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par

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TITRE

Impact clinique de la pneumonie acquise sous ventilation mécanique chez les patients atteints de Syndrome de Détresse Respiratoire Aiguë : une étude de cohorte rétrospective.

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Sganarelle:

« Oui ! c'est l'habit d'un vieux médecin, qui a été laissé en gage au lieu où je l'ai pris, et il m'en a coûté de l'argent pour l'avoir. Mais, savez-vous, Monsieur, que cet habit me met déjà en considération, que je suis salué des gens que je rencontre, et que l'on me vient consulter ainsi qu'un habile homme.

Don Juan:

- *Comment donc.*

Sganarelle:

- *Cinq ou six paysans et paysannes en me voyant passer, me sont venus demander mon avis sur différentes maladies.*

Don Juan:

- *Tu leur as répondu que tu n'y entendais rien ?*

Sganarelle:

- *Moi ? Point du tout. l'ai voulu soutenir l'honneur de mon habit : j'ai raisonné sur le mal et leur ai fait des ordonnances à chacun.*

Don Juan:

- *Et quels remèdes encore leur as tu ordonnés ?*

Sganarelle:

- *Ma foi ! Monsieur, j'en ai pris par où j'en ai pu attraper; j'ai fait des ordonnances à l'aventure et ce serait une chose plaisante si les malades guérissaient et qu'on m'en vint remercier.*

Don Juan:

- *Et pourquoi non ? Par quelles raisons n'aurais-tu pas les mêmes privilèges comme tous les autres médecins ? Ils n'ont pas plus de part que toi aux guérisons des malades, et tout leur art est pure grimace. Ils ne font rien que recevoir la gloire des heureux succès et tu peux profiter comme eux du bonheur du malade, et voir attribuer à tes remèdes tout ce qui peut venir des faveurs du hasard et des forces de la nature. »*

Résumé

L'impact clinique d'un premier épisode de pneumonie associée à la ventilation mécanique (PAVM) a été peu étudié chez les patients atteints du syndrome de détresse respiratoire aiguë (SDRA) ventilés selon des modalités protectrices.

Nous avons inclus rétrospectivement les patients admis sur une période de 18 mois dans les 2 unités de réanimation adulte du Centre Hospitalier Régional d'Orléans hôpital, ventilés pendant plus de 2 jours et présentant les critères de la classification de Berlin pour le SDRA. L'association entre un premier épisode de PAVM et la probabilité de décès au jour 90 (critère principal) a été évaluée par un modèle à risques proportionnels de Cox traitant la PAVM comme une variable à entrée différée. Les critères d'évaluation secondaires comprenaient l'évolution du rapport PaO_2 / FiO_2 et du score SOFA autour de la PAVM, la durée de la VM, le nombre de jours sans VM et sans vasopresseur au jour 28 et la durée du séjour chez les patients avec et sans PAVM. Des analyses de sous-groupes ont été effectuées chez des patients atteints de SDRA lié au COVID-19 et chez ceux atteints de SDRA d'autres causes.

Parmi les 336 patients inclus (101 atteints de COVID-19 et 235 avec autres SDRA), 176 (52,4 %) ont développé une première PAVM. La PAVM a induit une baisse transitoire et modérée du rapport PaO_2 /FiO_2 sans augmentation des valeurs du score SOFA. La survenue d'une PAVM était associée à moins de jours sans ventilateur [différence médiane et IC à 95 %, −19 (− 20 ; − 13,5) jours] et de jours sans vasopresseur [− 5 (− 9 ; − 2) jours) au jour 28, et des durées de séjour en réanimation [+ 13 (+ 9 ; + 15) jours] et à l'hôpital [+ 11,5 (+ 7,5 ; + 17,5) jours] plus longues. Ces effets ont été observés dans les deux sous-groupes. Les taux de mortalité globaux au jour 90 étaient de 35,8 % et 30,0 % chez les patients avec et sans PAVM, respectivement (p = 0,30). Dans l'ensemble de la cohorte, la présence d'une PAVM [risque relatif ajusté (aRR) 3,16, IC à 95 % 2,04–4,89, p < 0,0001], la valeur du SAPS-2 à l'admission, une maladie rénale chronique et une admission pour arrêt cardiaque prédisaient la mort au jour 90, tandis que le statut COVID-19 n'avait pas d'impact indépendant. Lorsque les deux sous-groupes étaient analysés séparément, la PAVM prédisait le décès chez les patients non-COVID-19 (aRR 3,43, IC à 95 % 2,11-5,58, p <0,0001) mais pas chez ceux atteints de COVID-19 (aRR 1,19, IC à 95 % 0,32-4,49, p = 0,80).

Nous concluons que la PAVM est un prédicteur indépendant de la mortalité à 90 jours chez les patients atteints de SDRA. Cette condition exerce un impact limité sur l'oxygénation mais est corrélée à une durée prolongée de la ventilation mécanique, de support vasopresseur et de séjour en réanimation et à l'hôpital.

Title

Clinical impact of ventilator-associated pneumonia in patients with the acute respiratory distress syndrome: a retrospective cohort study

Abstract

Background: The clinical impact and outcomes of ventilator-associated pneumonia (VAP) have been scarcely investigated in patients with the acute respiratory distress syndrome (ARDS).

Methods: Patients admitted over an 18-month period in two intensive care units (ICU) of a university-affiliated hospital and meeting the Berlin criteria for ARDS were retrospectively included. The association between VAP and the prob- ability of death at day 90 (primary endpoint) was appraised through a Cox proportional hazards model handling VAP as a delay entry variable. Secondary endpoints included (i) potential changes in the PaO_2/FiO_2 ratio and SOFA score values around VAP (linear mixed modelling), and (ii) mechanical ventilation (MV) duration, numbers of ventilator- and vasopressor-free days at day 28, and length of stay (LOS) in patients with and without VAP (median or absolute risk difference calculation). Subgroup analyses were performed in patients with COVID-19-related ARDS and those with ARDS from other causes.

Results: Among the 336 included patients (101 with COVID-19 and 235 with other ARDS), 176 (52.4%) experienced a first VAP. VAP induced a transient and moderate decline in the PaO_2/FiO_2 ratio without increase in SOFA score values. VAP was associated with less ventilator-free days (median difference and 95% CI, − 19 [− 20; − 13.5] days) and vasopressor-free days (− 5 [− 9; − 2] days) at day 28, and longer ICU (+ 13 [+ 9; + 15] days) and hospital (+ 11.5 [+ 7.5; + 17.5] days) LOS. These effects were observed in both subgroups. Overall day-90 mortality rates were 35.8% and 30.0% in patients with and without VAP, respectively (P = 0.30). In the whole cohort, VAP (adjusted HR 3.16, 95% CI 2.04–4.89, P < 0.0001), the SAPS-2 value at admission, chronic renal disease and an admission for cardiac arrest predicted death at day 90, while the COVID-19 status had no independent impact. When analysed separately, VAP predicted death in non-COVID-19 patients (aHR 3.43, 95% CI 2.11–5.58, P < 0.0001) but not in those with COVID-19 (aHR 1.19, 95% CI 0.32–4.49, P = 0.80).

Conclusions: VAP is an independent predictor of 90-day mortality in ARDS patients. This condition exerts a limited impact on oxygenation but correlates with extended MV duration, vasoactive support, and LOS.

Mots-clés

- Syndrome de détresse respiratoire aiguë
- Pneumonie acquise sous ventilation mécanique
- Réanimation
- Ventilation mécanique
- Infections nosocomiales
- COVID-19
- Pronostic

Keywords

- Acute respiratory distress syndrome
- Ventilator-associated pneumonia
- Intensive care unit
- Mechanical ventilation
- Hospital-acquired infection
- COVID-19
- Outcome

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SERMENT D'HIPPOCRATE

En présence des Maîtres de cette Faculté,
de mes chers condisciples
et selon la tradition d'Hippocrate,
je promets et je jure d'être fidèle aux lois de l'honneur
et de la probité dans l'exercice de la Médecine.

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

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

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je rendrai à leurs enfants
l'instruction que j'ai reçue de leurs pères.

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

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Tables des matières

Introduction

Le syndrome de détresse respiratoire aiguë (SDRA) a été décrit pour la première fois en 1967 sur une série autopsique de 12 patients (1). Les critères histologiques du SDRA sont composés d'un ensemble morphologique réuni sous le terme de dommages alvéolaires diffus, qui comprend la présence de membranes hyalines, un œdème alvéolaire, une congestion des capillaires, un infiltrat alvéolaire à polynucléaires neutrophiles et macrophages, riche en protéines, évoluant vers une prolifération alvéolaire fibroblastique puis une phase de fibrose interstitielle organisée (2, 3).

Une première conférence de consensus se réunie en 1994 afin d'établir une définition universelle du SDRA et permettre ainsi une meilleure coordination des équipes internationales pour la réalisation d'essais cliniques d'envergure (4). Cette définition sera révisée par *The ARDS Definition Task Force* en 2012 avec la publication des critères de Berlin (5).

Table 3. The Berlin Definition of Acute Respiratory Distress Syndrome

	Acute Respiratory Distress Syndrome
Timing	Within 1 week of a known clinical insult or new or worsening respiratory symptoms
Chest imaging[a]	Bilateral opacities—not fully explained by effusions, lobar/lung collapse, or nodules
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload Need objective assessment (eg, echocardiography) to exclude hydrostatic edema if no risk factor present
Oxygenation[b]	
Mild	200 mm Hg < PaO_2/FIO_2 ≤ 300 mm Hg with PEEP or CPAP ≥5 cm H_2O[c]
Moderate	100 mm Hg < PaO_2/FIO_2 ≤ 200 mm Hg with PEEP ≥5 cm H_2O
Severe	PaO_2/FIO_2 ≤ 100 mm Hg with PEEP ≥5 cm H_2O

Abbreviations: CPAP, continuous positive airway pressure; FIO_2, fraction of inspired oxygen; PaO_2, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure.
[a] Chest radiograph or computed tomography scan.
[b] If altitude is higher than 1000 m, the correction factor should be calculated as follows: [PaO_2/FIO_2 × (barometric pressure/760)].
[c] This may be delivered noninvasively in the mild acute respiratory distress syndrome group.

Le SDRA est une entité clinique fréquente dans les unités de soins intensifs. Dans l'étude prospective internationale LUNG-SAFE réalisée en 2016, on estimait à 23% la proportion de patients de soins intensifs ventilés ayant les critères de Berlin du SDRA (6-7). Les principales

étiologies du SDRA sont, par ordre de fréquence, les pneumonies virales ou bactériennes, les sepsis d'origine extra-pulmonaire, l'inhalation du contenu gastrique, les états de choc non cardiogéniques, les pancréatites aiguës graves, les polytraumatismes, la chirurgie lourde (digestive ou thoracique), et le syndrome d'ischémie-reperfusion (6).

Le diagnostic de SDRA n'est pas univoque et repose sur un faisceau d'éléments clinico-radio-biologiques, définis par les critères de Berlin. Comme l'a montré l'étude LUNG SAFE, le SDRA n'est reconnu par les cliniciens que dans 60% des cas, d'autant plus lorsqu'il s'agit d'un SDRA léger qui n'est reconnu que dans 51% des cas (7). L'imagerie est la pierre angulaire de son diagnostic avec la réalisation de radiographies thoraciques, éventuellement complétées par la tomodensitométrie thoracique, la radiographie pouvant être mise en défaut par la mauvaise interprétation d'opacités radiologiques pouvant mimer les *patterns* du SDRA (épanchement pleural, tumeur, atélectasies) (6).

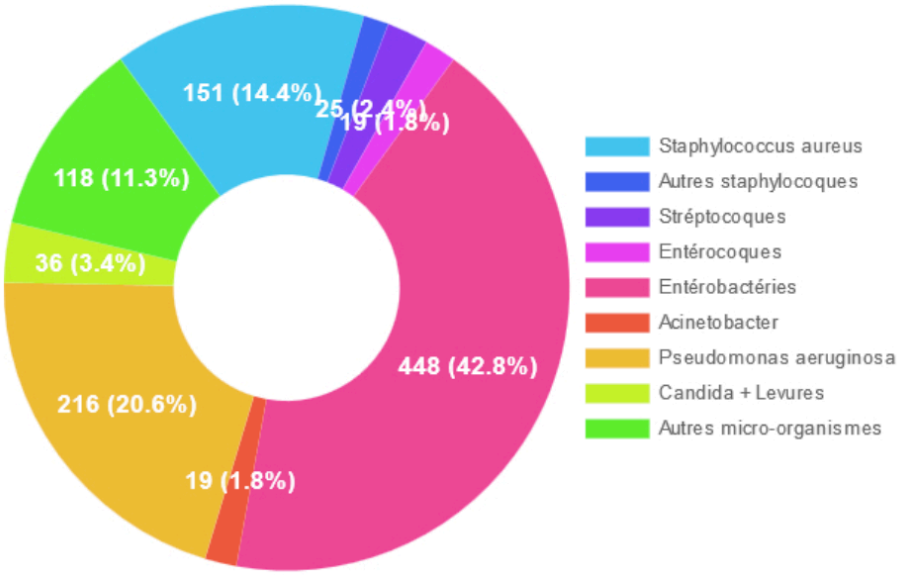
La prise en charge des patients présentant un SDRA est codifiée depuis plusieurs années et fait l'objet de recommandations récentes (2019) de la Société de Réanimation de Langue Française (8). Cette prise en charge repose sur une ventilation protectrice (volume courant de 6 mL/kg de poids idéal théorique, pression de plateau monitorée et n'excédant pas 30 cmH_2O, PEEP réglée à au moins 5 cmH_2O), une perfusion continue d'agents bloquants neuromusculaires et un positionnement en décubitus ventral (≥16 heures par jour) dans les formes modérées à sévères (PaO_2/FiO_2 ≤150 mmHg), l'inhalation de monoxyde d'azote en cas d'hypoxémie sévère et/ou de cœur pulmonaire aigu lié au SDRA, et l'utilisation de l'oxygénation veino-veineuse par membrane extracorporelle (*veino-veinous extra-corporeal membrane oxygenation*, VV-ECVMO) pour les patients éligibles présentant une hypoxémie réfractaire (PaO_2 /FiO_2 < 60-80 mmHg) et/ou une pression de plateau >30 cmH_2O malgré la mise en œuvre des procédures de ventilation protectrice susmentionnées.

L'impact pronostique de ce syndrome n'est pas négligeable : il est en effet associé à une mortalité hospitalière comprise entre 35 et 45% (7). Par ailleurs, le retentissement économique de cette pathologie est à prendre en compte du fait d'une consommation de soins accrue, de durées de ventilation mécanique et de séjour hospitalier augmentées (9). Chez les

survivants, seulement 50% ont repris une activité professionnelle 5 ans après la sortie de réanimation : un grand nombre de malades garde des limitations fonctionnelles invalidantes et une qualité de vie altérée malgré une récupération complète ou quasi-complète de leur fonction pulmonaire (9).

Les patients atteints de SDRA sont à haut risque de pneumonie associée à la ventilation mécanique (PAVM). La PAVM est la complication infectieuse nosocomiale la plus fréquente chez les patients de soins intensifs ventilés : son incidence globale est estimée entre 5 et 40% avec de larges disparités entre les pays, le type d'unités de réanimation (*case-mix*) et les critères diagnostics de PAVM (10). Son écologie est dominée par les Entérobactérales, *Pseudomonas aeroginosa* et *Staphylococcus aureus* (10).

Extrait du rapport national du réseau de Surveillance des infections associés aux dispositifs invasifs (2020).



La susceptibilité des patients en SDRA pour le développement de PAVM peut s'expliquer par trois mécanismes. Le premier est le dysfonctionnement des cellules immunitaires activées, qui tout en participant aux dommages tissulaires, manifestent des capacités de défenses anti-microbiennes altérées (11). Fait intéressant, ce déficit immunitaire de la muqueuse pulmonaire se prolonge après la guérison de l'inflammation primaire, augmentant ainsi la sensibilité aux PAVM pendant des semaines après l'inflammation systémique (12). Le deuxième élément est la modification importante et rapide du microbiote

respiratoire, avec une perte rapide de sa diversité, de l'augmentation de la charge en Enterobacterales et la formation de biofilm (11). Ainsi il faudrait envisager le développement d'une PAVM non comme une infection *de novo* par un agent pathogène exogène, mais plutôt comme une réponse dysbiotique à une maladie grave avec prolifération de genres spécifiques de bactéries (13). Enfin, le troisième facteur participant possiblement à l'émergence de PAVM est l'hyperoxie, à laquelle les patients en SDRA sont exposés à la phase précoce de la prise en charge, comme l'a montré une analyse secondaire de l'étude LUNG SAFE (14). L'hyperoxie est responsable de la formation d'espèces réactives de l'oxygène, de phénomènes de dénitrogénation et d'inhibition de la production de surfactant favorisant le collapsus expiratoire et les atélectasies, d'altération de la clairance du mucus, et de la diminution de l'efficacité des macrophages alvéolaires à migrer et phagocyter les bactéries, entraînant une diminution de la clairance bactérienne (11).

L'acquisition d'une PAVM dans la population générale des patients ventilés est associée à une durée de ventilation mécanique plus élevée et à une durée de séjour en soins intensifs plus importante que les patients n'ayant pas présenté de PAVM (10). La mortalité attribuable d'un premier épisode de PAVM est débattue dans la littérature puisque certains auteurs l'estiment autour de 1% (15) alors que d'autres estiment cette mortalité attribuable à 13% (16) ; cette mortalité attribuable semble maximale chez des patients de réanimation chirurgicale ou de gravité intermédiaire à l'admission. Ces données ont été obtenues dans une population générale de patients ventilés sans prendre en compte spécifiquement le sous-groupe des patients atteints de SDRA. Concernant ce dernier, un petit nombre d'études anciennes (1997-2015) ont observé l'impact clinique d'un premier épisode de PAVM au cours du SDRA (17, 18, 19, 20, 21). Leurs principaux résultats sont exposés dans le tableau suivant :

Etudes	Design	Mortalité	Durée de VM	Ventilator-free days à J28	ICU-free days à J28
DELCLAUX 1997	Cohorte prospective monocentrique 30 patients	VAP No-VAP 14 11 NS[1]	VAP No-VAP 23.6 12.5 $p < 0.05$	-	-
CHASTRE 1997	Cohorte prospective monocentrique 243 patients	VAP No-VAP 16(52%) 18(72%) NS	VAP No-VAP 34 17 $p = 0.004$	-	-
MARKOWICZ 1999	Cohorte prospective multicentrique 134 patients	VAP No-VAP 28(57%) 50(59%) $p = 0.8$[1]	VAP No-VAP 33 11.3 $p < 0.0001$	-	-
FOREL 2012	RCT multicentrique 339 patients	VAP No-VAP 41(42%) 81(33%) $p = 0.15$[2]	-	VAP No-VAP 0 14 $p < 0.0001$	VAP No-VAP 0 4 $p < 0.0001$
AYZAC 2015	RCT multicentrique 466 patients	VAP No-VAP 31(33%) 95(25%) $p = 0.13$[1]	-	VAP No-VAP 9.1 11.7 $p = 0.25$	VAP No-VAP 7.2 9.2 $p < 0.001$

1 : mortalité en soins intensifs ; 2 : mortalité à J90

VAP Ventilator-associated pneumonia *; ICU* Intensive care unit *; RCT* Randomized controlled trial.

De surcroit, ces études ont été réalisées avant les dernières mises à jour des recommandations visant à prévenir et diagnostiquer l'apparition de PAVM chez les patients de soins critiques par *l'Infectious Disease Society of America* (IDSA) en 2016 et par les experts français de la SFAR et de la SRLF en 2018 (22, 23).

Un sous-groupe de patients a particulièrement retenu notre attention ces dernières années : les patients atteints de pneumonie sévère à SARS CoV-2, hospitalisés dans nos unités de soins intensifs. Il a été rapidement montré que la très grande majorité de ces patients présentait les critères de SDRA, selon la définition de Berlin, lorsqu'ils nécessitaient d'être ventilés de façon invasive (24, 25). Parallèlement à ces constatations, la littérature a rapporté une incidence plus élevée des PAVM dans ce sous-groupe, en comparaison aux patients atteints de SDRA grippaux ou de causes non virales (24, 26). Cela a notamment été montré dans un travail multicentrique Européen du *CoVAPid Study Group* (26) où l'incidence d'un premier épisode de PAVM [*subdistribution hazard ratio* et IC à 95% : 1,60 (1,26–2,04) pour SDRA sur COVID-19 versus pneumonie grippale et 1,70 (1,20–2,39) pour COVID-19 versus

pneumonies non virales]. Cependant, en novembre 2020, date à laquelle nous avons envisagé ce travail, il n'y avait pas dans la littérature d'études qui comparaient spécifiquement le pronostic des PAVM dans les sous-groupes de patients atteints de SDRA lié à la COVID-19 et ceux atteints de SDRA d'autres étiologies.

L'objectif principal de ce travail de thèse était d'évaluer l'impact d'un premier épisode de PAVM sur la mortalité à J90 dans une cohorte de patients présentant un SDRA et ventilés selon des modalités protectrices. Les objectifs secondaires étaient d'évaluer, dans cette population, l'impact d'une première PAVM sur le rapport pression partielle artérielle en oxygène sur fraction inspirée en oxygène (PaO_2/FiO_2); les défaillances d'organe évaluées par le score SOFA (*Sepsis-related Organ Failure Assessment*) ; la durée de ventilation mécanique ; le nombre de jours vivant sans ventilation mécanique à J28 (*ventilator-free days)* ; le nombre de jours vivant sans vasopresseurs à J28 (*vasopressor-free days*) et la durée de séjour en soins intensifs et à l'hôpital. L'impact d'une première PAVM sur ces variables a été évalué sur l'ensemble de la population d'étude, puis en distinguant les patients avec SDRA secondaire à la COVID-19 et ceux avec SDRA secondaire à d'autres étiologies. Ce travail de thèse a fait l'objet d'une publication en premier auteur dans un journal international à comité de lecture (Annals of Intensive Care, impact factor 2021 = 10,318).

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RESEARCH Open Access

Clinical impact of ventilator-associated pneumonia in patients with the acute respiratory distress syndrome: a retrospective cohort study

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Abstract

Background: The clinical impact and outcomes of ventilator-associated pneumonia (VAP) have been scarcely investigated in patients with the acute respiratory distress syndrome (ARDS).

Methods: Patients admitted over an 18-month period in two intensive care units (ICU) of a university-affiliated hospital and meeting the Berlin criteria for ARDS were retrospectively included. The association between VAP and the probability of death at day 90 (primary endpoint) was appraised through a Cox proportional hazards model handling VAP as a delay entry variable. Secondary endpoints included (i) potential changes in the PaO_2/FiO_2 ratio and SOFA score values around VAP (linear mixed modelling), and (ii) mechanical ventilation (MV) duration, numbers of ventilator- and vasopressor-free days at day 28, and length of stay (LOS) in patients with and without VAP (median or absolute risk difference calculation). Subgroup analyses were performed in patients with COVID-19-related ARDS and those with ARDS from other causes.

Results: Among the 336 included patients (101 with COVID-19 and 235 with other ARDS), 176 (52.4%) experienced a first VAP. VAP induced a transient and moderate decline in the PaO_2/FiO_2 ratio without increase in SOFA score values. VAP was associated with less ventilator-free days (median difference and 95% CI, − 19 [− 20; − 13.5] days) and vasopressor-free days (− 5 [− 9; − 2] days) at day 28, and longer ICU (+ 13 [+ 9; + 15] days) and hospital (+ 11.5 [+ 7.5; + 17.5] days) LOS. These effects were observed in both subgroups. Overall day-90 mortality rates were 35.8% and 30.0% in patients with and without VAP, respectively ($P = 0.30$). In the whole cohort, VAP (adjusted HR 3.16, 95% CI 2.04–4.89, $P < 0.0001$), the SAPS-2 value at admission, chronic renal disease and an admission for cardiac arrest predicted death at day 90, while the COVID-19 status had no independent impact. When analysed separately, VAP predicted death in non-COVID-19 patients (aHR 3.43, 95% CI 2.11–5.58, $P < 0.0001$) but not in those with COVID-19 (aHR 1.19, 95% CI 0.32–4.49, $P = 0.80$).

Conclusions: VAP is an independent predictor of 90-day mortality in ARDS patients. This condition exerts a limited impact on oxygenation but correlates with extended MV duration, vasoactive support, and LOS.

Keywords: Acute respiratory distress syndrome, Ventilator-associated pneumonia, Intensive care unit, Mechanical ventilation, Hospital-acquired infection, COVID-19, Outcome

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Introduction

The acute respiratory distress syndrome (ARDS) is a clinical entity resulting from a wide spectrum of infectious or non-infectious conditions and combining bilateral pulmonary infiltrates, altered lung compliance, severe hypoxemia, and histopathological patterns of diffuse alveolar damage [1]. This syndrome may affect up to one fourth of intensive care unit (ICU) patients requiring invasive mechanical ventilation (MV) and is linked with hospital mortality rates ranging from 35 to 45%, poor long-term functional prognosis, and substantial utilization of healthcare resources [2–4].

Patients with ARDS appear at high risk for ventilator-associated pneumonia (VAP) due to protracted MV exposure, impaired innate as well as adaptative lung immunity, and dysregulation of the respiratory microbiota [5]. In the general population of intubated patients, the occurrence of VAP is associated with delayed MV weaning and extended ICU length of stay (LOS); however, the attributable mortality of this condition is still debated, varying from ~ 1% to ~ 13% in the available literature [6, 7]. Such data are scarce in the specific subgroup of patients with ARDS and mainly come from studies conducted before the implementation of current policies for VAP prevention and lung protection [8–12].

A vast majority of patients receiving MV for severe coronavirus disease 2019 (COVID-19) meet the Berlin criteria for ARDS [13–16]. These subjects are at increased hazard of VAP when compared to mixed (i.e., ARDS and no ARDS) and/or historical cohorts of non-COVID-19 patients [15, 17–19]. Yet, to the best of our knowledge, whether the epidemiological features, clinical impact and outcomes of VAP differ between patients with COVID-19-related ARDS and those with ARDS from other aetiologies has not been specifically investigated.

The objective of this study was to appraise the clinical impact and outcomes of a first VAP episode in a contemporary cohort of patients with ARDS. Day-90 mortality was the primary endpoint. Secondary endpoints included changes in the arterial partial pressure of oxygen/fraction of inspired oxygen (PaO_2/FiO_2) ratio and Sequential Organ Failure Assessment (SOFA) score values around VAP, MV duration, number of ventilator-free days and vasopressor-free days at day 28, and ICU and hospital LOS. These endpoints were investigated on the whole study cohort then separately in patients with COVID-19-related ARDS and those with ARDS from other causes.

Patients and methods

Study design and setting

This retrospective cohort study was conducted over an 18-month period (April 1, 2019–September 30, 2020) in the 32-bed medical ICU and the 30-bed surgical ICU of a 1100-bed tertiary care and university-affiliated hospital in France (see the Additional file 1 for details). In these ICUs, all intubated patients meeting the criteria for ARDS are managed with protective ventilatory settings, continuous infusion of neuromuscular blocking agents (NMBA) and routine prone positioning (PP) $\geq$ 16 h per day at the early phase of moderate-to-severe ARDS ($PaO_2/FiO_2 < 150$ mmHg), nitric oxide inhalation in case of severe hypoxemia and/or ARDS-related *acute cor pulmonale*, and the use of veno-venous extra-corporeal membrane oxygenation (ECMO-VV) for eligible patients with refractory hypoxemia ($PaO_2/FiO_2 < 60$–80 mmHg) and/or a plateau pressure > 30 cmH_2O despite the implementation of the aforementioned protective ventilatory settings and procedures, in accordance with current guidelines [20]. Corticosteroids are considered on a case-by-case basis in patients with early or late ARDS [21]. Dexamethasone was routinely administered to COVID-19 patients from July 2020 [22]. Bundles for VAP prevention and policies for VAP diagnosis and treatment are exposed in the Additional file 1.

Patient recruitment, data collection and definitions

All patients admitted over the inclusion period and intubated for $\geq$ 3 calendar days were identified using coding registries then screened for the Berlin criteria of ARDS through medical chart reviewing: those presenting these criteria for $\geq$ 2 calendar days were enrolled in the study cohort [23]. Variables exposed in the tables were extracted from (i) computerized medical charts including automatedly implemented biological, MV and monitoring data (ICCA software, Philips, Amsterdam, The Netherlands) and (ii) the microbiology laboratory database.

All episodes of VAP prospectively diagnosed by attending physicians and mentioned in the medical charts were retrospectively evaluated and retained for analyses provided that they fulfilled the following criteria: (i) new or progressive persistent pulmonary infiltrates on chest X-ray combined with (ii) purulent tracheal secretions, (iii) fever or hypothermia (body temperature $\geq$ 38.5 °C or $\leq$ 36.5 °C, respectively) and/or leukocytosis or leukopenia (white blood cells count $\geq$ 10.4 mL or $\leq$ 4 × 10.3 mL, respectively), and (iv) a positive

quantitative lower respiratory tract sample (endotracheal aspirate [ETA] ≥ 10.5 colony-forming unit [CFU]/mL, broncho-alveolar lavage [BAL] fluid ≥ 10.4 CFU/mL or plugged telescopic catheter [PTC] ≥ 10.3 CFU/mL) in patients with prior MV duration ≥ 3 calendar days. This definition was based on current guidelines [24–26]. Ambiguous cases were solved by consensus among the investigators. VAP without microbiological documentation were discarded. Ventilator-associated tracheobronchitis (VAT) episodes were not studied in this work.

COVID-19 was documented through detection of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) in nasopharyngeal or lower respiratory tract sample using real-time polymerase chain reaction. Adequate antimicrobial therapy was defined as the administration of at least one agent with *in-vitro* activity on the causative pathogens. The PaO_2/FiO_2 ratio was obtained from the results of blood gas collected at least once a day in every patient with ARDS in the participating ICUs—in cases of multiple blood gas samples collected on a given day, the worst daily PaO_2/FiO_2 ratio value was analysed. The SOFA score was calculated using the biological values of the corresponding day or, when not measured, those from the closest day. Ventilator-free days and vasopressor-free days at day 28 were, respectively, defined as the total number of calendar days without invasive MV and vasoactive support over the first 28 days following intubation (day 0), with a zero-value attributed to patients deceased during this timeframe [27].

The study protocol was approved on November 27th, 2020 by the Ethical committee of the French Society of Intensive Care (CE-SRLF-20-84). Results of this study are reported according to the STROBE guidelines [28]. Missing values are exposed in the Additional file 1: Table S1.

Statistical analyses

Data are expressed as median (interquartile range) for continuous variables and number (%) for categorical variables, unless otherwise indicated. Patient characteristics were compared using the Mann–Whitney *U* test for continuous variables and the Fisher's exact test or χ^2 test for categorical variables, as appropriate. Missing values were not imputed, since all analysed variables were available for ≥ 98% of patients.

The relationship between the cause of ARDS (that is, COVID-19 versus others) and the cumulative likelihood of VAP over time was appraised through the Gray test handling MV weaning and death as competing events, with calculation of sub-distribution hazard ratio (HR) and 95% confidence interval (CI).

Temporal changes in the PaO_2/FiO_2 ratio and SOFA score values around the day of VAP diagnosis (i.e., from $Day_{VAP} - 2$ [$D_{VAP} - 2$] to $D_{VAP}+7$) were analyzed by linear mixed modelling after preliminary checking of the normal distribution of these variables through inspection of density plots and quantile–quantile plots. For this analysis, ARDS aetiologies (COVID-19 versus others), time-points and the interaction term "group by time" were entered as fixed-effect variables, while patients were entered as random-effect variables with correlated intercept and slope. Post-hoc comparisons of estimated marginal means with 95% CI were adjusted by the Tukey method.

Outcome variables (that is, numbers of ventilator-free and vasopressor-free days at day 28, ICU and hospital LOS, and in-ICU, in-hospital and day-90 mortality rates) were compared between patients with and without VAP through the calculation of median or absolute risk differences with corresponding 95% CI. The Kruskal–Wallis rank sum test was used to assess differences in the number of ventilator-free days between COVID-19 and non-COVID-19 patients and/or according to whether patients developed VAP within the first 28 days or not and/or were discharged alive from the ICU or not. The relationship between the occurrence of VAP and the cumulative likelihood of MW weaning over time, presented as sub-distribution HR and 95% CI, was evaluated through the Gray test handling VAP as a delay entry variable and death as a competing event.

The associations of VAP occurrence and COVID-19 status with the probability of death at day 90 were studied in the framework of a Cox proportional hazards model with robust variance and adjustment for baseline covariables linked with death in bivariable analysis ($P < 0.2$). VAP was handled as a delay entry variable [29]. VAP and COVID-19 as the cause of ARDS were forced in the model. Collinearity was checked by calculation of the variance inflation factor for each other variable introduced in the model. Potential violation of the proportional assumption was appraised by examining the Schoenfeld residual plots. For patients discharged alive from the hospital but lost to follow-up before day 90, the vital status was censored at the date of last available information. The cumulative probability of survival after the onset of VAP was compared between the two subgroups using the log-rank test.

All analyses were conducted using the R software version 3.5.1 (http://www.R-project.org). Two-tailed *P* values < 0.05 were considered statistically significant.

Results

Study population

A total of 336 patients were enrolled in the study, including 101 with COVID-19-related ARDS and 235 with ARDS from other causes (Additional file 1: Fig. S1). Among the latter, 152 (64.7%) were admitted

Table 1 Characteristics of the study population

Characteristics	All patients with ARDS (n = 336)	Patients with COVID-19-related ARDS (n = 101)	Patients with ARDS from other causes (n = 235)	*P* value
Male sex	247 (73.5)	73 (72.3)	174 (74.0)	0.79
Age, years	67 (57–74)	67 (58–72)	66 (55–74)	0.73
BMI, $kg.m^{-2}$	28.5 (25.0–32.6)	29.4 (26.1–32.1)	27.8 (24.1–32.9)	0.13
Immune deficiency	53 (15.8)	11 (10.9)	42 (17.9)	0.14
SAPS 2 at ICU admission	50 (38–67)	40 (33–49)	56 (43–71)	< 0.0001
SOFA score at ICU admission	8 (5–11)	5 (3–8)	9 (7–12)	< 0.0001
ARDS aetiology				
COVID-19[a]	101 (30.0)	101 (100)	–	NA
Bacterial or non-SARS-CoV-2 viral pneumonia	106 (31.6)	–	106 (45.1)	
Aspiration	60 (17.9)	–	60 (25.5)	
Extra-pulmonary sepsis	45 (13.4)	–	45 (19.1)	
Miscellaneous	24 (7.1)	–	24 (10.2)	
ARDS and MV characteristics[b]				
Lowest Vt, mL kg^{-1} (PBW)	6.1 (5.8–6.6)	6.0 (5.8–6.3)	6.1 (5.7–6.8)	0.02
Highest PEEP, cmH_2O	10 (7–13)	12 (11–14)	8 (6–12)	< 0.0001
Highest plateau pressure, cmH_2O	24 (20–27)	26 (24–28)	23 (18–26)	< 0.0001
Highest driving pressure, cmH_2O	13 (10–16)	13 (11–15)	13 (10–16)	0.91
Lowest PaO_2/FiO_2 ratio, mmHg	100 (74–163)	91 (76–138)	105 (74–172)	0.17
Highest $PaCO_2$, mmHg	44 (40–52)	43 (38–49)	46 (40–55)	0.0005
Lowest pH	7.36 (7.25–7.4)	7.36 (7.30–7.42)	7.35 (7.22–7.39)	< 0.0001
ARDS classification (Berlin definition)[b] Mild	50 (14.9)	11 (10.9)	39 (16.6)	0.09
Moderate	116 (34.5)	30 (29.7)	86 (36.6)	
Severe	170 (50.6)	60 (59.4)	110 (46.8)	
ARDS-targeted therapies				
Prone positioning	127 (37.8)	75 (74.3)	52 (22.1)	< 0.0001
Number of days	5 (2–11)	8 (3–16)	2 (1–5)	< 0.0001
Nitric oxide inhalation	90 (26.8)	46 (45.5)	44 (19.1)	< 0.0001
Neuromuscular blocking agents	209 (62.2)	86 (85.1)	123 (52.3)	< 0.0001
Organ support during the ICU stay				
Invasive MV duration, overall, days Vasopressors	11 (7–20)	17 (10–26)	9 (6–16)	< 0.0001
Renal replacement therapy	280 (83.3)	82 (81.2)	198 (84.2)	0.52
VV-ECMO	85 (25.3)	23 (22.8)	62 (26.4)	0.58
VA-ECMO	15 (4.5)	7 (6.9)	8 (3.4)	0.16
	7 (2.1)	0	7 (3.0)	0.11
Ventilator-associated pneumonia				
First episode	176 (52.4)	69 (68.3)	107 (45.5)	0.0001
Prior MV duration, days	7 (4–11)	9 (8–13)	6 (4–10)	0.01
More than one episode	59 (17.6)	35 (34.6)	24 (10.2)	< 0.0001

Data are expressed as number (%) or median (interquartile range)

ARDS acute respiratory distress syndrome, *COVID-19* coronavirus disease 2019, *BMI* body mass index, *COPD* chronic obstructive pulmonary disease, *ICU* intensive care unit, *LOS* length of stay, *SAPS 2* simplified acute physiology score 2, *SOFA* sepsis-related organ failure assessment, *MV* mechanical ventilation, *Vt* tidal volume, *PBW* predicted body weight, *PEEP* positive end-expiratory pressure, *VV/VA-ECMO* veno-venous/veno-arterial extracorporeal membrane oxygenation

[a] Including 8 cases (7.9%) with bacterial and/or viral co-infection

[b] First day with ARDS criteria

Full characteristics of the study population are provided in Additional file 1: Table S1

between April 2019 and February 2020 (that is, before the beginning of the pandemic) and the remaining 83 (35.3%) between March and September 2020. The characteristics of the study population are summarized in Table 1 and fully exposed in Additional file 1: Table S1. Bacterial or non-SARS-CoV-2 viral pneumonia, aspiration and extra-pulmonary sepsis were the leading causes of ARDS in non-COVID-19 patients. ARDS was classified as mild, moderate and severe in 50 (14.9%), 116 (34.5%) and 170 (50.6%) patients, respectively—this

Table 2 Factors associated with the occurrence of VAP

	Patients with VAP (n = 176)	Patients without VAP (n = 160)	*P* value
Male sex	141 (80.1)	106 (66.2)	0.004
Age, years	66 (57–73)	68 (57–74)	0.38
BMI, kg m^{-2}	28.5 (25.0–31.6)	28.5 (24.9–33.1)	0.64
Past or current smoking	70 (39.8)	62 (38.7)	0.91
Chronic diseases			
Diabetes mellitus	49 (27.8)	46 (28.7)	0.90
COPD	19 (10.8)	21 (13.1)	0.61
Respiratory, others	28 (15.9)	17 (10.6)	0.20
Cardiac	55 (31.2)	44 (27.5)	0.47
Hepatic	17 (9.7)	12 (7.5)	0.56
Renal	11 (6.2)	17 (10.6)	0.17
Immune deficiency	20 (11.4)	33 (20.6)	0.02
Solid or haematological malignancy	11 (6.2)	23 (14.4)	0.02
Others	9 (5.1)	12 (7.5)	0.38
ARDS aetiology			
COVID-19	69 (39.2)	32 (20.0)	0.0001
Other causes	107 (60.8)	128 (80.0)	
SAPS 2 at ICU admission	49 (38–66)	51 (38–67)	0.60
SOFA score at ICU admission	8 (5–10)	8 (6–11)	0.11
Lymphocyte count, mm^{-3}			
ICU admission	760 (500–1220)	705 (400–1152)	0.18
Day 7	775 (487–1202)	810 (520–1210)	0.78
Day 14	970 (637–1407)	1000 (620–1505)	0.73
ARDS classification (Berlin definition)[a]			
Mild	23 (13.1)	27 (16.9)	0.29
Moderate	57 (32.4)	59 (36.9)	
Severe	96 (54.5)	74 (46.2)	
ARDS-targeted therapies			
Prone positioning	92 (52.3)	35 (21.9)	< 0.0001
Number of days	7 (2–13)	2 (1–6)	0.0006
Neuromuscular blocking agents	128 (72.7)	81 (50.6)	< 0.0001
Corticosteroids (all pooled)[b]	81 (46.0)	88 (55.0)	0.10
Proton pump inhibitor[b]	161 (91.5)	143 (89.4)	0.58
Intra-hospital transport[b]	107 (60.8)	77 (48.1)	0.02
Life-sustaining therapies			
Invasive MV duration, overall, days	17 (12–29)	7 (5–10)	< 0.0001
Vasopressors	157 (89.2)	123 (76.9)	0.003
Renal replacement therapy	52 (29.5)	33 (20.6)	0.08
VA-ECMO	4 (2.3)	3 (1.9)	1
VV-ECMO	13 (7.4)	2 (1.2)	0.007

Data are expressed as number (%) or median (interquartile range)

VAP ventilator-associated pneumonia, *ARDS* acute respiratory distress syndrome, *COVID-19* coronavirus disease 2019, *BMI* body mass index, *COPD* chronic obstructive pulmonary disease, *ICU* intensive care unit, *LOS* length of stay, *SAPS 2* simplified acute physiology score 2, *SOFA* sepsis-related organ failure assessment, *MV* mechanical ventilation, *VA/VV-ECMO* veno-arterial/veno-venous extracorporeal membrane oxygenation

[a] First day with ARDS criteria

[b] Before the occurrence of first ventilator-associated pneumonia (VAP), or during the whole ICU stay in patients without VAP

distribution was similar in patients with and without COVID-19.

Incidence and clinical features of VAP

Overall, a first episode of VAP was documented in 176 patients (52.4%) after a median of 7 (4–11) days of MV. Factors associated with the occurrence of VAP are exposed in Table 2. The hazard of VAP was higher in COVID-19 patients (cumulative incidence, 69 out of 101, 68.3%) than in those with ARDS from other causes (107 out of 235, 45.5%) after adjustment on the competing risks of extubation and death (sub-distribution HR 1.64, 95% CI 1.23–2.18, $P = 0.0007$) (Additional file 1: Fig. S2). The crude prevalence of VAP in patients with

non-COVID-19-related ARDS remained stable after the beginning of the pandemic (67/152 [44.1%] before March 2020 and 40/83 patients [48.2%] from March 2020, $P=0.58$).

The microbiological documentation of VAP was obtained through ETA, BAL and PTC in 135 (76.7%), 27 (15.3%) and 14 (8.0%) patients, respectively. Prior antimicrobial exposure and the distribution of pathogens responsible for VAP are exposed in Additional file 1: Table S2. Enterobacterales (60.8%), *Pseudomonas aeruginosa* (18.2%), *Staphylococcus aureus* (11.4%) and *Stenotrophomonas maltophilia* (10.8%) were the most common causative microorganisms. One hundred and twenty patients (68.2%) received adequate antimicrobial therapy within 24 h following the diagnosis of VAP (COVID-19 patients versus others, 46 [66.7%] versus 74 [69.2%], $P=0.74$).

Primary study endpoint

Crude day-90 mortality rates did not differ between patients with and without VAP (65 [35.8%] versus 48 [30.0%] deceased patients, mean difference and 95% CI, 5.8% [− 4.3%; 15.6%], $P=0.30$) (Table 3). After adjustment on potential confounders, VAP (adjusted HR [aHR] 3.16, 95% CI 2.04–4.89, $P<0.0001$), the SAPS 2 value at ICU admission (aHR per 1-point increase 1.02, 1.00–1.03, $P=0.005$), chronic renal disease (aHR 2.11, 1.10–4.05, $P=0.02$) and cardiac arrest as the mean reason for ICU admission (aHR 2.00, 1.02–3.92, $P=0.04$) predicted death at day 90, while the COVID-19 status had no independent effect (aHR 0.94, 0.54–1.66, $P=0.84$) (Additional file 1: Table S3; Fig. 1). The association between VAP and day-90 mortality was not modified when forcing prone positioning and steroid use during the ICU stay into the model (aHR, 2.67, 1.72–4.14, $P<0.0001$) (Additional file 1: Table S3). However, when applying the same model separately to both subgroups, the occurrence of VAP was an independent predictor of death at day 90 in patients with non-COVID-19-related ARDS (aHR 3.43, 95% CI 2.11–5.58, $P\leq 0.0001$) but not in those with COVID-19-related ARDS (aHR 1.19, 95% CI 0.32–4.49, $P=0.80$) (Fig. 1). The cumulative probability of survival after the onset of VAP was higher in COVID-19 patients than in those with other ARDS (log-rank test, $P=0.02$) (Additional file 1: Fig. S3).

Secondary study endpoints

The PaO_2/FiO_2 ratio declined from 174 (162–185) mmHg at D_{VAP} − 2 to 155 (144–166) mmHg at D_{VAP} then re-increased to 177 (165–188) mmHg at $D_{VAP}+3$ and 181

Table 3 Main outcome measures

Outcome measures	All patients with ARDS			Patients with COVID-19-related ARDS			Patients with ARDS from other causes		
	VAP (n = 176)	No VAP (n = 160)	Difference (95% CI)	VAP (n = 69)	No VAP (n = 32)	Difference (95% CI)	VAP (n = 107)	No VAP (n = 128)	Difference (95% CI)
MV duration, days	17 (12–29)	7 (5–10)	10 (8; 12)	22 (17–33)	8 (7–13)	14 (10; 17.5)	15 (9–24)	7 (5–10)	8 (6; 10)
Ventilator-free days at day 28[1] All patients ICU survivors	0 (0–12) 11 (0–15)	19 (0–22) 21 (18–23)	− 19 (− 20; − 13.5) − 10 (− 13; − 9)	2 (0–11) [b] 7 (0–11.5)	19 (11–21) 20 (16.5–21)	− 17 (− 20; − 9.5) − 13 (− 17; − 9)	0 (0–14) [b] 12 (2–17)	19 (0–22) 21 (19–23)	− 19 (− 20; − 10) − 9 (− 11; − 6)
Vasopressor-free days at day 28 [a]	18 (0–24)	23 (0–27)	− 5 (− 9; − 2)	18 (10–25)	25 (20.5–28)	− 7 (− 11; − 1)	16 (0–24)	23 (0–26)	− 7 (− 15; − 2)
ICU LOS, days [a]	23 (16–36)	10 (8–14)	13 (9; 15)	27 (19–41)	11 (10–16)	15 (11.5; 21.5)	19 (13–28)	10 (8–14)	9 (7; 13)
Hospital LOS, days [a]	32 (21–48)	21 (12–31)	11.5 (7.5; 17.5)	37 (25–50)	21 (16–28)	15.5 (11; 24)	29 (17–47)	20 (11–34)	8.5 (2; 15)
In-ICU mortality	59 (33.5)	43 (26.9)	6.6 (− 3.2; 16.2)	18 (26.1)	6 (18.7)	7.3 (− 11.5; 22.4)	41 (38.3)	37 (28.9)	9.4 (− 2.6; 21.3)
In-hospital mortality	63 (35.8)	45 (28.1)	7.7 (− 2.3; 17.4)	18 (26.1)	6 (18.7)	7.3 (− 11.5; 22.4)	45 (42.1)	39 (30.5)	11.6 (− 0.7; 23.5)
Mortality at day 90 [c]	63 (35.8)	48 (30.0)	5.8 (− 4.3; 15.6)	18 (26.1)	6 (18.7)	7.3 (− 11.5; 22.4)	45 (42.1)	42 (32.8)	9.2 (− 3.1; 21.3)

Data are expressed as number (%) or median (interquartile range), with median difference for continuous variable and absolute risk difference for ICU and in-hospital mortality rates

ARDS acute respiratory distress syndrome, *VAP* ventilator-associated pneumonia, *CI* confidence interval, *COVID-19* coronavirus disease 2019, *MV* mechanical ventilation, *ICU* intensive care unit, *LOS* length of stay

[a] $P<0.001$ for the comparison between COVID-19 and non-COVID-19 patients and/or according to whether patients developed VAP within the first 28 days or not

[b] Median difference (95% CI), 2 (− 8; 6) days

[c] Nine patients were lost to follow-up at day 90 (5 patients with VAP and 4 patients without VAP)

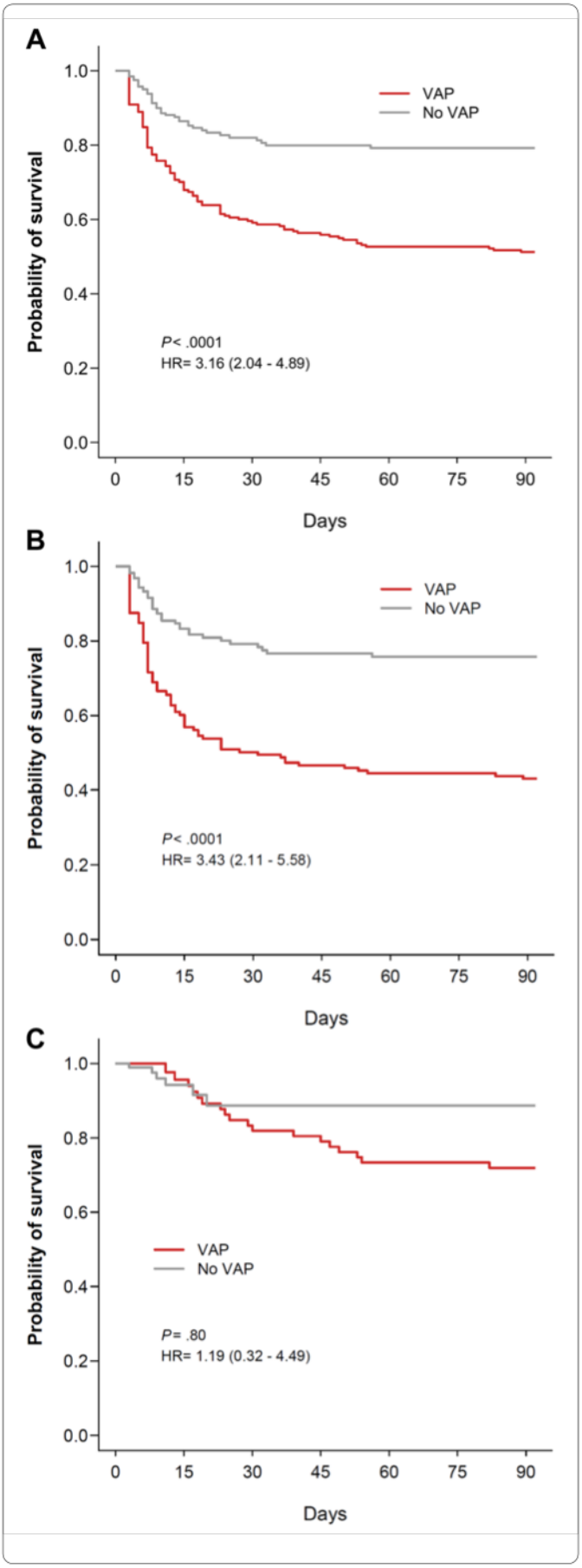

Fig. 1 Cumulative likelihood of survival over time in patients with and without VAP. *VAP* ventilator-associated pneumonia, *HR* hazard ratio (indicated with 95% confidence interval). Day 0 indicates the date of intubation. Panel **A**, all patients with acute respiratory distress syndrome (ARDS); Panel **B**, patients with non-coronavirus disease 2019 (COVID-19)-related ARDS; Panel **C**, patients with COVID-19-related ARDS

(168–194) mmHg and $D_{VAP}+7$ (estimated marginal means and 95% CI, $P<0.05$ for the comparison with D_{VAP} at each other timepoint) (Fig. 2A). Time courses of the PaO_2/FiO_2 ratio around D_{VAP} did not differ between the two subgroups though absolute values were lower in COVID-19 patients ($P=0.01$ at each timepoint) (Fig. 2B). Of note, the level of PEEP was similar and remained unchanged around D_{VAP} in both subgroups (median value at D_{VAP}, overall, 10 [8–13] cmH_2O) (Additional file 1: Fig. S4).

The extra-respiratory and total SOFA score values did not evolve significantly between $D_{VAP}-2$ and D_{VAP} then decreased after D_{VAP} in non-COVID-19 patients (Fig. 2D, F). In COVID-19 patients, no variation was observed in the extra-respiratory and total SOFA score values around D_{VAP}; these values were significantly lower than those observed in patients with ARDS from other causes.

Overall, patients with VAP experienced less ventilator-free days at day 28 than those not developing this condition (median difference and 95% CI, − 19 [− 20; − 13.5] days), with a similar difference in both subgroups (Table 3). After adjustment on the competing risk of death, the cumulative likelihood of MV weaning differed neither between patients with and without VAP (sub-distribution HR 1.17, 95% CI 0.91–1.50, $P=0.22$) (Fig. 3) nor according to the COVID-19 status in patients with VAP (sub-distribution HR 1.10, 95% CI 0.75–1.60, $P=0.62$). Finally, the occurrence of VAP correlated with less vasopressor-free days (− 5 [− 9; − 2] days) at day 28 and longer ICU (+13 [+9;+15] days) and hospital (+11.5 [+7.5;+17.5] days) LOS. These differences were observed in both subgroups (Table 3). Of note, when handling death as a competing event, the cumulative likelihood of ICU discharge over time was significantly lower in patients with VAP than in those without VAP (sub-distribution HR 0.57, 95% CI 0.44–0.74, $P<0.0001$) (Additional file 1: Fig. S5).

Discussion

The occurrence of a first episode of VAP was an independent predictor of death at day 90 in this cohort of 336 ARDS patients. This condition exerted a moderate impact on the PaO_2/FiO_2 ratio but correlated with a

dramatic increase in MV duration, vasopressor use, and LOS.

The prognosis of VAP in ARDS patients managed with protective ventilatory settings has been the focus of merely two publications, both being ancillary analyses of randomized controlled studies conducted in the 2000's [11, 12]. In the ACURASYS trial, VAP was linked with a substantial reduction in the number of ventilator-free days and ICU-free days at day 28 but not with a higher hazard of in-ICU death (adjusted odds ratio 1.41, 95% CI 0.83–2.39) [11]. Conversely, in the PROSEVA trial, VAP had a less pronounced effect on MV duration and LOS but was a strong risk factor for in-ICU death (aHR 2.21, 95% CI 1.39–3.52) [12]. In our population of unselected ARDS patients, VAP was associated with a more than twofold rise in MV duration and ICU LOS and a significant increase in the likelihood of death at day 90 (aHR 3.16, 95% CI 2.04–4.89). These discrepancies may result from case-mix variations. Notwithstanding its limited impact on oxygenation, VAP likely extends lung inflammation and alveolar damage as well as extra-respiratory organ dysfunctions. Indeed, in the present cohort, patients with VAP had less vasopressor-free days, VAP-related circulatory failure being associated with short-term mortality [30]. Hence, the higher mortality associated with VAP during ARDS could be primarily explained by prolonged exposure to the risk of dying due to delayed weaning from organ supports and increased ICU LOS, as proposed for the global population of critically ill patients receiving MV [6]. Interestingly, the cumulative likelihood of MV weaning did not differ between patients with and without VAP after adjustment on the competing risk of death, suggesting that VAP was rather a consequence than the cause of protracted MV duration.

Trends in PaO_2/FiO_2 and SOFA values following the diagnosis of VAP correlate with the hazard of clinical failure, pneumonia recurrence and death in the general population of intubated patients [31–33]. In ARDS patients, hypoxemia has been shown to resolve partly over the first days of adequate antimicrobial therapy [34, 35]; however, the consequences of VAP on oxygenation remain under-investigated in this population. In our cohort of patients with baseline criteria for severe ARDS in half of cases, VAP induced an only slight and transient alteration of gas exchanges, suggesting that the infectious process mainly affects lung areas with pre-existing consolidation and ventilation/perfusion mismatches. Interestingly, in a recent study including 255 patients (ARDS, 12.9%) with suspected VAP, PaO_2/FiO_2 values were poorly predictive of microbiological confirmation (area under the receiver operating curve 0.64, 95% CI 0.57–0.72) [36]. In addition, the limited correlation between VAP and ventilator-associated complications (VAC) or infection-related VAC (iVAC) partly results from a lack of sensitivity of the respiratory criteria for VAC/iVAC (that is, an increase in the FiO_2 and/or PEEP levels after ≥ 2 calendar days of stability or decrease) for the detection of VAP [37]. Along this line, our data indicate that a decline in PaO_2/FiO_2 should not be considered as a pivotal trigger for VAP suspicion in patients with ARDS. Extra-respiratory organ failures could predict this diagnosis more reliably; indeed, SOFA values remained stable over the 2 days preceding VAP then significantly decrease thereafter, which may be ascribed to sepsis control and resolution under antimicrobial therapy.

Patients with COVID-19-related ARDS and those with ARDS from other aetiologies shared noteworthy similarities regarding VAP including pathogen distribution, time-courses of PaO_2/FiO_2 and SOFA values, and the cumulative likelihood of post-VAP extubation. PaO_2/FiO_2 values around VAP were lower in COVID-19 patients, a finding that corroborates the results of a recent work demonstrating worse oxygenation in these subjects—regardless of the occurrence of VAP—than in those with other ARDS despite comparable initial severity and respiratory system compliance after the third day of MV [38]. Nevertheless, VAP did not predict day-90 mortality in COVID-19 patients, contrary to what was observed in those with other ARDS, possibly due to a lesser extent of extra-pulmonary organ failures as suggested by the lower SOFA score values around VAP. An independent relationship between VAP and day-28 mortality has been reported in a multicentre cohort of critically ill COVID-19 patients (aHR 1.70, 95% CI 1.16–2.47); yet, in this study, the day-28 fatality rate was lower in patients with VAP than in those without ventilator-associated respiratory tract infection (25.9% versus 34.2%, respectively) [39].

This work has certain limitations. First, that the study was conducted in two ICUs of a single hospital may restrain its external validity; however, patients were managed according to current standards of care [20] and the epidemiological features of ARDS and VAP were concordant with those reported elsewhere [2, 11, 12, 40–43]. Second, diagnosing VAP is challenging

(See figure on next page.)

Fig. 2 Trends in PaO_2/FiO_2 ratio, extra-respiratory SOFA score values and total SOFA score values in patients with VAP. *VAP* ventilator-associated pneumonia, *ARDS* acute respiratory distress syndrome, *COVID-19* coronavirus disease 2019, *SOFA* sepsis-related organ failure assessment. Panels **A**, **C** and **E**, all patients with ARDS; panels **B**, **D** and **F**, patients with COVID-19-related ARDS versus patients with ARDS from other causes

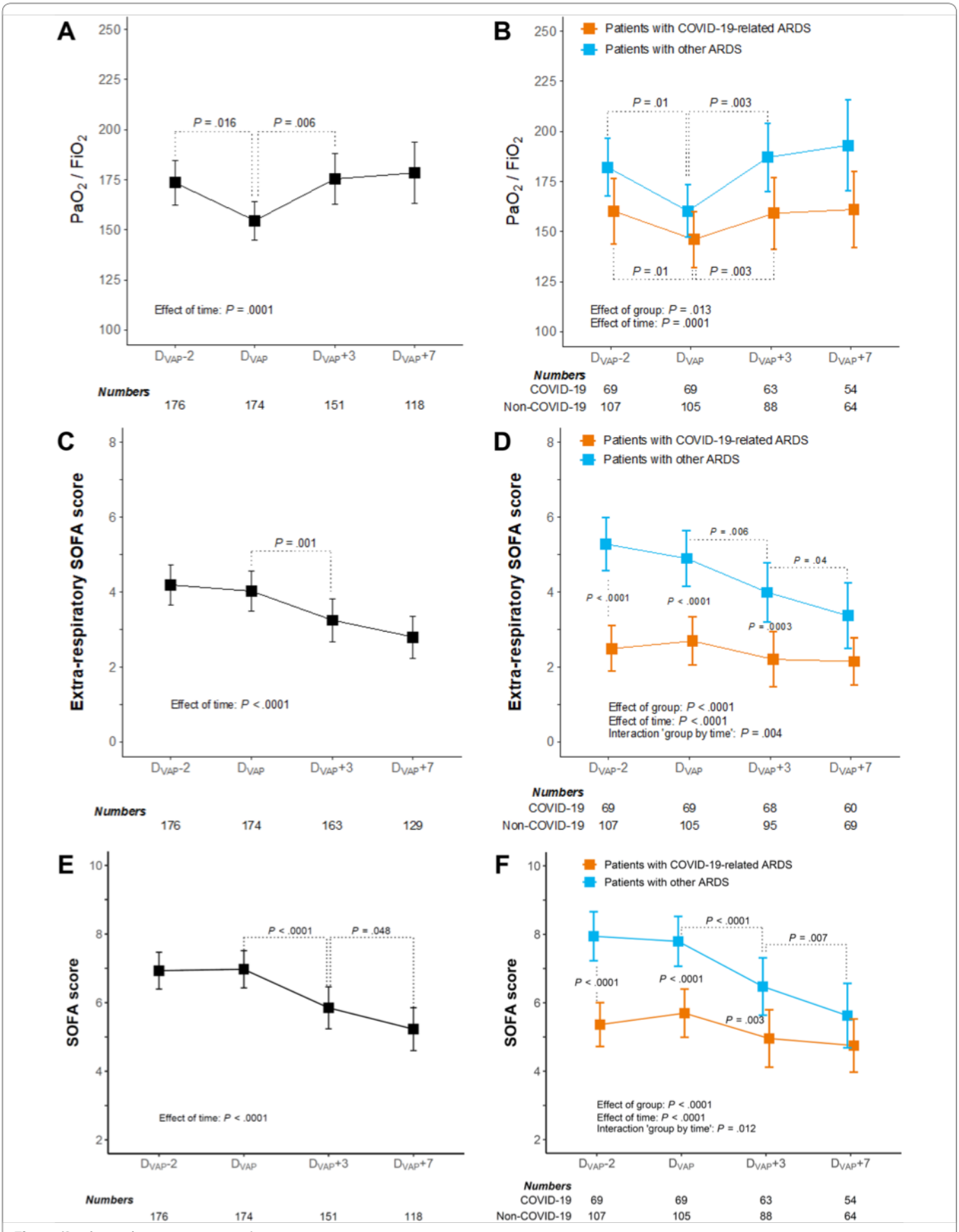

Fig. 2 (See legend on previous page.)

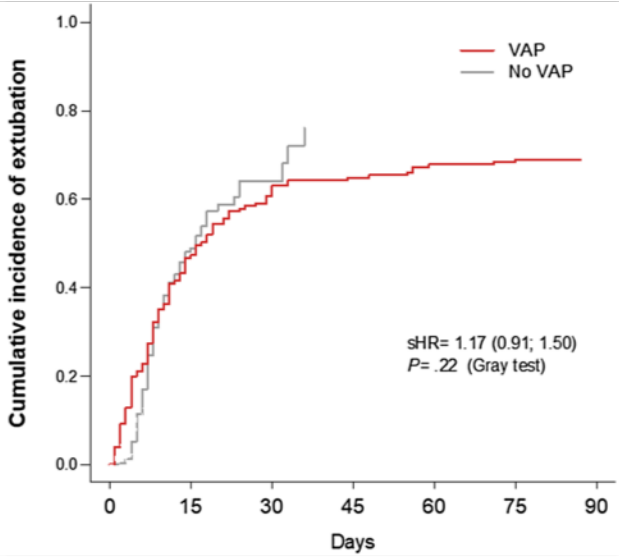

Fig. 3 Cumulative likelihood of MV weaning in patients with and without VAP. *MV* mechanical ventilation, *VAP* ventilator-associated pneumonia, *sHR* cause-specific hazard ratio (indicated with 95% confidence interval). day 0 indicates the date of intubation. Note that the curve of the no-VAP subgroup ends at day 36 of MV, since all patients without VAP had been extubated or had died at this time. For the VAP subgroup, the curve ends at day 89 of MV for the same reasons

in ARDS patients, especially in those with COVID-19 [5]; therefore, it cannot be firmly excluded that some patients with VAT were misclassified as having VAP though the divergent outcomes that we observed in the VAP and no VAP subgroups do not support this assumption, VAT being not associated with mortality in dedicated studies [44]. In addition, the SOFA score values at VAP onset in our cohort were higher than those previously reported in patients with VAT [45]. Third, the management of patients with severe COVID-19 has evolved since recruitment closing; while the early use of dexamethasone does not appear to increase the risk of VAP [46], other specific therapies such as anti-IL6 drugs might have modified the epidemiology of ICU-acquired infections [47]. Fourth, the relatively low number of COVID-19 patients could have precluded the detection of a significant effect of VAP on mortality in this subgroup. In addition, the prognostic impact of VAP might have been different in cohorts or settings with higher overall mortality rates. Finally, that prone positioning was used in only 22% of patients with non-COVID-19-related ARDS may have impacted the measured outcomes in this subgroup.

In conclusion, VAP is an independent predictor of day-90 mortality in ARDS patients. This effect was not observed in the COVID-19 subgroup; however, these analyses may have been underpowered. In both COVID-19 and non-COVID-19 patients, VAP exerts a limited effect on oxygenation but correlates with extended MV duration, vasoactive support, and LOS.

Abbreviations

ARDS: Acute respiratory distress syndrome; BMI: Body mass index; CI: Confidence interval; COPD: Chronic obstructive pulmonary disease; COVID-19: Severe coronavirus disease 2019; HR: Hazards ratio; ICU: Intensive care unit; LOS: Length of stay; MV: Mechanical ventilation; NMBA: Neuromuscular blocking agents; PaO_2/FiO_2: Partial pressure of oxygen/fraction of inspired oxygen ratio; PBW: Predicted body weight; PEEP: Positive end-expiratory pressure; PP: Prone positioning; SAPS 2: Simplified acute physiology score 2; SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2; SOFA: Sepsis-related organ failure assessment score; VAP: Ventilator-associated pneumonia; Vt: Tidal volume; VV-ECMO: Veno-venous extra-corporeal membrane oxygenation.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13613-022-00998-7.

Additional file 1. Additional tables and figures.

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None.

Authors' contributions

MLP and FB designed the study; MLP, CB, CA and FB collected the data; FB and TB analysed the data and interpreted the results; MLP and FB drafted the manuscript; all other authors revised the draft critically for important intellectual content. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethical approval and consent to participate

The study protocol was approved on November 27th, 2020 by the Ethical committee of the French Society of Intensive Care (CE-SRLF-20-84). The requirement for patient's informed consent was waived due to the retrospective design of the study.

Consent for publication

Not applicable.

Competing interests

FB declares interests with MSD (consulting and lecture fees, and conference invitation), BioMérieux (lecture fees), and Pfizer (conference invitation), outside the scope of the submitted work. Other authors have no potential conflict of interest to declare.

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Publisher's Note

Electronic supplement

Clinical impact of ventilator-associated pneumonia in patients with the acute respiratory distress syndrome: a retrospective cohort study

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ADDITIONAL METHODS

Characteristics of the participating ICUs

- Usual ventilator-bed capacities are 20 and 15 for the medical and surgical intensive care units (MICU/SICU), respectively, with only single-bed rooms and a 1:2.5 nurse-to-patients ratio in both units. These capacities transiently increased to 38 and 30 ventilator-beds during the study period (2 months, April-May 2020) due to the first COVID-19 wave, with a 1:3 nurse-to-patients ratio.
- Contact precautions are routinely applied in patients colonized or infected with multidrug-resistant bacteria.
- Full-barrier precautions are applied for COVID-19 patients.

Bundles for prevention of ventilator-associated pneumonia

- Orotracheal intubation (rather than nasotracheal intubation) whenever possible
- Semi-recumbent position >30°
- Control of endotracheal tube cuff pressure (continuous or every 4-6 hours, target 20-30 cmH_2O)
- Oral care every 4-6 hours with saline 0.9%
- Strict application of standard precautions, including alcohol-based hand hygiene
- Endotracheal tubes with subglottic secretion drainage system are not routinely used in the participating ICUs
- Limitation of mechanical ventilation duration through (i) protocolized sedation in both participating ICUs, with nurse-driven titration of sedative agents (fentanyl

and midazolam as first-line drugs; propofol, ketamine and/or dexmedetomidine as second-line drugs) every 2 to 4 hours according to a prescribed target of the Richmond Agitation-Sedation Scale, daily interruption except in patients with specified contraindication (e.g., acute brain injury or severe hypoxemia), and the use of enterally-administered oxazepam and/or haloperidol as step-down drugs when required, and (ii) management of mechanical ventilation weaning by both intensivists and specialized physiotherapists, with daily spontaneous breathing trial for patients meeting usual eligibility criteria and the routine preventive use of non-invasive ventilation ± high-flow nasal oxygen following extubation in patients with risk factors for weaning failure

Policies for diagnosis and treatment of ventilator-associated pneumonia

- Lower tract respiratory samples (either endotracheal aspirate, bronchoalveolar lavage or plugged telescopic catheter) are collected in every patient with suspected VAP before the start of a new antimicrobial therapy.
- Empirical single-drug or combination regimen are prescribed according to the patient's risk factors for multidrug-resistant bacteria and de-escalation whenever possible once culture and susceptibility test results become available, in keeping with current guidelines (ATS/IDSA 2016 and ESICM/ESCMID/ERS 2017, available at www.thoracic.org and www.esicm.org, respectively).
- Follow-up respiratory samples are collected under therapy when required (*e.g.*, persistent or worsening clinical, biological and/or radiological signs of pulmonary infection). The usual treatment duration is 7 days – longer durations may be decided by the treating physicians in case of immune deficiency, abscessed

pneumonia or empyema, and evidence for clinical and/or microbiological failure at day 7.

Table S1. Full characteristics of the study population

	Missing values	**All patients with ARDS (n = 336)**	**Patients with COVID-19-related ARDS (n = 101)**	**Patients with ARDS from other causes (n = 235)**	***P* value**
Unit of admission					
MICU	*0*	254 (75.6)	84 (83.2)	170 (72.3)	NA
SICU	*0*	82 (24.4)	17 (16.8)	65 (27.7)	
Male sex	*0*	247 (73.5)	73 (72.3)	174 (74.0)	0.79
Age, years	*0*	67 (57-74)	67 (58-72)	66 (55-74)	0.73
BMI, kg.m^{-2}	*7*	28.5 (25.0-32.6)	29.4 (26.1-32.1)	27.8 (24.1-32.9)	0.13
Past or current smoking	*0*	132 (39.3)	30 (29.7)	102 (43.4)	0.02
Chronic diseases					
Hypertension	*0*	176 (52.4)	55 (54.4)	121 (51.5)	0.63
Diabetes mellitus	*0*	95 (28.3)	40 (39.6)	55 (23.4)	0.003
COPD	*0*	40 (11.9)	6 (5.9)	34 (14.5)	0.03
Respiratory, other than COPD	*0*	49 (14.6)	17 (16.8)	32 (13.6)	0.50
Cardiac	*0*	99 (29.5)	25 (24.8)	74 (31.5)	0.24
Hepatic	*0*	29 (8.6)	2 (2.0)	27 (11.5)	0.003
Renal	*0*	28 (8.3)	5 (4.9)	23 (9.8)	0.19
Receiving chronic haemodialysis	*0*	4 (1.2)	1 (1.0)	3 (1.3)	1
Neurological	*0*	35 (10.4)	6 (5.9)	29 (12.3)	0.08
Immune deficiency	*0*	53 (15.8)	11 (10.9)	42 (17.9)	0.14
Solid cancer	*0*	24 (7.1)	3 (2.9)	21 (8.9)	0.06
Haematological malignancy	*0*	10 (3.0)	3 (2.9)	7 (3.0)	1
Others	*0*	21 (6.2)	5 (4.9)	16 (6.8)	0.63
Knaus score					
A-B	*0*	308 (91.7)	100 (99.0)	208 (88.5)	0.0008
C-D	*0*	28 (8.3)	1 (1.0)	27 (11.5)	
Type of ICU admission					
Direct (Emergency department)	*0*	200 (59.5)	52 (51.5)	148 (63.0)	0.05
Transfer	*0*	136 (40.5)	49 (48.5)	87 (37.0)	
Prior hospital LOS, days	*0*	2 (1-5)	3 (1-5)	2 (1-5)	0.82

Reason for ICU admission					
Acute respiratory failure	*0*	181 (53.8)	101 (100)	80 (34.0)	NA
Impaired consciousness	*0*	45 (13.4)	0	45 (19.1)	
Sepsis/septic shock	*0*	37 (11.0)	0	37 (15.7)	
Cardiac arrest	*0*	35 (10.4)	0	35 (14.9)	
Trauma	*0*	12 (3.6)	0	12 (5.2)	
Scheduled surgery	*0*	6 (1.8)	0	6 (2.6)	
Miscellaneous	*0*	20 (6.0)	0	20 (8.5)	

Table S1 (continued).

	Missing values	**All patients with ARDS (n = 336)**	**Patients with COVID-19-related ARDS (n = 101)**	**Patients with ARDS from other causes (n = 235)**	***P* value**
SAPS 2 at ICU admission	*0*	50 (38-67)	40 (33-49)	56 (43-71)	<0.0001
SOFA score at ICU admission	*0*	8 (5-11)	5 (3-8)	9 (7-12)	<0.0001
Lymphocyte count at ICU admission, mm^{-3}	*0*	730 (447-1185)	660 (470-870)	780 (420-1310)	0.03
Colonization with MDR-GNB	*0*	79 (23.5)	49 (48.5)	30 (12.8)	<0.0001
All (pooled)	*0*	64 (19.0)	40 (39.6)	24 (10.2)	<0.0001
ESBLE					
ARDS aetiology	*0*				
COVID-19, no co-infection	*0*	93 (27.7)	93 (92.1)	-	NA
COVID-19, bacterial or viral co-infection		8 (2.4)	8 (7.9)	-	
Bacterial or non-SARS-CoV-2 viral pneumonia	*0*	106 (31.4)	-	106 (45.1)	
		60 (17.9)	-	60 (25.5)	
Aspiration	*0*	45 (13.4)	-	45 (19.1)	
Extra-pulmonary sepsis	*0*	6 (1.8)	-	6 (2.6)	
Trauma	*0*	6 (1.8)	-	6 (2.6)	
Haemorrhagic shock	*0*	12 (3.6)	-	12 (5.2)	
Miscellaneous	*0*				

ARDS and MV characteristics [1]					
Lowest Vt, mL.kg^{-1} (PBW)	*0*	6.1 (5.8-6.6)	6.0 (5.8-6.3)	6.1 (5.7-6.8)	0.02
Highest PEEP, cmH_2O	*0*	10 (7-13)	12 (11-14)	8 (6-12)	<0.0001
Highest plateau pressure, cmH_2O	*0*	24 (20-27)	26 (24-28)	23 (18-26)	<0.0001
Highest driving pressure, cmH_2O	*0*	13 (10-16)	13 (11-15)	13 (10-16)	0.91
Lowest PaO_2/FiO_2 ratio, mmHg	*0*	100 (74-163)	91 (76-138)	105 (74-172)	0.17
Highest $PaCO_2$, mmHg	*0*	44 (40-52)	43 (38-49)	46 (40-55)	0.0005
Lowest pH	*0*	7.36 (7.25-7.4)	7.36 (7.30-7.42)	7.35 (7.22-7.39)	<0.0001
ARDS classification (Berlin definition) [1]					
Mild	*0*	50 (14.9)	11 (10.9)	39 (16.6)	0.09
Moderate	*0*	116 (34.5)	30 (29.7)	86 (36.6)	
Severe	*0*	170 (50.6)	60 (59.4)	110 (46.8)	
ARDS-targeted therapies					
Prone positioning	*0*	127 (37.8)	75 (74.3)	52 (22.1)	<0.0001
Number of days	*0*	5 (2-11)	8 (3-16)	2 (1-5)	<0.0001
Nitric oxide inhalation	*0*	90 (26.8)	46 (45.5)	44 (19.1)	<0.0001
Neuromuscular blocking agents	*0*	209 (62.2)	86 (85.1)	123 (52.3)	<0.0001

Table S1 (continued).

	Missing values	**All patients with ARDS (n = 336)**	**Patients with COVID-19-related ARDS (n = 101)**	**Patients with ARDS from other causes (n = 235)**	***P* value**
Corticosteroids [1]					
All (pooled)	*0*	169 (50.3)	53 (52.5)	116 (49.4)	0.64
Dexamethasone	*0*	39 (11.6)	34 (33.7)	5 (2.1)	<0.0001
Hydrocortisone	*0*	61 (18.2)	6 (5.9)	55 (23.4)	<0.0001
Methylprednisolone/ prednisolone	*0*	75 (22.3)	13 (12.9)	62 (26.4)	0.006
Surgery during the ICU stay	*0*	48 (14.3)	5 (4.9)	43 (18.3)	0.001
Decision to withhold or withdraw life-sustaining therapies	*0*	67 (19.9)	13 (12.9)	54 (23.0)	0.04
Life-sustaining therapies during the ICU stay					
Invasive MV duration, overall, days Vasopressors	*0*	11 (7-20)	17 (10-26)	9 (6-16)	<0.0001
Renal replacement therapy	*0*	280 (83.3)	82 (81.2)	198 (84.2)	0.52
VA-ECMO	*0*	85 (25.3)	23 (22.8)	62 (26.4)	0.58
VV-ECMO	*0*	7 (2.1)	0	7 (3.0)	0.11
	0	15 (4.5)	7 (6.9)	8 (3.4)	0.16
Ventilator-associated pneumonia	*0*	176 (52.4)	69 (68.3)	107 (45.5)	0.0001
First episode	*0*	7 (4-11)	9 (8-13)	6 (4-10)	0.01
Prior MV duration, days	*0*	59 (17.6)	35 (34.6)	24 (10.2)	<0.0001
More than one episode					

Table S1 footnote

Data are expressed as number (%) or median (interquartile range).

MICU/SICU, medical/surgical intensive care unit; ARDS, acute respiratory distress syndrome; COVID-19, conoravirus disease 2019; BMI, body mass index; COPD, chronic obstructive pulmonary disease; MDRB, multidrug-resistant bacteria; LOS, length of stay; SAPS 2, simplified acute physiology score 2; SOFA, sepsis-related organ failure assessment; GNB, Gram-negative bacteria; ESBLE, extended-

spectrum β-lactamase-producing Enterobacterales; MV, mechanical ventilation; Vt, tidal volume; PBW, predicted body weight; PEEP, positive end-expiratory pressure; VA/VV-ECMO, veno-arterial/veno-venous extracorporeal membrane oxygenation

[1] First day with ARDS criteria

Table S2. Prior antimicrobial exposure, lower respiratory tract samples used for microbiological diagnosis, and pathogens responsible for VAP

Variables [1]	All patients with ARDS (n = 176)	Patients with COVID-19-related ARDS (n = 69)	Patients with ARDS from other causes (n = 107)
Antimicrobial exposure in the ICU before VAP			
Any antibiotic	167 (94.5)	67 (97.1)	100 (93.4)
BL/BLI	101 (57.4)	20 (29.0)	81 (75.7)
Duration, days	5 (3-7)	4 (3-5)	5 (4-7)
Non-antipseudomonal cephalosporins	92 (52.3)	55 (79.7)	37 (34.6)
Duration, days	4 (3-5)	4 (3-5)	4 (2-6)
Antipseudomonal cephalosporins	15 (8.5)	8 (11.6)	7 (6.5)
Duration, days	4 (3-5)	4 (3-5)	5 (4-6)
Carbapenems	22 (12.5)	9 (13.1)	13 (12.1)
Duration, days	5 (3-7)	5 (4-7)	4 (3-7)
Other β-lactams	24 (13.6)	9 (13.1)	15 (14.0)
Duration, days	5 (3-6)	5 (4-6)	5 (2-6)
Fluoroquinolones	7 (4.0)	1 (1.4)	6 (5.6)
Duration, days	5 (3-8)	6 (NA)	5 (3-8)
Aminoglycosides	19 (10.8)	6 (8.7)	13 (12.1)
Duration, days	1 (1-1)	1 (1-2)	1 (1-1)
Anti-MRSA drugs	39 (22.2)	12 (17.4)	27 (25.2)
Duration, days	4 (2-6)	2 (2-3)	4 (2-6)
Metronidazole	23 (13.1)	3 (4.3)	20 (18.7)
Duration, days	4 (3-5)	4 (NA)	4 (3-5)
Macrolides	72	48	24
Duration, days	3 (2-4)	2 (2-3)	3 (2-4)
Other antimicrobials	5	2	3
Duration, days	8 (NA)	4 (NA)	8 (NA)
Microbiological documentation			
Endotracheal aspirate	135 (76.7)	56 (81.2)	79 (73.8)
Bronchoalveolar lavage	27 (15.3)	11 (15.9)	16 (15.0)
Telescopic protected catheter	14 (8.0)	2 (2.9)	12 (11.2)

Pathogens responsible for VAP			
Enterobacterales	107 (60.8)	41 (59.4)	66 (61.7)
Enterobacter cloacae	26 (14.7)	11 (15.9)	15 (14.0)
Escherichia coli	24 (13.6)	7 (10.1)	17 (15.9)
Klebsiella pneumoniae	15 (8.5)	7 (10.1)	8 (7.5)
Klebsiella aerogenes	12 (6.8)	6 (8.7)	6 (5.6)
Hafnia alvei	12 (6.8)	6 (8.7)	6 (5.6)
Serratia marcescens	10 (5.7)	7 (10.1)	3 (2.8)
Citrobacter koseri	10 (5.7)	3 (4.3)	7 (6.5)
Proteus spp	6 (3.4)	2 (2.9)	4 (3.7)
Others	9 (5.1)	0	9 (8.4)
ESBL-producing isolates [2]	21 (11.9)	12 (17.4)	9 (8.4)
Pseudomonas aeruginosa	32 (18.2)	12 (17.4)	20 (18.7)
Stenotrophomonas maltophilia	19 (10.8)	6 (8.7)	13 (12.1)
Acinetobacter baumannii	10 (5.7)	6 (8.7)	4 (3.7)
Haemophilus spp	6 (3.4)	2 (2.9)	4 (3.7)
Staphylococcus aureus	20 (11.4)	8 (11.6)	12 (11.2)
Enterococcus spp	14 (7.9)	4 (5.8)	10 (9.3)
Streptococcus spp	13 (7.4)	7 (10.1)	6 (5.6)
Others	7 (4.0)	1 (1.5)	6 (5.6)
Polymicrobial VAP [3]	58 (32.9)	19 (27.5)	39 (36.4)

Table S2 footnote

Data exposed as number (%) or median (interquartile range).

VAP, ventilator-associated pneumonia; COVID-19, coronavirus disease 2019; ARDS, acute respiratory distress syndrome; ICU, intensive care unit; ESBL, extended-spectrum β-lactamase; BL/BLI, β-lactam/β-lactamase inhibitor; MRSA, methicillin-resistant *Staphylococcus aureus*; NA, non appropriate

Anti-MRSA drugs indicate linezolide, daptomycin and glycopeptides.

Comparison between COVID-19-related ARDS and ARDS from other causes: [1] P = 0.64 (overall pathogen distribution); [2] P = 0.09; [3] P = 0.25

Table S3. Independent predictors of Day 90 mortality in patients with ARDS

	Full Cox proportional hazards model		Modified Cox proportional hazards model [1]	
	aHR (95% CI)	***P* value**	**aHR (95% CI)**	***P* value**
Age, per 1-year increase	1.02 (0.99-1.04)	0.07	1.02 (0.99-1.04)	0.09
Weight	0.98 (0.96-1.00)	0.13	0.98 (0.95-1.00)	0.13
Chronic cardiac disease	1.48 (0.96-2.29)	0.07	1.61 (1.04-2.49)	0.03
Chronic renal disease	2.11 (1.10-4.05)	0.02	2.11 (1.09-4.09)	0.03
Chronic neurological disease	1.32 (0.73-2.37)	0.36	1.27 (0.72-2.27)	0.41
Cancer (solid or haematological)	2.22 (0.71-6.95)	0.17	2.5 (0.82-7.88)	0.10
Immune deficiency, any	0.76 (0.30-1.87)	0.54	0.71 (0.28-1.79)	0.46
SICU admission (versus MICU admission)	0.71 (0.42-1.20)	0.20	0.69 (0.40-1.7)	0.17
ICU admission for cardiac arrest	2.00 (1.02-3.92)	0.04	2.01 (1.01-4.01)	0.04
ICU admission for trauma or scheduled surgery	0.39 (0.09-1.63)	0.20	0.36 (0.08-1.50)	0.16
SAPS 2 at ICU admission, per 1-point increase	1.02 (1.00-1.03)	0.005	1.02 (1.00-1.03)	0.02
SOFA score at ICU admission, per 1-point increase	1.04 (0.96-1.13)	0.35	1.06 (0.98-1.15)	0.16
Lymphocyte count at ICU admission, per 1000.mm^{-3}	1.01(0.83-1.23)	0.91	1.05 (0.87-1.27)	0.63
pH value on the first day with ARDS criteria	1.97 (0.34-11.36)	0.45	2.50 (0.43-14.38)	0.31
COVID-19-related ARDS (versus ARDS from other causes)	0.94 (0.54-1.66)	0.84	0.71 (0.39-1.30)	0.27
Prone positioning (at least once during ICU stay)	-	-	1.65 (1.01-2.70)	0.04
Steroid therapy	-	-	1.12 (0.73-1.69)	0.61
Occurrence of a first episode of VAP	**3.16 (2.04-4.89)**	**<0.0001**	**2.67 (1.72-4.14)**	**<0.0001**

Table S3 footnote

ARDS, acute respiratory distress syndrome; BMI, body mass index; SICU/MICU, medical/surgical intensive care unit; SAPS 2, simplified acute physiology score 2; SOFA, sepsis-related organ failure assessment; COVID-19, coronavirus disease 19; VAP, ventilator-associated pneumonia

[1] With prone positioning and steroids use during the ICU stay being forced into the model (*P* >0.20 in bivariate analysis)

Figure S1. Study flowchart

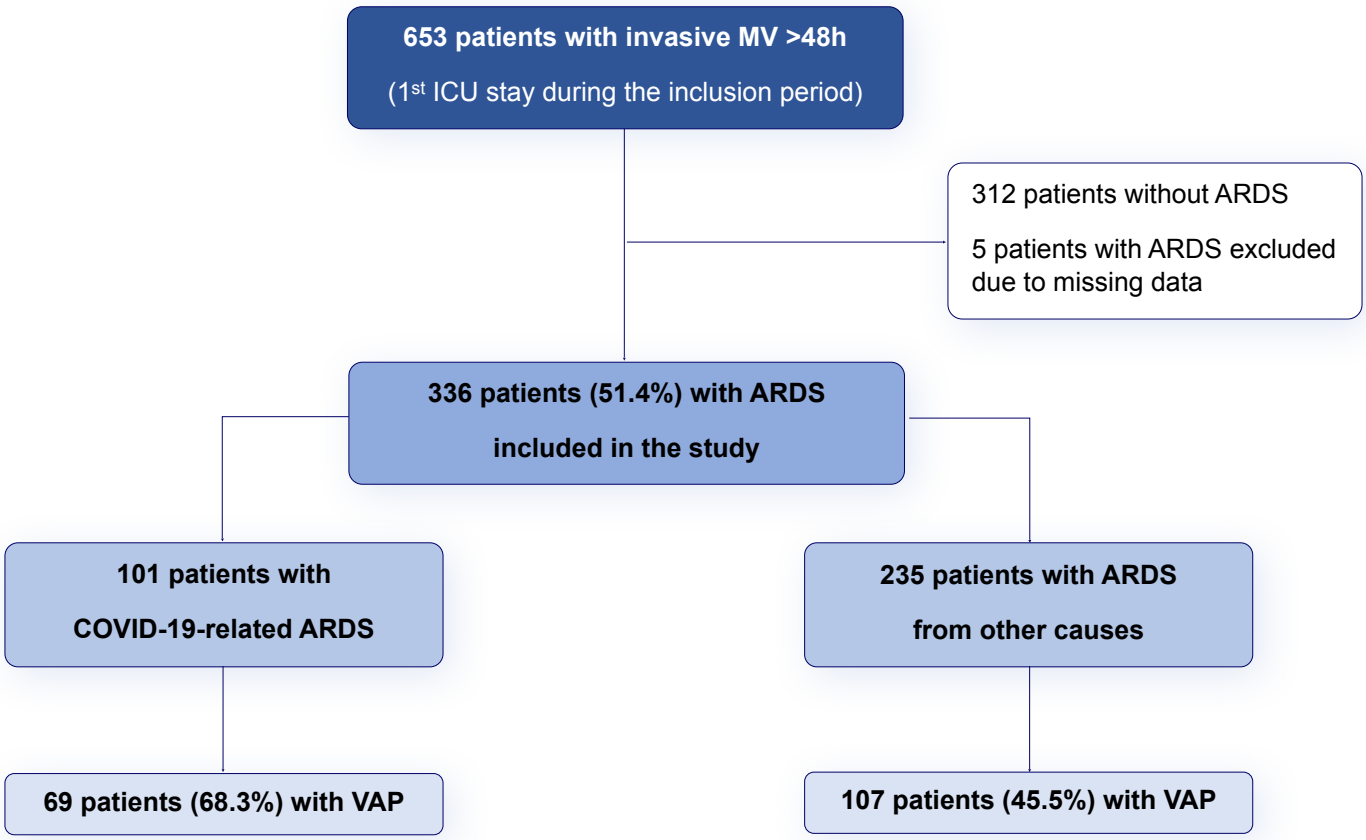

Figure S1 footnote

MV, mechanical ventilation; VAP, ventilator-associated pneumonia; ARDS, acute respiratory distress syndrome

Figure S2. Cumulative incidence of VAP

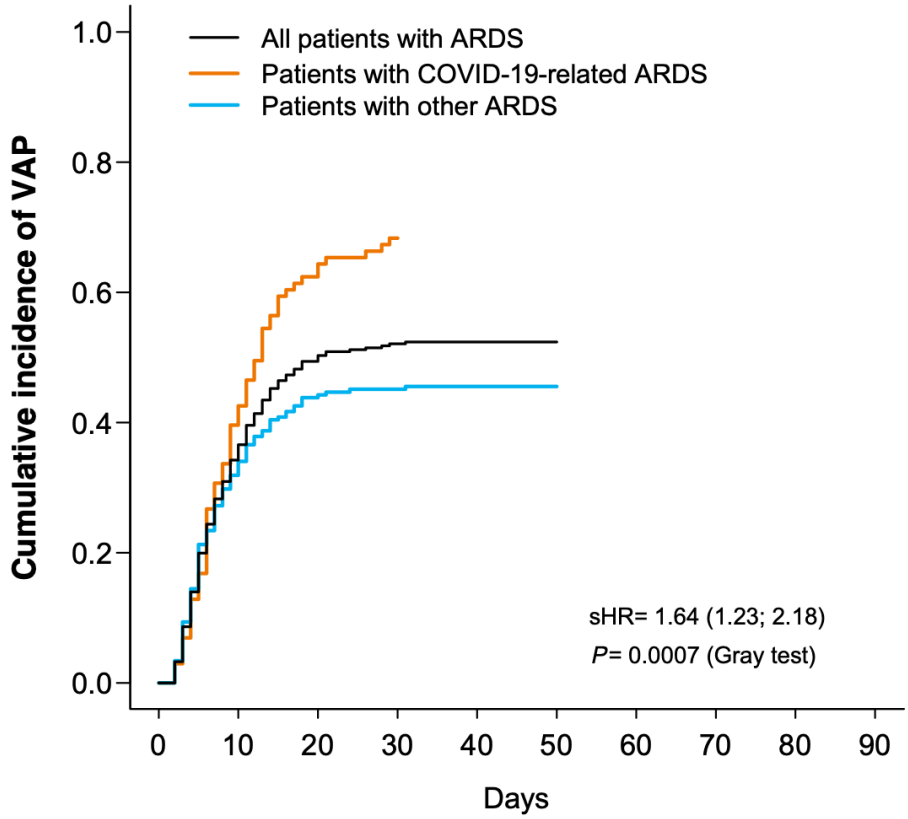

Figure S2 footnote

VAP, ventilator-associated pneumonia; ARDS, acute respiratory distress syndrome; COVID-19, conoravirus disease 2019; sHR, cause-specific hazard ratio (COVID-19-related ARDS versus ARDS from other causes, indicated with 95% incidence interval)

Day 0 indicates the date of intubation. Note that the curves are truncated at the time when every patients in each group had developed VAP, had died or had been weaned from mechanical ventilation.

Figure S3. Cumulative probability of survival after VAP onset in patients with COVID-19-related ARDS and ARDS from other causes

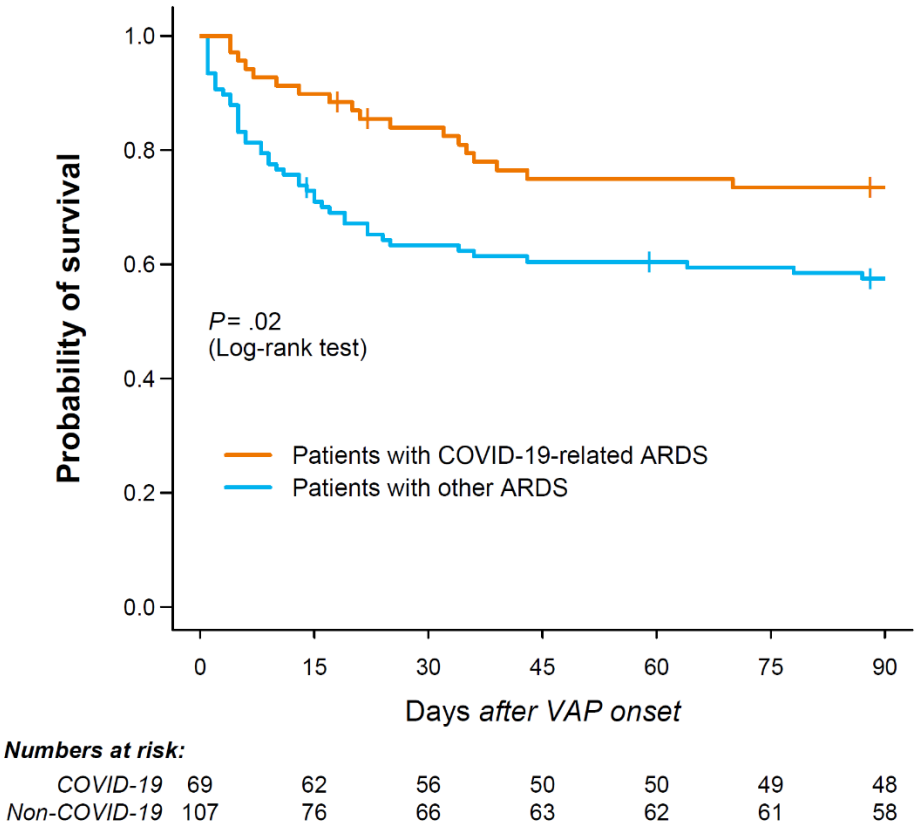

Figure S3 footnote

VAP, ventilator-associated pneumonia; COVID-19, coronavirus disease 2019; ARDS, acute respiratory distress syndrome

Day 0 indicates the date of VAP onset.

Figure S4. Trends in the level of PEEP in patients with VAP

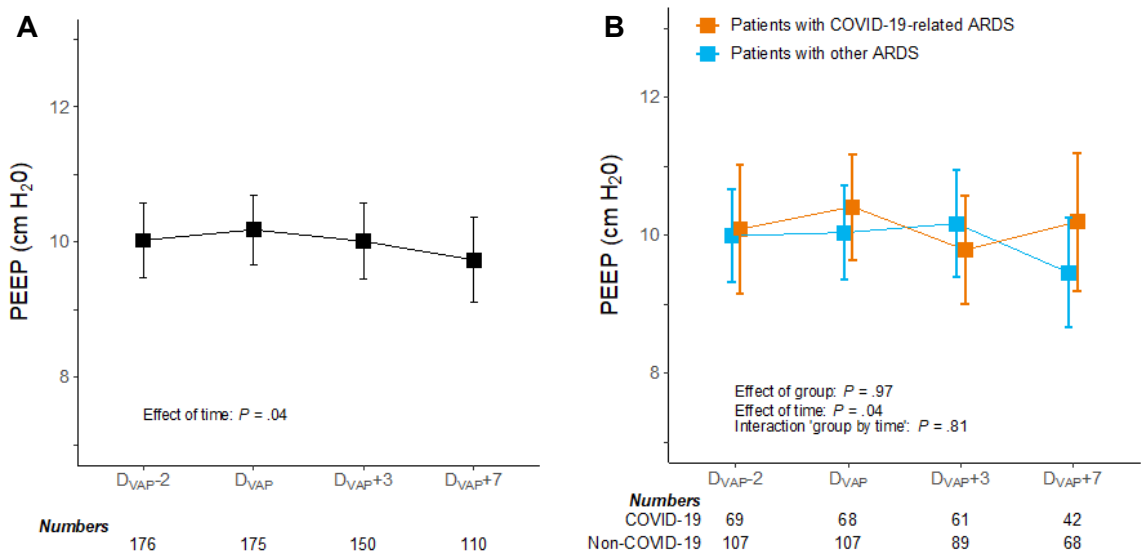

Figure S4 footnote

PEEP, positive end-expiratory pressure; VAP, ventilator-associated pneumonia; ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019

Panels A, all patients with ARDS; panel B, patients with COVID-19-related ARDS versus patients with ARDS from other causes

Figure S5. Cumulative incidence of discharge alive from the ICU in patients with and without VAP

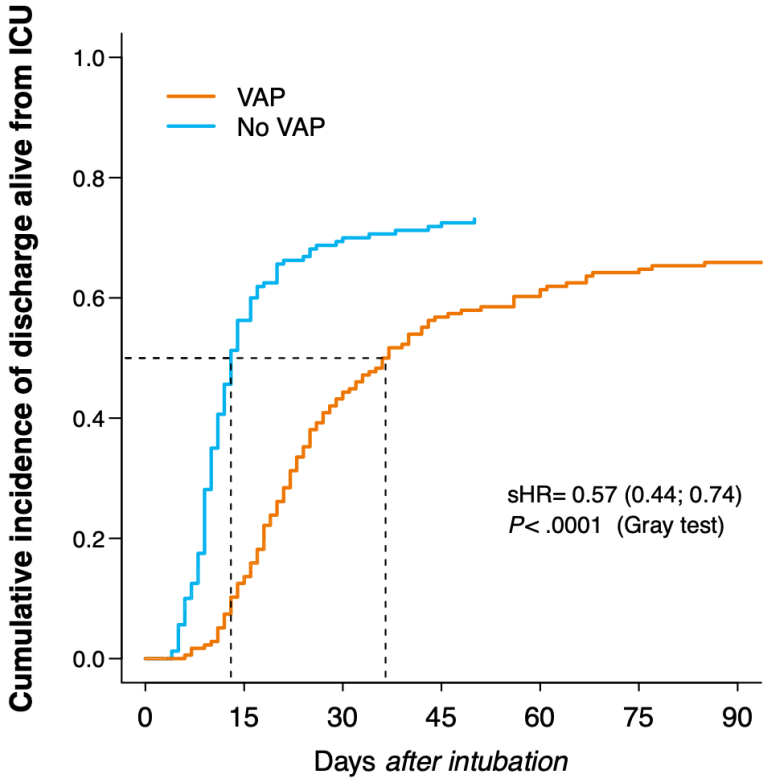

Figure S5 footnote

VAP, ventilator-associated pneumonia

Day 0 indicates the date of intubation. The correlation between the occurrence of VAP and the cumulative likelihood of discharge alive from the ICU was analysed handling VAP as a baseline characteristic (i.e., not a delay entry variable) and death as a competing event.

Conclusion

La pneumonie acquise sous ventilation mécanique est un prédicteur indépendant de la mortalité à 90 jours chez les patients atteints de SDRA. Cet effet n'a pas été observé dans le sous-groupe COVID-19 ; cependant, ces analyses peuvent avoir été sous-dimensionnées. Chez les patients COVID-19 et non-COVID-19, la PAVM exerce un effet limité sur l'oxygénation mais est en corrélation avec des durées prolongées de VM, de support vasoactif et de séjour.

Un certain nombre de nos résultats sont concordants avec les données de la littérature à propos de l'incidence augmentée des PAVM au cours du SDRA lié à la COVID-19 ; de l'augmentation de durée de ventilation mécanique au décours d'un premier épisode de PAVM ; de l'impact modéré d'un épisode de PAVM sur l'oxygénation. L'épidémiologie des germes en causes dans les PAVM de notre cohorte correspond aux données déjà connues.

Cependant, une étude de Vacheron et al., publiée en février 2022 dans l'*American Journal of Respiratory and Critical Care Medicine* apporte un résultat contradictoire à l'absence de surmortalité retrouvée dans notre travail chez le sous-groupe des patients atteints de SDRA lié à la COVID-19 (28). En effet, cette large étude multicentrique met en évidence une mortalité attribuable à un premier épisode de PAVM chez les patients atteints de la COVD-19 de 9,2% (IC 95%, 3,5% à 12,2%). Nous pouvons attribuer l'absence de résultat dans notre étude, concernant ce point, à un manque de puissance et le peu de patients COVID-19 inclus.

Les résultats de ce travail suggèrent que la prévention de l'apparition d'un premier épisode de PAVM est un enjeu majeur au sein de nos unités de soins intensifs. Ces mesures de préventions, détaillées dans des récentes recommandations de la SRLF (29), comprennent le recours préférentiel à la ventilation non invasive dans ses indications validées, l'intubation par voie orotrachéale plutôt que nasotrachéale, la limitation des doses et des durées de sédatifs et d'analgésiques associés à la ventilation mécanique, l'initiation d'une alimentation

entérale précoce, la vérification régulière de la pression du ballonnet de la sonde d'intubation, la réalisation d'aspirations (au mininum toutes les 6-8 heures) en utilisant une sonde endotrachéale appropriée, et l'installation des patients avec une élévation de la tête du lit à 30° ou plus.

Un autre axe de prévention des PAVM pourrait être de contrôler la balance hydrique chez les patients en SDRA. En effet, dans cette population, une balance hydrique positive (BHP) a été associée à un sevrage retardé de la VM, à une durée plus longue du séjour en unité de soins intensifs et, dans certaines études, à une mortalité accrue à l'hôpital. D'autres études suggèrent qu'une BHP peut amplifier le risque de PAVM chez les patients en état de choc dans les unités de soins intensifs et chez ceux qui entament un processus de sevrage de la VM.

À partir de la base de données que nous avions constituée pour ce travail de thèse, nous avons souhaité étudier l'existence d'une relation potentielle entre BHP et risque d'un premier épisode de PAVM : cette association n'a, à ce jour, pas été étudiée spécifiquement chez les patients atteints de SDRA. L'objectif principal de cette étude était d'évaluer si la BHP est en corrélation avec le risque de PAVM à J28 chez les patients atteints de SDRA. L'impact de la BHP sur la durée de la VM et la mortalité à J28 a été étudié comme objectif secondaire. Ce second travail a été soumis pour publication le 6 août 2022 à *Annals of the American Thoracic Society* : le manuscrit soumis est présenté en annexe de ce mémoire de thèse.

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Fluid overload and the hazard of ventilator-associated pneumonia in patients with the acute respiratory distress syndrome: a propensity score-based analysis

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Running title

Fluid overload and VAP in ARDS patients

Key words

Acute respiratory distress syndrome; Ventilator-associated pneumonia; Fluid balance; Intensive care unit; Mechanical ventilation; Hospital-acquired infection; Outcome

Content

Main text (1,245 words), 21 references, one table, two figures

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TEXT

Patients with the acute respiratory distress syndrome (ARDS) are especially at risk for ventilator-associated pneumonia (VAP) as a result of impaired lung immunity, dysregulation of the respiratory microbiota, and protracted exposure to invasive mechanical ventilation (MV) (1). Besides, these patients may cumulate predisposing factors for positive fluid balance (PFB) including ARDS-related acute *cor pulmonale*, the use of high levels of positive end-expiratory pressure (PEEP), and underlying conditions such as sepsis or acute renal failure (2). In this population, both VAP and PFB have been linked with delayed MV weaning, longer duration of the intensive care unit (ICU) stay and, though inconstantly, increased in-hospital mortality (3-8).

Previous studies suggest that PFB may amplify the risk of VAP in ICU patients with shock and in those entering the MV weaning process (9-10), a finding mostly attributable to MV extension. Yet, the potential relationship between PFB and VAP has not been specifically studied in ARDS patients.

The primary objective of this study was to appraise whether PFB correlates with the hazard of VAP at Day 28 in ARDS patients. The impact of PFB on MV duration and mortality at Day 28 was investigated as a secondary objective.

Patients and methods

All patients (i) admitted between April 2019 and September 2020 in the 32-bed medical ICU and the 30-bed surgical ICU of a 1100-bed university-affiliated hospital in France, (ii) meeting the Berlin criteria of ARDS for ≥2 calendar days (11) and (iii) with at least one body weight measurement after ICU admission (see below) were included in this retrospective study. Methods for data collection and diagnostic

criteria for VAP have been described elsewhere (5). Variables exposed in **Table 1** were extracted from the ICCA medical record software (Philips, Amsterdam, The Netherlands). This software enables automated daily calculation of FB by measured fluid input minus output; however, certain fluid losses are not (i.e., insensible cutaneous or respiratory losses) or not accurately (e.g., diarrhoea or drainage systems) integrated in this calculation. Therefore, and similarly to previous works in this field (9, 12-15), body weight variations (BWV) from ICU admission were used as a surrogate marker of FB. In both participating ICUs, BW is routinely monitored every 24-36 hours using a standardised procedure (Multicare-System computerized beds, Linet, Czech Republic).

Data are expressed as mean (standard deviation) or median (interquartile range) for continuous variables and number (%) for categorical variables. Patient characteristics were compared using the Mann–Whitney U test for continuous variables and the Fisher's exact test or χ^2 test for categorical variables, as appropriate. Missing values were not imputed since all analysed variables were available for ≥98% of patients. Day 1 was defined as the first day with ARDS criteria.

Since baseline characteristics may influence both the extent of fluid accumulation and the outcomes of interest (that is, the cumulative incidence of VAP and death at Day 28, and MV duration), a propensity score (PS) for maximum BWV ≥10% during the ICU stay was first built on age, sex, weight and body mass index at admission, chronic conditions (as listed in **Table 1**), initial SAPS 2 and SOFA score values, reason for admission, ARDS aetiology, and PaO_2/FiO_2 ratio and arterial pH at Day 1. This PS was calculated by logistic regression incorporating nonlinearities and interactions among the covariates ("cmprskcoxmsm" package of the R software). The average treatment effect (ATE) of BWV ≥10% on the aforementioned outcomes

was thereafter investigated through a competing-risk, time-to-event analysis with stabilized PS-based inverse probability of exposure weighting (IPW), with BWV ≥10% as a delay entry variable. Analyses were restricted to the first episode in patients with multiple VAP. All statistical procedures were conducted using the R software version 3.5.1 (http://www.R-project.org). Two-tailed *P* values < 0.05 were considered significant.

The study protocol was approved by the Ethical committee of the French Society of Intensive Care (CE-SRLF-20-84). Results of this study are reported according to the STROBE guidelines (16).

Results

A total of 322 patients were enrolled in the study cohort (**Table 1**), including 48 (14.9%), 111 (34.5%) and 163 (50.6%) with mild, moderate and severe ARDS, respectively. Non-COVID-19-related pneumonia (31.4%), COVID-19 (29.2%) and aspiration (18.3%) accounted for most ARDS aetiologies.

A first episode of VAP occurred in 167 patients (51.9%) after a median MV duration of 7 (4-11) days. Enterobacterales (106/167, 63.5%), *Pseudomonas aeruginosa* (30/167, 17.9%), *Staphylococcus aureus* (19/167, 11.4%) and *Stenotrophomonas maltophilia* (19/167, 11.4%) were the most common pathogens responsible for VAP, with 62 (37.1%) polymicrobial cases. Adequate antimicrobial therapy was initiated within 24 hours following the diagnosis of VAP in 111 patients (66.5%).

The median interval between two BW measurements during MV exposure was 1.3 (1.2-1.5) days, with a daily BW value available for 75.0% (65.3%-83.3%) of MV

days. Maximum BWV during the ICU stay was 6.00 (3.00-9.40) kg in patients with VAP and 5.50 (2.50-8.50) kg in patients without VAP (*P* = 0.42), corresponding to a relative increase of 7.3% (3.1%-11.5%) and 6.2% (2.7%-11.9%) from baseline BW, respectively (*P* = 0.78). The time-course of BWV over the ICU stay in the two subgroups is exposed in **Figure 1**. The crude proportion of patients with maximum BWV ≥10% did not differ between those with and without VAP (32.9% [55/167] versus 30.3% [47/155], *P* = 0.70). However, in time-to-event analysis with PS-based IPW for BWV ≥10% and extubation or death handled as competing events, BWV ≥10% was independently associated with the occurrence of VAP within the first 28 days of MV (adjusted hazard ratio [aHR] 1.38, 95% confidence interval [CI] 1.11-1.72, *P* = 0.004) (**Figure 2A**).

The median MV duration was 17 (12-28) days and 7 (5-10) days in patients with and without VAP (*P* <0.001). Though the estimated cumulative incidence of extubation after Day 8 was higher in patients with BWV <10% when compared to those with BWV ≥10% (**Figure 2B**), this difference did not reach the significance threshold after PS-based IPW for BWV ≥10% and integration of death as a competing event (aHR for extubation 0.91, 95% CI 0.73-1.14, *P* = 0.42).

Mortality rate at Day 28 was 23.4% (39/167) and 25.2% (39/155) in patients with and without VAP (*P* = 0.79). BWV ≥10% did not independently predict death at Day 28 (aHR 0.97, 95% CI 0.75-1.26, *P* = 0.82).

Discussion

Our results suggest that fluid overload with BWV ≥10% during MV exposure is an independent risk factor for VAP in ARDS patients. Similarly to what was reported

in previous studies not focused on ARDS patients (9-10), this finding may result from PFB-induced extension of MV though the association between BWV ≥10% and the cumulative incidence of extubation over time was not significant in our cohort, probably due to lack of statistical power. In a context of increased permeability of the alveolar-capillary barrier, a key pathophysiological feature of ARDS, the rise of hydrostatic pressure ensuing from PFB amplifies alveolar oedema and could potentiate local inflammation through mechanical stretch of pulmonary endothelial cells (2), thereby worsening respiratory failure and lengthening MV exposure. In addition, experimental models suggest that alveolar oedema might impair bacterial clearance and, therefore, contribute to the higher risk of VAP in ICU patients with fluid overload (17-19).

A recent meta-analysis pooling the results of major randomized controlled trials on this issue found that restrictive fluid administration in ARDS patients increases the number ventilator-free days and shortens the duration of the ICU stay when compared to liberal strategies (20). On the basis of our results, this beneficial effect could be partly attributable to a reduced hazard of VAP. Further prospective studies are necessary to assess whether conservative fluid strategies should be integrated in VAP prevention bundles in ARDS patients.

TRANSPARENCY DECLARATION

FB declares interests with MSD (consulting and lecture fees, and conference invitation) and BioMérieux (lecture fees) over the past 3 years, outside the scope of the submitted work. Other authors have no potential conflict of interest to declare.

FUNDING

None.

ETHICAL APPROVAL

The study protocol was approved on November 27th, 2020 by the Ethical committee of the French Society of Intensive Care (CE-SRLF-20-84). The requirement for patient's informed consent was waived due to the retrospective design of the study.

CONTRIBUTIONS

MLP and FB designed the study; MLP, CB, CA and FB collected the data; FB and TB analysed the data and interpreted the results; MLP and FB drafted the manuscript; all other authors revised the draft critically for important intellectual content. All authors read and approved the final manuscript.

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FIGURE CAPTIONS

Figure 1. Body weight variations before VAP, extubation or Day 28 (whichever occurred first)

Figure 1 footnotes

Variations are measured from baseline (*i.e.*, ICU admission) weight.

P = 0.23 for the difference in body weight variations between patients with and without VAP (mixed linear model)

VAP, ventilator-associated pneumonia

Figure 2. Estimated cumulative incidence of VAP (panel A) and MV weaning (panel B) in patients with maximum body weight variation <10% or >10%

Figure 2 footnotes

Time-to-event analyses with stabilized propensity score-based inverse probability of exposure weighting, handling weight gain >10% as a delay entry variable and MV weaning or death before Day 28 (panel A) or death (panel B) as competing events

VAP, ventilator-associated pneumonia; MV, mechanical ventilation; HR, hazard ratio; CI, confidence interval

Table 1. Characteristics of the study population

	Missing values	**All patients** (n = 322)	**Patients without VAP at Day 28** (n = 155)	**Patients with VAP at Day 28** (n = 167)	***P*-value**
Male sexe	0	236 (73.3)	102 (65.8)	134 (80.2)	0.005
Age, years	0	63.1 (14.7)	63.7 (15.1)	62.5 (14.4)	0.44
Weight at ICU admission, kg	0	84.0 (19.8)	83.3 (22.1)	84.6 (17.6)	0.54
Height, m	4	1.69 (0.10)	1.68 (0.09)	1.71 (0.10)	0.003
Body mass index, kg.m^{-2}	4	29.4 (6.9)	29.6 (7.5)	29.2 (6.4)	0.55
Chronic conditions					
Hypertension	0	168 (52.2)	88 (56.8)	80 (47.9)	0.14
Diabetes mellitus	0	89 (27.6)	44 (28.4)	45 (26.9)	0.87
COPD	0	38 (11.8)	20 (12.9)	18 (10.8)	0.61
Cardiac	0	93 (28.9)	44 (28.4)	49 (29.3)	0.95
Hepatic	0	28 (8.7)	12 (7.7)	16 (9.6)	0.70
Renal	0	28 (8.7)	17 (11.0)	11 (6.6)	0.23
Neurological	0	34 (10.6)	15 (9.7)	19 (11.4)	0.75
Cancer	0	32 (9.9)	22 (14.2)	10 (6.0)	0.02
Immunosuppression other than cancer	0	20 (6.2)	12 (7.7)	8 (4.8)	0.39
MacCabe score					
0	0	155 (48.1)	75 (48.4)	80 (47.9)	0.39
1	0	146 (45.3)	67 (43.2)	79 (47.3)	
2	0	21 (6.5)	13 (8.4)	8 (4.8)	
Knaus score					
A-B	0	296 (91.9)	143 (92.2)	153 (91.7)	0.99
C-D	0	26 (8.1)	12 (7.8)	14 (8.3)	
Main reason for ICU admission					
Acute respiratory failure	0	171 (53.1)	80 (51.6)	91 (54.5)	0.96
Coma	0	44 (13.7)	23 (14.8)	21 (12.6)	
Sepsis	0	36 (11.2)	19 (12.3)	17 (10.2)	
Cardiac arrest	0	33 (10.2)	17 (11.0)	16 (9.6)	
Trauma	0	12 (3.7)	5 (3.2)	7 (4.2)	
Miscellaneous	0	26 (8.1)	11 (7.1)	15 (8.9)	
SAPS 2 at ICU admission	0	52.7 (18.5)	53.1 (18.3)	52.3 (18.6)	0.67
SOFA score at ICU admission	0	8.0 (5.0-11.0)	8.0 (6.0-11.0)	8.0 (5.0-10.0)	0.13
ARDS aetiology					0.008
Pneumonia (other than COVID-19)	0	101 (31.4)	50 (32.3)	51 (30.5)	
COVID-19 [1]	0	94 (29.2)	30 (19.3)	64 (38.3)	
Aspiration	0	59 (18.3)	31 (20.0)	28 (16.8)	
Extra-pulmonary sepsis	0	44 (13.7)	27 (17.4)	17 (10.2)	
Miscellaneous	0	24 (7.4)	17 (11.0)	7 (4.2)	
ARDS and MV characteristics [2]					
Time from intubation to ARDS criteria, days	0	0 (0-0)	0 (0-1)	0 (0-0)	0.73
Lowest Vt, mL.kg^{-1} (PBW)	2	6.1 (5.8-6.6)	6.2 (5.8-6.7)	6 (5.7-6.5)	0.02
Highest PEEP, cmH_2O	0	10 (7-12)	10 (7-12)	10 (7-14)	0.14
Highest plateau pressure, cmH_2O	7	24 (20-27)	23 (20-26)	24 (21-28)	0.02
Highest driving pressure, cmH_2O	7	13 (10-16)	13 (10-15.5)	13 (10-16)	0.55
Lowest PaO_2/FiO_2 ratio, mmHg	0	100 (74-162)	105 (79-164)	93 (73-157)	0.14
Highest $PaCO_2$, mmHg	0	44 (39-52)	44 (39-52)	45 (40-52.5)	0.52
Lowest pH	0	7.33 (7.24-7.40)	7.33 (7.22-7.40)	7.33 (7.25-7.38)	0.73

Table 1 (continued).

	Missing values	**All patients** (n = 322)	**Patients without VAP at Day 28** (n = 155)	**Patients with VAP at Day 28** (n = 167)	***P*-value**
ARDS classification [2]					
Mild	0	48 (14.9)	27 (17.4)	21 (12.6)	0.21
Moderate	0	111 (34.5)	57 (36.8)	54 (32.3)	
Severe	0	163 (50.6)	71 (45.8)	92 (55.1)	
ARDS-targeted therapies					
Prone positioning	0	118 (36.6)	32 (20.6)	86 (51.5)	<0.001
Duration, days	0	5.5 (2-12)	2 (1.5-6)	7 (3-13)	<0.001
Nitric oxide inhalation	0	84 (26.1)	24 (15.5)	60 (35.9)	<0.001
Neuromuscular blocking agents	0	197 (61.2)	77 (49.7)	120 (71.9)	<0.001
Steroid use during the ICU stay [3]	0	164 (50.9)	85 (54.8)	79 (47.3)	0.21
PPI use during the ICU stay [3]	0	291 (90.4)	139 (89.7)	152 (91.0)	0.83
Intra-hospital transport [3]	0	1 (0-2)	0 (0-1)	1 (0-2)	<0.001
Organ support during the ICU stay					
Invasive MV duration, overall, days	0	11 (7-19)	7 (5-10)	17 (12-28)	<0.001
Ventilator-free days at Day 28 [4]	0	17 (9-21)	21 (18-23)	11 (10-16)	<0.001
Vasopressor	0	259 (80.4)	115 (74.2)	144 (86.2)	0.14
Renal replacement therapy	0	75 (23.8)	30 (19.7)	45 (27.6)	0.13
VV-ECMO	0	7 (2.2)	3 (1.9)	4 (2.4)	1.00
VA-ECMO	0	12 (3.8)	2 (1.3)	10 (6.1)	0.05
Surgery during the ICU stay	0	46 (14.3)	20 (12.9)	26 (15.6)	0.60
Decision to withhold or withdraw life-sustaining therapies	0	61 (18.9)	23 (14.8)	38 (22.8)	0.09
BWV from ICU admission					
Maximum variation, kg	0	5.55 (2.70-9.07)	5.50 (2.50-8.50)	6.00 (3.00-9.40)	0.42
Maximum variation, %	0	6.8 (2.8-11.7)	6.2 (2.7-11.9)	7.3 (3.1-11.5)	0.78
Variation >10%	0	102 (31.7)	47 (30.3)	55 (32.9)	0.70
Outcomes					
ICU LOS, days	0	15 (10-25)	10 (8-14)	23 (15-36)	<0.01
Hospital LOS, days	0	25.5 (16-41)	21 (12.5-32)	32 (21-48)	<0.01
Alive at Day 28	0	244 (75.8)	116 (74.8)	128 (76.6)	0.79
Alive at ICU discharge	0	227 (70.5)	114 (73.5)	113 (67.7)	0.30
Alive at hospital discharge	0	221 (68.6)	112 (72.3)	109 (65.3)	0.22

Table 1 footnotes

Data are presented as number (%) for categorical variable and mean (standard deviation) or median (interquartile range) for continuous variables.

VAP, ventilator-associated pneumonia; ICU, intensive care unit; SAPS 2, simplified acute physiology score 2; SOFA, sepsis-related organ failure assessment; ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; VT, tidal volume; PEEP, positive end-expiratory pressure; MV, mechanical ventilation; VA/VV-ECMO, veno-arterial/veno-venous extracorporeal membrane oxygenation; LOS, length of stay

[1] Positive SARS-CoV-2 rt-PCR on respiratory tract sample; [2] First day with ARDS criteria; [3] Before the occurrence of first VAP, or during the whole ICU stay in patients without VAP; [4] Defined as the total number of calendar days without invasive MV and vasoactive support over the first 28 days following intubation (day 0), with a zero-value attributed to patients deceased during this timeframe (21).

Figure 1.

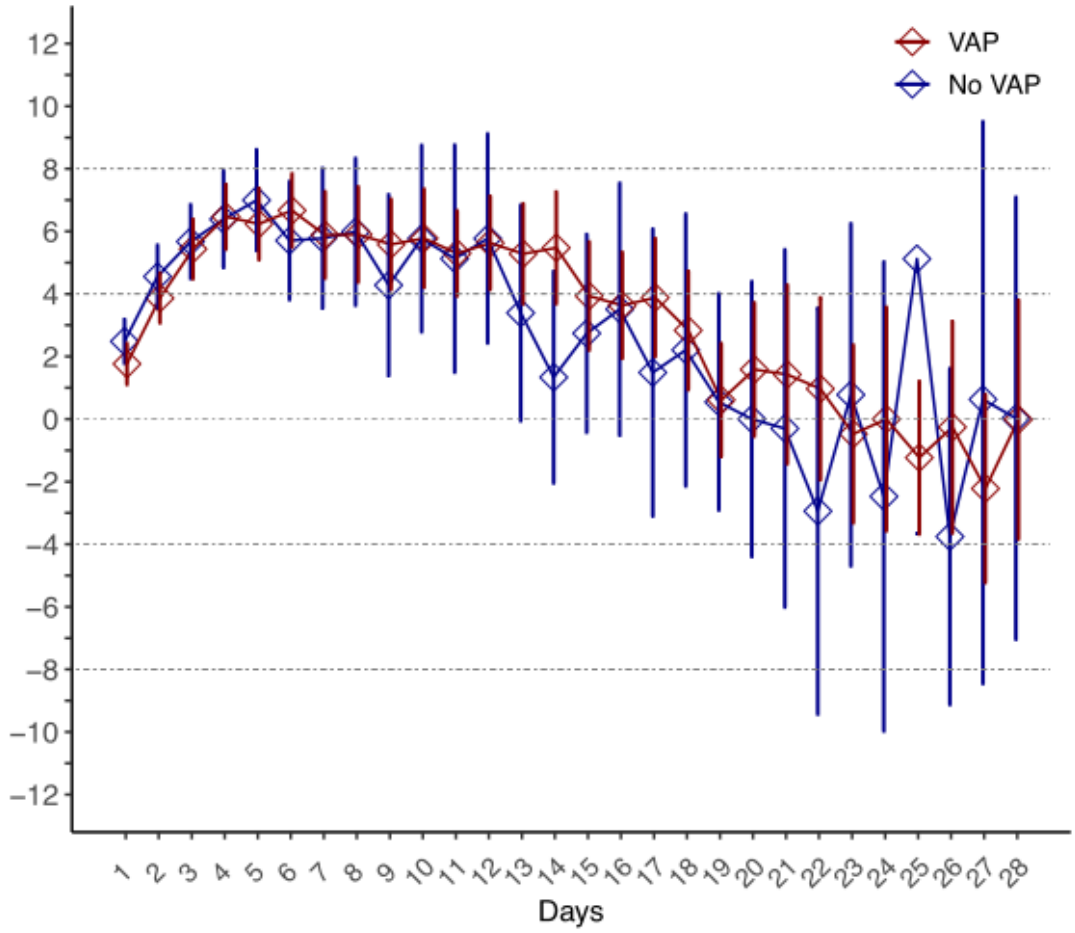
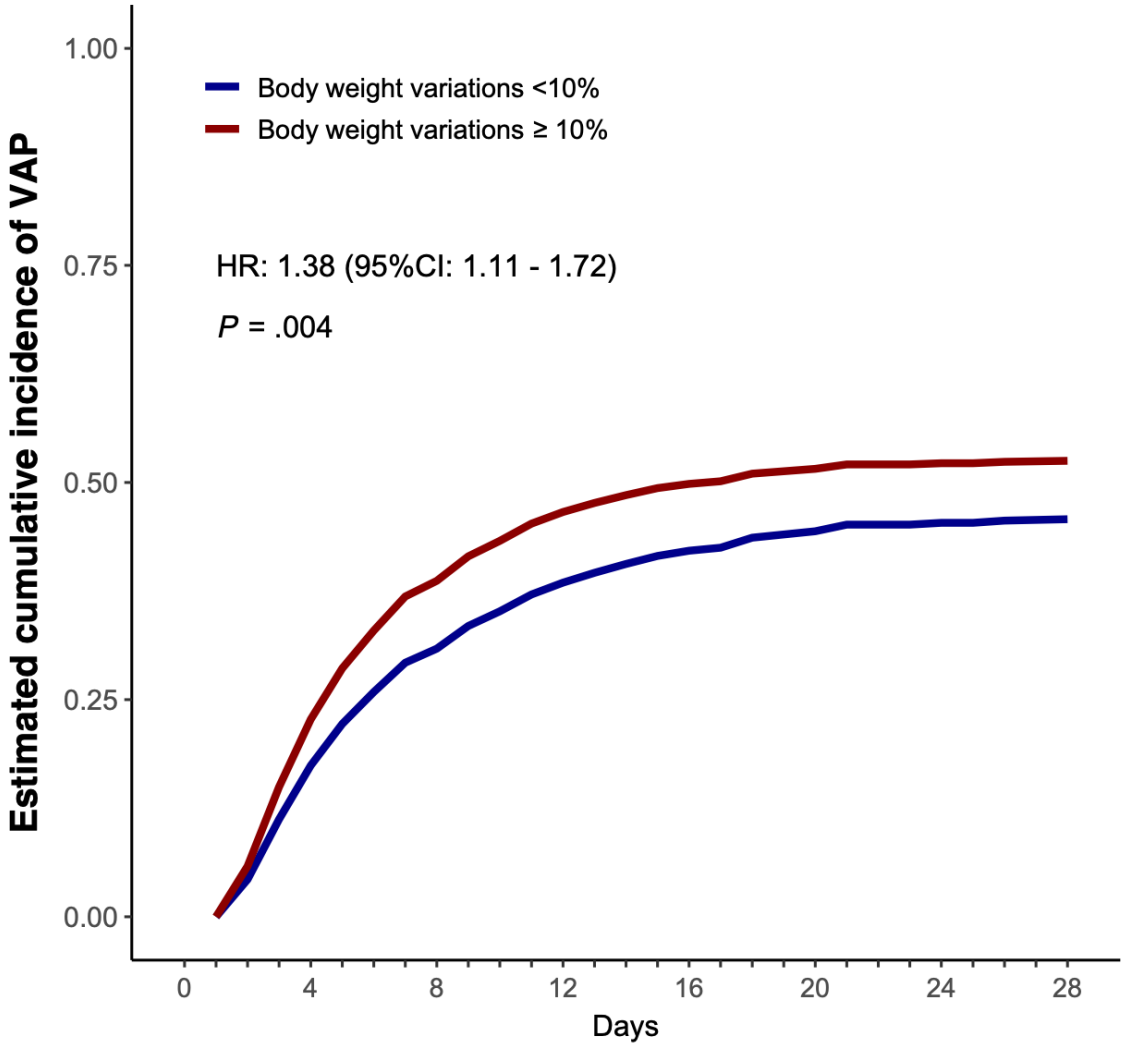
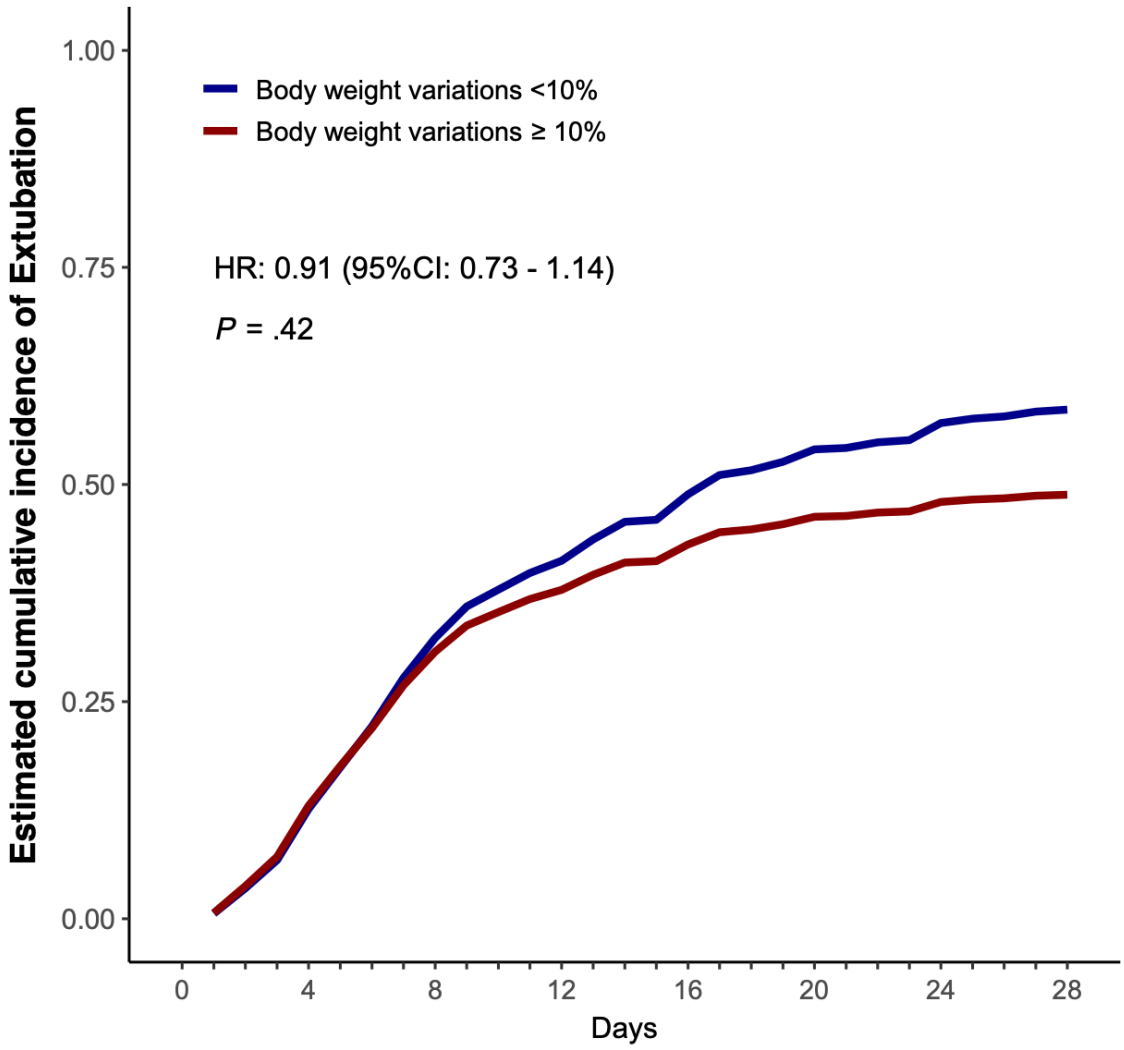

VAP
No VAP
12
10
8
6
4
2
0
−2
−4
−6
−8
−10
−12
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28
Days

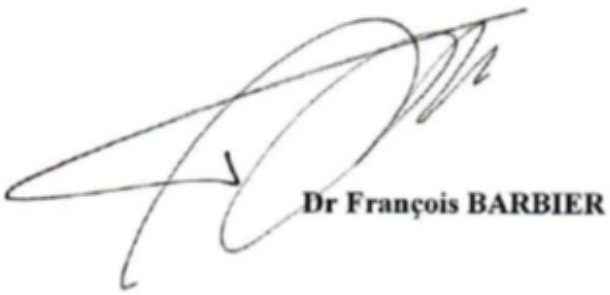
Figure 2.


Body weight variations <10%
Body weight variations ≥ 10%
HR: 1.38 (95%CI: 1.11 - 1.72)
P = .004
Estimated cumulative incidence of VAP
1.00
0.75
0.50
0.25
0.00
0
4
8
12
16
20
24
28
Days


Body weight variations <10%
Body weight variations ≥ 10%
HR: 0.91 (95%CI: 0.73 - 1.14)
P = .42
Estimated cumulative incidence of Extubation
1.00
0.75
0.50
0.25
0.00
0
4
8
12
16
20
24
28
Days

Page des signatures

Vu, le Directeur de Thèse



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LE PAPE Marc

76 pages – **9** tableaux – **11** figures – **1** illustrations.

Résumé :

Nous avons étudié l'impact clinique d'un premier épisode de pneumonie associée à la ventilation (PAV) dans une cohorte rétrospective de patients répondant aux critères de Berlin pour le SDRA. Le critère principal était l'association entre un premier épisode de PAV et la probabilité de décès au jour 90. Les critères d'évaluation secondaires comprenaient, les modifications potentielles de la PaO_2 /FiO_2, les valeurs du ratio et du score SOFA autour de la PAV, la durée de la ventilation mécanique, le nombre de jours sans ventilateur ni vasopresseur au jour 28 et la durée du séjour chez les patients avec et sans PAV. Des analyses de sous-groupes ont été effectuées chez des patients atteints de SDRA lié au COVID-19 et chez ceux atteints de SDRA d'autres causes.

Parmi les 336 patients inclus, 176 (52,4 %) ont eu une première PAV. La PAV a induit une baisse transitoire et modérée du rapport PaO_2 /FiO_2 sans augmentation des valeurs du score SOFA. La PAV était associée à moins de jours sans ventilateur et de jours sans vasopresseur au jour 28, et une durée de séjour en USI et à l'hôpital plus longue. Ces effets ont été observés dans les deux sous-groupes. Les taux de mortalité globaux au jour 90 étaient de 35,8 % et 30,0 % chez les patients avec et sans PAV, respectivement (P = 0,30). Analysée séparément, la PAV a prédit le décès chez les patients non-COVID-19 mais pas chez ceux atteints de COVID-19.

Mots clés :
Syndrome de détresse respiratoire aigu, pneumonie acquise sous ventilation, unité de soins intensifs, ventilation mécanique, infections nosocomiales, COVID-19, impacts cliniques.

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