection of de-identified data.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests. IIS serves as Associate Editor for the Journal.

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Publisher's Note

Online Data Supplement

Supplemental Table 1. Baseline characteristics of patients according to status on day 21.

	Ventilated in Control modes[1]			Ventilated in Assisted modes[1]			Extubated			Deceased		
	ARDSNet (n=124)	**CARDS (n=96)**	**p value**	**ARDSNet (n=302)**	**CARDS (n=51)**	**p value**	**ARDSNet (n=1937)**	**CARDS (n=58)**	**p value**	**ARDSNet (n=546)**	**CARDS (n=144)**	**p value**
Age	52.5 (41.0 - 65.8)	71.0 (61.0 - 75.8)	<0.001	54.0 (42.0 - 65.0)	69.0 (61.0 - 74.0)	<0.001	50.0 (39.0 - 60.0)	63.5 (53.0 - 75.0)	<0.001	58.0 (45.0 - 71.0)	72.0 (64.0 - 77.0)	<0.001
Female sex % (n)	50 (40.3)	32 (33.3)	0.288	138 (45.7)	20 (39.2)	0.389	975 (50.3)	23 (39.7)	0.109	246 (45.1)	45 (31.5)	0.003
Total SOFA score	7 (5 - 9)	4 (4 - 6)	<0.001	7 (5 - 9)	4 (4 - 8)	<0.001	6 (4 - 8)	4 (4 - 6)	<0.001	8 (6 - 10)	5 (4 -7)	<0.001
Non-respiratory SOFA score	3 (1 - 6)	1 (0 - 3)	<0.001	4 (2 - 6)	1 (0 - 4)	<0.001	3 (1 - 5)	1 (0 - 2)	<0.001	5 (3 - 7)	1 (0 - 3)	<0.001
PaO_2:FiO_2 at baseline	103 (81 - 147)	120 (88 - 153)	0.266	146 (107 - 195)	131 (110 - 181)	0.289	150 (106 - 200)	118 (101 - 158)	0.003	127 (89 - 177)	101 (76 - 147)	<0.001
Crs at baseline[2]	27 (22 - 35)	36 (30 - 45)	<0.001	28 (21 - 36)	40 (35 - 48)	<0.001	30 (23 - 40)	38 (33 - 45)	<0.001	28 (21 - 38)	32 (26 - 39)	0.001
MH-LoC at baseline[2]	13/108 (12.0)	2/94 (2.1)	0.007	56/223 (25.1)	0/43 (0.0)	<0.001	357/1527 (23.4)	2/55 (3.6)	<0.001	76/405 (18.8)	6/128 (4.7)	<0.001

Abbreviations: ARDS, acute respiratory distress syndrome; CARDS, COVID-19-related ARDS; n, number; SOFA, sequential organ failure assessment; PaO_2:FiO_2, partial pressure of arterial oxygen to fraction of inspired oxygen ratio; Crs, compliance; MH-LoC, mild-moderate hypoxemia and low compliance.

[1]Study population consisted of patients who were ventilated in control modes, and had available data on oxygenation and Crs on day 21. Most of the patients on mechanical ventilation without available data on mechanics were on assisted modes (details on the modes of ventilation are not available for patients in the FACTT ARDSNet trial). [2]Due to missing data on respiratory system compliance at baseline, the total number of patients is less for this variable (shown as denominator).

Supplemental Figure 1. Detailed patient flow diagram for both study cohorts.

Supplemental Figure 2. Kaplan-Meier curves of mortality up to day 21 of patients categorized by their oxygenation-compliance combination at baseline.

Supplemental Table 2. Baseline characteristics and lung mechanics of patients with pneumonia as primary risk factor for ARDS.

	ARDSNet cohort (n=66)	CARDS cohort (n=96)	p value
Age	51.5 (42.0 - 63.3)	71.0 (61.0 - 75.8)	<0.001
Female sex % (n)	31 (47.0)	32 (33.3)	0.080
Baseline SOFA score	6 (5 - 8)	4.0 (4.0 - 6.0)	<0.001
Baseline non-respiratory SOFA score	3 (1 - 5)	1.0 (0.0 - 3.0)	<0.001
PaO_2:FiO_2	99 (76 - 130)	120 (88 – 153)	0.058
Crs	27 (21 - 35)	36 (30 - 45)	<0.001
MH-LoC	6/55 (10.9)	2/94 (2.1)	0.052
60-day mortality	22 (33.3)	59 (61.5)	<0.001

Abbreviations: ARDS, acute respiratory distress syndrome; CARDS, COVID-19-related ARDS; n, number; SOFA, sequential organ failure assessment; PaO_2:FiO_2, partial pressure of arterial oxygen to fraction of inspired oxygen ratio; Crs, compliance; MH-LoC, mild-moderate hypoxemia and low compliance.

Supplemental Table 3. Outcomes on day 21 of patients categorized by their oxygenation-compliance combination at baseline.												
	ARDSNet cohort (n=2909)						**CARDS cohort (n=349)**					
	MH-LoC (n = 502)	MH-HiC (n = 548)	SH-HiC (n = 561)	SH-LoC (n = 652)	Missing (n = 646)	p value	MH-LoC (n = 10)	MH-HiC (n = 96)	SH-HiC (n = 140)	SH-LoC (n = 74)	Missing (n = 29)	p value
Extubated	359 (71.5)	421 (76.8)	367 (65.4)	382 (58.6)	411 (63.6)	<0.001	2 (20.0)	17 (17.7)	31 (22.1)	5 (6.8)	3 (10.3)	0.055
21-day mortality	76 (15.1)	69 (12.6)	110 (19.6)	153 (23.5)	141 (21.8)	<0.001	6 (60.0)	32 (33.3)	46 (32.9)	44 (59.5)	16 (55.2)	<0.001

Abbreviations: ARDS, acute respiratory distress syndrome; CARDS, COVID-19-related ARDS; MH-LoC, mild-moderate hypoxemia and low compliance; MH-HiC, mild-moderate hypoxemia and high compliance; SH-HiC, severe hypoxemia and high compliance; SH-LoC, severe hypoxemia and low compliance; n, number.

Baseline was day 0 or, if missing, day 1.

The "Missing" category includes patients that did not have compliance measured at baseline.

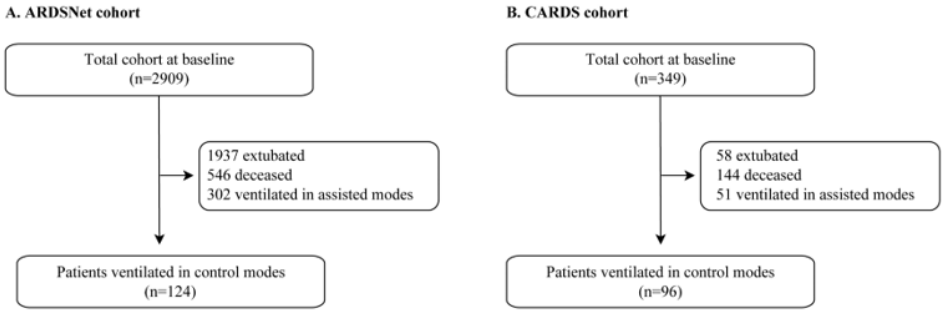
Supplemental Table 4. Data on 60-day mortality of patients categorized by their oxygenation-compliance combination on day 21.										
	ARDSNet cohort (n=124)					**CARDS cohort (n=96)**				
	MH-LoC (n = 53)	MH-HiC (n = 25)	SH-HiC (n = 15)	SH-LoC (n = 31)	p value	MH-LoC (n = 32)	MH-HiC (n = 36)	SH-HiC (n = 6)	SH-LoC (n = 22)	p value
60-day mortality	15 (28.3)	5 (20.0)	10 (66.7)*	10 (32.3)	0.017	18 (56.3)	18 (50.0)	5 (83.3)	18 (81.8)	0.056

Abbreviations: ARDS, acute respiratory distress syndrome; CARDS, COVID-19-related ARDS; MH-LoC, mild-moderate hypoxemia and low compliance; MH-HiC , mild-moderate hypoxemia and high compliance; SH-HiC, severe hypoxemia and high compliance; SH-LoC, severe hypoxemia and low compliance; n, number.

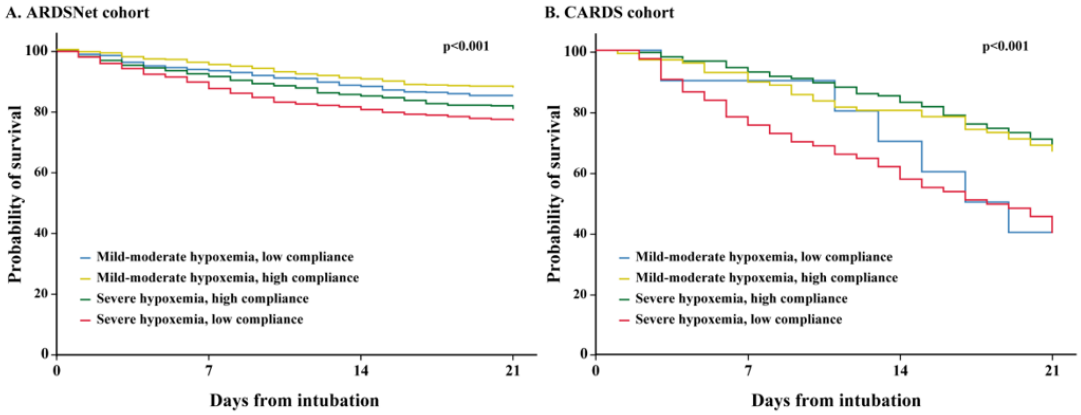
Baseline was day 0 or, if missing, day 1.

* SH-HiC vs MH-LoC, MH-HiC, p<0.05.

Supplemental Figure 1. Detailed patient flow diagram for both study cohorts. The "extubated" group consisted of patients who were liberated from mechanical ventilation by day 21; the "deceased" group consisted of patients who died by day 21; and the "ventilated in assisted modes" group consisted of patients who remained on mechanical ventilation but did not have data on compliance, mostly because they were ventilated on assisted or partially assisted modes by day 21 (details on the modes of ventilation are not available for patients in the FACTT ARDSNet trial.). The "ventilated in control modes" group consisted of patients who were on mechanical ventilation and had available data on oxygenation and compliance on day 21.



Supplemental Figure 2. Kaplan-Meier curves of mortality up to day 21 of patients categorized by their oxygenation-compliance combination at baseline.



B7. Summary (in Greek)

Εισαγωγή: Το Σύνδρομο Οξείας Αναπνευστικής Δυσχέρειας (ARDS) αποτελεί μια ετερογενή κλινική οντότητα, της οποίας η πορεία μπορεί να κυμαίνεται από ταχέως βελτιούμενες περιπτώσεις έως ασθενείς που απαιτούν παρατεταμένο μηχανικό αερισμό (Prolonged Mechanical Ventilation, PMV). Ο παρατεταμένος μηχανικός αερισμός έχει αναγνωριστεί ως σημαντική αιτία κλινικής και οικονομικής επιβάρυνσης των συστημάτων υγείας, ωστόσο τα διαθέσιμα δεδομένα ειδικά για ασθενείς με ARDS παραμένουν περιορισμένα. Σκοπός της παρούσας διατριβής ήταν η αξιοποίηση των μεγάλων βάσεων δεδομένων υψηλής ποιότητας των τυχαιοποιημένων κλινικών δοκιμών του Δικτύου ARDS (ARDS Network), προκειμένου να εκτιμηθούν οι διαχρονικές τάσεις στη συχνότητα εμφάνισης και τη θνητότητα του PMV, να αναγνωριστούν οι παράγοντες κινδύνου που σχετίζονται με τη θνητότητα των ασθενών με ARDS που υποβάλλονται σε PMV, να μελετηθεί η πορεία της οξυγόνωσης και της μηχανικής του αναπνευστικού συστήματος, καθώς και να διερευνηθεί η σχέση μεταξύ της μηχανικής του πνεύμονα, της οξείας νεφρικής βλάβης (Acute Kidney Injury, AKI) και του PMV.

Μέθοδοι:Για τη διερεύνηση της συχνότητας εμφάνισης και των παραγόντων κινδύνου θνητότητας των ασθενών με ARDS που απαιτούν PMV, καθώς και της συχνότητας εμφάνισης της «όψιμης AKI» και της επίδρασής της στην έκβαση των ασθενών, πραγματοποιήθηκε δευτερογενής ανάλυση ατομικών δεδομένων ασθενών από τις τυχαιοποιημένες κλινικές δοκιμές του ARDS Network. Ως PMV ορίστηκε η ανάγκη για μηχανικό αερισμό για περισσότερες από 21 συνεχόμενες ημέρες, ενώ ως «όψιμη AKI» ορίστηκε η ανάπτυξη οξείας νεφρικής βλάβης μετά τις πρώτες 48 ώρες από την έναρξη του μηχανικού αερισμού. Για τη μελέτη της σχέσης μεταξύ ενδοτικότητας (compliance) και οξυγόνωσης χρησιμοποιήθηκε επιπλέον μια ανεξάρτητη ομάδα ασθενών με ARDS σχετιζόμενο με COVID-19 (CARDS), οι οποίοι νοσηλεύτηκαν σε δύο Μονάδες Εντατικής Θεραπείας στην Ελλάδα. Χρησιμοποιώντας ως όρια τιμή PaO_2/FiO_2 ίση με 150 mmHg και ενδοτικότητα ίση με 30 mL/cmH_2O, εκτιμήθηκε η συχνότητα των τεσσάρων δυνατών συνδυασμών οξυγόνωσης και ενδοτικότητας κατά την έναρξη και έως την 21η ημέρα νοσηλείας.

Αποτελέσματα: Από τους 4.216 ασθενείς με ARDS, οι 646 (15,3%) υποβλήθηκαν σε παρατεταμένο μηχανικό αερισμό. Η συχνότητα εμφάνισης του PMV παρουσίασε σταδιακή μείωση από 18,4% στη μελέτη ARMA (2000) σε 10,9% στη μελέτη SAILS (2014) (R^2=0,728, p=0,031). Ωστόσο, η θνητότητα στις 90 ημέρες των ασθενών που έλαβαν PMV δεν μεταβλήθηκε σημαντικά με την πάροδο του χρόνου (R^2=0,271, p=0,290) και παρέμεινε υψηλή, στο 36,8%. Παράγοντες που συσχετίστηκαν ανεξάρτητα με αυξημένη θνητότητα στους ασθενείς αυτούς ήταν η μεγαλύτερη ηλικία, η παρουσία κακοήθειας, η πνευμονία ως αιτία του ARDS, καθώς και η ανάπτυξη διαταραχών της πηκτικότητας και ηπατικής ανεπάρκειας κατά τις πρώτες 21 ημέρες από την ένταξη στη μελέτη. Επιπλέον, η τραχειοστομία συσχετίστηκε επίσης με τη θνητότητα.

Η ανάλυση τόσο της ομάδας ARDSNet όσο και της ομάδας CARDS ανέδειξε σταδιακή αύξηση της συχνότητας ενός ιδιαίτερου φαινοτύπου που χαρακτηρίζεται από ήπια έως μέτρια υποξυγοναιμία σε συνδυασμό με χαμηλή ενδοτικότητα του αναπνευστικού συστήματος. Η συχνότητα αυτού του φαινοτύπου αυξήθηκε από 22,2% σε 42,7% στην ομάδα ARDSNet και από 3,1% σε 33,3% στην ομάδα CARDS μέχρι την 21η ημέρα.Η οξυγόνωση βελτιώθηκε στη πορεία του χρόνου στους επιζώντες ασθενείς με χαμηλή ενδοτικότητα. Παρά τη βελτίωση της οξυγόνωσης στους επιζώντες ασθενείς με χαμηλή ενδοτικότητα, η θνητότητα στις 60 ημέρες παρέμεινε υψηλότερη σε σύγκριση με ασθενείς που εμφάνιζαν αντίστοιχη οξυγόνωση αλλά υψηλότερη ενδοτικότητα. Η «όψιμη AKI» αναπτύχθηκε στο 33,8% των ασθενών. Σε σύγκριση με τους ασθενείς χωρίς AKI, οι ασθενείς με όψιμη AKI παρουσίασαν σημαντικά υψηλότερη θνητότητα στις 90 ημέρες (39% έναντι 17%, $p<0,001$), μεγαλύτερη διάρκεια νοσηλείας στη ΜΕΘ και λιγότερες ημέρες ελεύθερες μηχανικού αερισμού, γεγονός που συνδέθηκε με αυξημένη ανάγκη για παρατεταμένο μηχανικό αερισμό. Επιπλέον, η αρχική τιμή της οδηγού πίεσης (driving pressure, DP) συσχετίστηκε ανεξάρτητα με την ανάπτυξη όψιμης AKI. Συγκεκριμένα, κάθε αύξηση κατά μία τυπική απόκλιση στην DP συνδεόταν με αύξηση κατά 35% της πιθανότητας εμφάνισης όψιμης AKI (OR=1,35, 95% CI: 1,15–1,58), ενώ αναγνωρίστηκε κατώφλι κινδύνου στα 15 cmH_2O.Συμπεράσματα: Παρότι η συχνότητα εμφάνισης του παρατεταμένου μηχανικού αερισμού στους ασθενείς με ARDS μειώθηκε διαχρονικά, η θνητότητα παρέμεινε αμετάβλητα υψηλή. Οι παράγοντες που σχετίζονται με αυξημένη θνητότητα είναι κατά κύριο λόγο μη τροποποιήσιμοι. Στους ασθενείς αυτούς παρατηρείται προοδευτικά μια αποσύνδεση μεταξύ οξυγόνωσης και ενδοτικότητας, με βελτίωση της οξυγόνωσης αλλά εμμένουσα μειωμένη ενδοτικότητα. Η όψιμη οξεία νεφρική βλάβη είναι συχνή και συνδέεται με δυσμενή έκβαση και παρατεταμένο μηχανικό αερισμό. Τέλος, η συσχέτιση της αυξημένης DP με την επακόλουθη ανάπτυξη AKI υποδηλώνει ότι ο επιβλαβής μηχανικός αερισμός ενδέχεται να συμβάλλει στην εμφάνιση νεφρικής βλάβης στους ασθενείς με ARDS. Τα ευρήματα αυτά ενδέχεται να έχουν σημαντικές επιπτώσεις στον σχεδιασμό μελλοντικών κλινικών μελετών και στη βελτιστοποίηση της φροντίδας των ασθενών με ARDS.

B8. Summary

Introduction: Acute respiratory distress syndrome (ARDS) is a heterogenous entity whose trajectory may span from rapidly improving cases to cases receiving prolonged mechanical ventilation (PMV). PMV has been recognized to put an immense clinical and financial burden on health-care systems, yet relevant evidence specifically involving patients with ARDS is limited. We endeavored to take advantage of the large high-quality databases of randomized controlled trials conducted by the ARDS Network in order to estimate temporal trends of prevalence and mortality of PMV, identify risk factors associated with mortality of patients with ARDS receiving PMV, assess the trajectory of oxygenation and lung mechanics, as well assess the association between lung mechanics, acute kidney injury (AKI) and PMV. **Methods**: To investigate the prevalence and risk factors of mortality of ARDS patients requiring PMV, as well as the prevalence of "late AKI" and its effect on ARDS outcome, we performed a secondary analysis of individual patient data from the randomized controlled clinical trials conducted by the ARDS Network. All enrolled patients with ARDS were endotracheally intubated receiving or not PMV. PMV was defined as the need for mechanical ventilation for more than 21 consecutive days. "Late AKI" was defined as AKI developing after 48 hours of initiation of mechanical ventilation. To investigate the trajectory of the association of compliance with oxygenation apart from the ARDSNetwork cohort we used an additional cohort of ARDS patients with COVID-19 associated ARDS (CARDS) that were hospitalized in two intensive care units in Greece. We used a threshold of 150 for PaO_2/FiO_2 and 30 ml/cmH_2O for compliance, estimated the prevalence of each of the four combinations of oxygenation and compliance at baseline, and examined the change in its prevalence from baseline to day 21 in the ARDSNet and CARDS cohorts. **Results:** Out of 4216 patients with ARDS, 646 (15.3%) received PMV. Prevalence of PMV gradually declined from 18.4% in the ARMA (published in 2000) trial to 10.9% in the SAILS (2014) trial (R2=0.728, p=0.031). 90-day mortality of patients receiving PMV did not change over time (R2=0.271, p=0.290) and remained as high as 36.8%. Risk factors for mortality in patients with ARDS that require PMV included age, malignancy, pneumonia as the cause of ARDS, coagulation and hepatic failure during the first 21 days after trial enrolment, and tracheostomy. Data analysis from both the ARDS and CARDS patient cohorts showed an increase in the trajectory of prevalence of the combination of mild-

moderate hypoxemia and low compliance from baseline to day 21 both in the ARDSNet cohort (from 22.2% to 42.7%) and in the CARDS cohort (from 3.1% to 33.3%). Among surviving patients with low compliance, oxygenation improved over time. The 60-day mortality rate was higher for patients who had mild-moderate hypoxemia and low compliance on day 21 (28% and 56% in ARDSNet and CARDS), compared to those who had mild-moderate hypoxemia and high compliance (20% and 50%, respectively). Finally, "late AKI" developed in 33.8% patients. Patients with "late AKI" when compared to no AKI patients had a higher 90-day mortality [39% vs 17% ($p<0.001$)] and had a longer ICU admission [(mean ICU free days 6(0-20) vs 19 (7-23), $p<0.001$)] requiring prolonged mechanical ventilation [(median ventilator free days 7(0-22) vs 21 (4-25), p<001)]. Baseline driving pressure was independently associated with development of late AKI [each 1 standard deviation increase in driving pressure was associated with a 35% increase in the odds of late AKI (OR=1.35, 95% CI: 1.15-1.58)]. There was a threshold of driving pressure equal to 15 cm H_2O for its association with development of late AKI. **Conclusions:** Although prevalence of PMV among patients enrolled in ARDS Network trials gradually declined, mortality did not change. Risk factors associated with mortality were mostly non-modifiable. In these patients, a dissociation between oxygenation and compliance characterized by mild-moderate hypoxemia but low compliance becomes increasingly prevalent. "Late AKI" is common among ARDS patients and is associated with worse outcome and prolonged mechanical ventilation. Driving pressure was associated with subsequent development of AKI in patients with ARDS, suggesting that injurious mechanical ventilation may lead to AKI. These findings may have important implications for clinical trialists.

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