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**EPIDEMIOLOGY, RISK FACTORS AND PROGNOSIS OF VENTILATOR-ASSOCIATED PNEUMONIA
DURING SEVERE COVID-19: MULTICENTER OBSERVATIONAL STUDY ACROSS 149
EUROPEAN INTENSIVE CARE UNITS**

Marc Garnier^a, MD; Jean-Michel Constantin^b, MD; Nicholas Heming^c, MD; Laurent Camous^d, MD; Alexis Ferré^e, MD; Keyvan Razazi^f, MD; Nathanaël Lapidus^g, MD; on behalf of the COVID-ICU Investigators*.

**COVID-ICU Investigators are listed at the end of the manuscript.*

^a Sorbonne University, GRC29, Assistance Publique-Hôpitaux de Paris (APHP), DMU DREAM, Anesthesiology and Critical Care Medicine Department, Tenon Hospital, Paris, France

^b Sorbonne University, GRC29, Assistance Publique-Hôpitaux de Paris (APHP), DMU DREAM, Anesthesiology and Critical Care Medicine Department, Pitié-Salpêtrière Hospital, Paris, France

^c Department of Intensive Care, Hôpital Raymond Poincaré, APHP University Versailles Saint Quentin - University Paris Saclay, France; Laboratory of Infection & Inflammation - U1173, School of Medicine Simone Veil, University Versailles Saint Quentin - University Paris Saclay, INSERM, Garches, France; FHU SEPSIS (Saclay and Paris Seine Nord Endeavour to Personalize Interventions for Sepsis) & RHU RECORDS (Rapid recognition of Corticosteroid resistant or sensitive Sepsis), Garches, France

^d Antilles-Guyane University, Medical and Surgical Intensive Care Unit, Guadeloupe Teaching Hospital, Les Abymes, France

^e Intensive Care Unit, Versailles Hospital, Le Chesnay, France

^f AP-HP, Hôpitaux Universitaires Henri-Mondor, Service de Médecine Intensive Réanimation, F-94010, Créteil, France; Université Paris Est Créteil, Faculté de Médecine de Créteil, IMRB, GRC CARMAS, Créteil, 94010, France

^g Sorbonne University, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique, AP-HP, Saint-Antoine Hospital, Public Health Department, F75012, Paris, France

Corresponding author: Marc Garnier; marc.garnier@aphp.fr - Anesthesiology and critical care department, Tenon University Hospital, 4 rue de la Chine, 75020 Paris, France.

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MG, NH, LC, AF, KR and JMC contributed to conceptualization and design of the protocol. Data were analyzed by MG and NL who have accessed and verified the data. NL performed the statistical analyses. MG wrote the first draft of this submission. All authors revised the report critically for important intellectual content and approved the final version of the manuscript. All authors confirmed that they had full access to all the data in the study and accepted responsibility to submit for publication.

Participating Sites and COVID-ICU Investigators

CHU Angers, Angers, France (Alain Mercat, Pierre Asfar, François Beloncle, Julien Demiselle), APHP - Hôpital Bicêtre, Le Kremlin-Bicêtre, France (Tài Pham, Arthur Pavot, Xavier Monnet, Christian Richard), APHP - Hôpital Pitié Salpêtrière, Paris, France (Alexandre Demoule, Martin Dres, Julien Mayaux, Alexandra Beurton), CHU Caen Normandie - Hôpital Côte de Nacre, Caen, France, (Cédric Daubin, Richard Descamps, Aurélie Joret, Damien Du Cheyron), APHP - Hôpital Cochin, Paris, France (Frédéric Pene, Jean-Daniel Chiche, Mathieu Jozwiak, Paul Jaubert), APHP - Hôpital Tenon, Paris (France, Guillaume Voiriot, Muriel Fartoukh, Marion Teulier, Clarisse Blayau), CHRU de Brest – La Cavale Blanche, Brest, France (Erwen L'Her, Cécile Aubron, Laetitia Bodenes, Nicolas Ferriere), Centre Hospitalier de Cholet, Cholet, France (Johann Auchabie, Anthony Le Meur, Sylvain Pignal, Thierry Mazzoni), CHU Dijon Bourgogne, Dijon, France (Jean-Pierre Quenot, Pascal Andreu, Jean-Baptiste Roudau, Marie Labruyère), CHU Lille - Hôpital Roger Salengero, Lille, France (Saad Nseir, Sébastien Preau, Julien Poissy, Daniel Mathieu), Groupe Hospitalier Nord Essonne, Longjumeau, France (Sarah Benhamida, Rémi Paulet, Nicolas Roucaud, Martial Thyrault), APHM - Hopital Nord, Marseille, France (Florence Daviet, Sami Hraiech, Gabriel Parzy, Aude Sylvestre), Hôpital de Melun-Sénart, Melun, France (Sébastien Jochmans, Anne-Laure Bouilland, Mehran Monchi), Élément Militaire de Réanimation du SSA, Mulhouse, France (Marc Danguy des Déserts, Quentin Mathais, Gwendoline Rager, Pierre Pasquier), CHU Nantes - Hôpital Hotel Dieu, Nantes, France (Jean Reignier, Amélie Seguin, Charlotte Garret, Emmanuel Canet), CHU Nice - Hôpital Archet, Nice, France (Jean Dellamonica, Clément Saccheri, Romain Lombardi, Yanis Kouchit), Centre Hospitalier d'Orléans, Orléans, France (Sophie Jacquier, Armelle Mathonnet, Mai-Ahn Nay, Isabelle Runge), Centre Hospitalier Universitaire de la Guadeloupe, Pointe-à-Pitre, France (Frédéric Martino, Laure Flurin, Amélie Rolle, Michel Carles), Hôpital de la Milétrie, Poitiers, France (Rémi Coudroy, Arnaud W Thille, Jean-Pierre Frat, Maeva Rodriguez), Centre Hospitalier Roanne, Roanne, France (Pascal Beuret, Audrey Tientcheu, Arthur Vincent, Florian Michelin), CHU Rouen - Hôpital Charles Nicolle, Rouen, France (Fabienne Tamion, Dorothée Carpentier, Déborah Boyer, Christophe Girault), CHRU Tours - Hôpital Bretonneau, Tours, France (Valérie Gissot, Stéphan Ehrmann, Charlotte Salmon Gandonniere, Djilali Elaroussi), Centre Hospitalier Bretagne Atlantique, Vannes, France (Agathe Delbove, Yannick Fedun, Julien Huntzinger, Eddy Lebas), CHU Liège, Liège, Belgique (Grâce Kisoka, Céline Grégoire, Stella Marchetta, Bernard Lambermont), Hospices Civils de Lyon - Hôpital Edouard Herriot, Lyon, France (Laurent Argaud, Thomas Baudry, Pierre-Jean Bertrand, Auguste Dargent), Centre Hospitalier Du Mans, Le Mans, France (Christophe Guitton, Nicolas Chudeau, Mickaël Landais, Cédric Darreau), Centre Hospitalier de Versailles, Le Chesnay, France (Alexis Ferre, Antoine Gros, Guillaume Lacave, Fabrice Bruneel), Hôpital Foch, Suresnes, France (Mathilde Neuville, Jérôme Devaquet, Guillaume Tachon, Richard Gallot), Hôpital Claude Galien, Quincy sous Senart, France (Riad Chelha, Arnaud Galbois, Anne Jallot, Ludivine Chalumeau Lemoine), GHR Mulhouse Sud-Alsace, Mulhouse, France (Khalidoun Kuteifan, Valentin Pointurier, Louise-Marie Jandeaux, Joy Mootien), APHP - Hôpital Antoine Bécélère, Clamart, France (Charles Damoisel, Benjamin Sztrymf), APHP - Hôpital Pitié-Salpêtrière, Paris, France (Matthieu Schmidt, Alain Combes, Juliette Chommeloux, Charles Edouard Luyt), Hôpital Intercommunal de Créteil, Créteil, France (Frédérique Schortgen, Leon Rusel, Camille Jung), Hospices Civils de Lyon - Hôpital Neurologique, Lyon, France (Florent Gobert), APHP - Hôpital Necker, Paris, France (Damien

Vimpere, Lionel Lamhaut), Centre Hospitalier Public du Cotentin - Hôpital Pasteur, Cherbourg-en-cotentin, France (Bertrand Sauneuf, Liliane Charrier, Julien Calus, Isabelle Desmeules), CHU Rennes - Hôpital du Pontchaillou, Rennes, France (Benoît Painvin, Jean-Marc Tadie), CHU Strasbourg - Hôpital Hautepierre, Strasbourg, France (Vincent Castelain, Baptiste Michard, Jean-Etienne Herbrecht, Mathieu Baldacini), APHP - Hôpital Pitié Salpêtrière, Paris, France (Nicolas Weiss, Sophie Demeret, Clémence Marois, Benjamin Rohaut), Centre Hospitalier Territorial Gaston-Bourret, Nouméa, France (Pierre-Henri Moury, Anne-Charlotte Savida, Emmanuel Couadau, Mathieu Série), Centre Hospitalier Compiègne-Noyon, Compiègne, France (Nica Alexandru), Groupe Hospitalier Saint-Joseph, Paris, France (Cédric Bruel, Candice Fontaine, Sonia Garrigou, Juliette Courtiade Mahler), Centre hospitalier mémorial de Saint-Lô, Saint-Lô, France (Maxime Leclerc, Michel Ramakers), Grand Hôpital de l'Est Francilien, Jossigny, France (Pierre Garçon, Nicole Massou, Ly Van Vong, Juliane Sen), Gustave Roussy, Villejuif, France (Nolwenn Lucas, Franck Chemouni, Annabelle Stoclin), Centre Hospitalier Intercommunal Robert Ballanger, Aulnay-sous-Bois, France (Alexandre Avenel, Henri Faure, Angélie Gentilhomme, Sylvie Ricome), Hospices Civiles de Lyon - Hôpital Edouard Herriot, Lyon, France (Paul Abraham, Céline Monard, Julien Textoris, Thomas Rimmel), Centre Hospitalier d'Avignon, Avignon, France (Florent Montini), Groupe Hospitalier Diaconesses - Croix Saint Simon, Paris, France (Gabriel Lejour, Thierry Lazard, Isabelle Etienney, Younes Kerroumi), CHU Clermont-Ferrand - Hôpital Gabriel Montpied, Clermont Ferrand, France (Claire Dupuis, Marine Bereziat, Elisabeth Coupeuz, François Thouy), Hôpital d'Instruction des Armées Percy, Clamart, France (Clément Hoffmann, Nicolas Donat, Anne Chrisment, Rose-Marie Blot), CHU Nancy - Hôpital Brabois, Vandœuvre-les-Nancy, France (Antoine Kimmoun, Audrey Jacquot, Matthieu Mattei, Bruno Levy), Centre Hospitalier de Vichy, Vichy, France (Ramin Ravan, Loïc Dopeux, Jean-Mathias Liteaudon, Delphine Roux), Hopital Pierre Bérégoovoy, Nevers, France (Brice Rey, Radu Anghel, Deborah Schenese, Vincent Gevrey), Centre Hospitalier de Tarbes, Tarbes, France (Jermy Castanera, Philippe Petua, Benjamin Madeux), Hôpitaux Civils de Colmar - Hôpital Louis Pasteur, Colmar, France (Otto Hartman), CHU Charleroi - Hôpital Marie Curie, Bruxelles, Belgique (Michael Piagnerelli, Anne Joosten, Cinderella Noel, Patrick Biston), Centre hospitalier de Verdun Saint Mihiel, Saint Mihiel, France (Thibaut Noel), CH Eure-Seine - Hôpital d'Evreux-Vernon, Evreux, France (Gurvan LE Bouar, Messabi Boukhanza, Elsa Demarest, Marie-France Bajolet), Hôpital René Dubos, Pontoise, France (Nathanaël Charrier, Audrey Quenet, Cécile Zylberfajn, Nicolas Dufour), APHP - Hôpital Lariboisière, Paris, France (Buno Mégarbane, Sébastien Voicu, Nicolas Deye, Isabelle Malissin), Centre Hospitalier de Saint-Brieuc, Saint-Brieuc, France (François Legay, Matthieu Debarre, Nicolas Barbarot, Pierre Fillatre), Polyclinique Bordeaux Nord Aquitaine, Bordeaux, France (Bertrand Delord, Thomas Laterrade, Tahar Saghi, Wilfried Pujol), HIA Sainte Anne, Toulon, France (Pierre Julien Cungi, Pierre Esnault, Mickael Cardinale), Grand Hôpital de l'Est Francilien, Meaux, France (Vivien Hong Tuan Ha, Grégory Fleury, Marie-Ange Brou, Daniel Zafimahazo), HIA Robert Picqué, Villenave d'Ornon, France (David Tran-Van, Patrick Avargues, Lisa Carencio), Centre Hospitalier Fontainebleau, Fontainebleau, France (Nicolas Robin, Alexandre Ouali, Lucie Houdou), Hôpital Universitaire de Genève, Genève, Suisse (Christophe Le Terrier, Noémie Suh, Steve Primmaz, Jérôme Pugin), APHP - Hôpital Beaujon, Clichy, France (Emmanuel Weiss, Tobias Gauss, Jean-Denis Moyer, Catherine Paugam Burtz), Groupe Hospitalier Bretagne Sud, Lorient, France (Béatrice La Combe, Rolland Smonig, Jade Violleau, Pauline Cailliez), Centre Hospitalier Intercommunal Toulon, La Seyne sur Mer, France (Jonathan Chelly), Centre Hospitalier de Dieppe, Dieppe, France (Antoine Marchalot, Cécile Saladin, Christelle Bigot), CHU de Martinique, Fort-de-France, France (Pierre-Marie Fayolle,

Jules Fatséas, Amr Ibrahim, Dabor Resiere), Hôpital Fondation Adolphe de Rothchild, Paris, France (Rabih Hage, Clémentine Cholet, Marie Cantier, Pierre Trouiler), APHP - Bichat Claude Bernard, Paris, France (Philippe Montravers, Brice Lortat-Jacob, Sebastien Tanaka, Alexy Tran Dinh), APHP - Hôpital Universitaire Paris Sud, Bicêtre, France (Jacques Duranteau, Anatole Harrois, Guillaume Dubreuil, Marie Werner), APHP - Hôpital Européen Georges Pompidou, Paris, France (Anne Godier, Sophie Hamada, Diane Zlotnik, Hélène Nougue), APHP, GHU Henri Mondor, Créteil, France (Armand Mekontso-Dessap, Guillaume Carreaux, Keyvan Razazi, Nicolas De Prost), APHP - Hôpitaux Universitaires Henri Mondor, Créteil, France (Nicolas Mongardon, Nicolas Mongardon, Meriam Lamraoui, Claire Alessandri, Quentin de Roux), APHP - Hôpital Lariboisière, Paris, France (Charles de Roquetaillade, Benjamin G. Chousterman, Alexandre Mebazaa, Etienne Gayat), APHP - Hôpital Saint-Antoine, Paris, France (Marc Garnier, Emmanuel Pardo, LeaSatre-Buisson, Christophe Gutton), APHP Hôpital Saint-Louis, Paris, France (Elise Yvin, Clémence Marcault, Elie Azoulay, Michael Darmon), APHP - Hôpital Saint-Antoine, Paris, France (Hafid Ait Oufella, Geoffroy Hariri, Tomas Urbina, Sandie Mazerand), APHP - Hôpital Raymond Pointcarré, Garches, France (Nicholas Heming, Francesca Santi, Pierre Moine, Djillali Annane), APHP - Hôpital Pitié Salpêtrière, Paris, France (Adrien Bouglé, Edris Omar, Aymeric Lancelot, Emmanuelle Begot), Centre Hospitalier Victor Dupouy, Argenteuil, France (Gaétan Plantefève, Damien Contou, Hervé Mentec, Olivier Pajot), CHU Toulouse - Hôpital Rangueil, Toulouse, France (Stanislas Faguer, Olivier Cointault, Laurence Lavayssiere, Marie-Béatrice Nogier), Centre Hospitalier de Poissy, Poissy, France (Matthieu Jamme, Claire Pichereau, Jan Hayon, Hervé Outin), APHP - Hôpital Saint-Louis, Paris, France (François Dépret, Maxime Coutrot, Maité Chaussard, Lucie Guillemet), Clinique du MontLégia, CHC Groupe-Santé, Liège, Belgique (Pierre Goffin, Romain Thouny, Julien Guntz, Laurent Jadot), CHU Saint-Denis, La Réunion, France (Romain Persichini), Centre Hospitalier de Tourcoing, Tourcoing, France (Vanessa Jean-Michel, Hugues Georges, Thomas Caulier), Centre Hospitalier Henri Mondor d'Aurillac, Aurillac, France (Gaël Pradel, Marie-Hélène Hausermann, Thi My Hue Nguyen-Valat, Michel Boudinaud), Centre Hospitalier Saint Joseph Saint Luc, Lyon, France (Emmanuel Vivier, SylvèneRosseli, Gaël Bourdin, Christian Pommier) Centre Hospitalier de Polynésie Française, Polynésie, France (Marc Vinclair, Simon Poignant, Sandrine Mons), Ramsay Générale de Santé, Hôpital Privé Jacques Cartier, Massy, France (Wulfran Bougouin), Centre Hospitalier Alpes Léman, Contamine sur Arve, France (Franklin Bruna, Quentin Maestraggi, Christian Roth), Hospices Civils de Lyon - Hôpital de la Croix Rousse, Lyon, France (Laurent Bitker, François Dhelft, Justine Bonnet-Chateau, Mathilde Filippelli), Centre Cardiologique du Nord, Saint-Denis, France (Tristan Morichau-Beauchant, Stéphane Thierry, Charlotte Le Roy, Mélanie Saint Jouan), GHU - Hôpital Saint-Anne, Paris, France (Bruno Goncalves, Aurélien Mazeraud, Matthieu Daniel, Tarek Sharshar) CHR Metz - Hôpital Mercy, Metz, France (Cyril Cadoz, RostaneGaci, Sébastien Gette, Guillaume Louis), APHP - Hôpital Paul Brousse, Villejuif, France (Sophe-Caroline Sacleux, Marie-Amélie Ordan), CHRU Nancy - Hôpital Central, Nancy, France (Aurélié Cravoisy, Marie Conrad, Guilhem Courte, Sébastien Gibot), Centre Hospitalier d' Ajaccio, Ajaccio, France (Younès Benzidi, Claudia Casella, Laurent Serpin, Jean-Lou Setti), Centre Hospitalier de Bourges, Bourges, France (Marie-Catherine Besse, Anna Bourreau), Centre hospitalier de la Côte Basque, Bayonne, France (Jérôme Pillot, Caroline Rivera, Camille Vinclair, Marie-Aline Robaux), Hospices Civils de Lyon - Hôpital de la Croix Rousse, Lyon, France (Chloé Achino, Marie-Charlotte Delignette, Tessa Mazard, Frédéric Aubrun), CH Saint-Malo, Saint-Malo, France (Bruno Bouchet, Aurélien Frérou, Laura Muller, Charlotte Quentin), Centre Hospitalier de Mulhouse, Mulhouse, France (Samuel Degoul), Centre Hospitalier de

Briançon, Briançon, France (Xavier Stihle, Claude Sumian, Nicoletta Bergero, Bernard Lanaspres), CHU Nice, Hôpital Pasteur 2, Nice, France (Hervé Quintard, Eve Marie Maiziere), Centre Hospitalier des Pays de Morlaix, Morlaix, France (Pierre-Yves Egretreau, Guillaume Leloup, Florin Berteau, Marjolaine Cottrel), Centre Hospitalier Valence, Valence, France (Marie Bouteloup, Matthieu Jeannot, Quentin Blanc, Julien Saison), Centre Hospitalier Niort, Niort, France (Isabelle Geneau, Romaric Grenot, Abdel Ouchike, Pascal Hazera), APHP - Hôpital Pitié Salpêtrière, Paris, France (Anne-Lyse Masse, Suela Demiri, Corinne Vezinet, Elodie Baron, Deborah Benchetrit, Antoine Monsel), Clinique du Val d'Or, Saint Cloud, France (Grégoire Trebbia, Emmanuelle Schaack, Raphaël Lepecq, Mathieu Bobet), Centre Hospitalier de Béthune, Béthune, France (Christophe Vinsonneau, Thibault Dekeyser, Quentin Delforge, Imen Rahmani), Groupe Hospitalier Intercommunal de la Haute-Saône, Vesoul, France (Bérengère Vivet, Jonathan Paillet, Lucie Hierle, Claire Chaignat, Sarah Valette), Clinique Saint-Martin, Caen, France (Benoît Her, Jennifer Brunet), Ramsay Générale de Santé, Clinique Convert, Bourg en Bresse, France (Mathieu Page, Fabienne Boiste, Anthony Collin), Hôpital Victor Jousselein, Dreux, France (Florent Bavozet, Aude Garin, Mohamed Dlala, KaisMhamdi), Centre Hospitalier de Troye, Troye, France, (Bassem Beilouny, Alexandra Lavalard, Severine Perez), CHU de ROUEN- Hôpital Charles Nicolle, Rouen, France (Benoît Veber, Pierre-Gildas Guitard, Philippe Gouin, Anna Lamacz), Centre Hospitalier Agen-Nérac, Agen, France (Fabienne Plouvier, Bertrand P Delaborde, Aïssa Kherchache, Amina Chaalal), APHP - Hôpital Louis Mourier, Colombes, France (Jean-Damien Ricard, Marc Amouretti, Santiago Freitas-Ramos, Damien Roux), APHP - Hôpital Pitié-Salpêtrière, Paris, France (Jean-Michel Constantin, Mona Assefi, Marine Lecore, Agathe Selves), Institut Mutualiste Montsouris, Paris, France (Florian Prevost, Christian Lamer, Ruiying Shi, Lyes Knani), CHU Besançon – Hôpital Jean Minjot, Besançon, France, (Sébastien Pili Floury, Lucie Vettoretti), APHP - Hôpital Universitaire Robert-Debré, Paris, France (Michael Levy, Lucile Marsac, Stéphane Dager, Sophie Guilmin-Crépon), CHU Besançon – Hôpital Jean Minjot, Besançon, France, (Hadrien Winiszewski, Gael Piton, Thibaud Soumagne, Gilles Capellier) ; Médipôle Lyon-Villeurbanne, Villeurbanne, France, (Jean-Baptiste Putegnat, Frédérique Bayle, Maya Perrou, Ghyslaine Thao), APHP - Ambroise Paré, Boulogne-Billancourt, France (Guillaume Géri, Cyril Charron, Xavier Repessé, Antoine Vieillard-Baron), CHU Amiens Picardie, Amiens, France (Mathieu Guilbart, Pierre-Alexandre Roger, Sébastien Hinard, Pierre-Yves Macq), Hôpital Nord-Ouest, Villefranche-sur-Saône, France (Kevin Chaulier, Sylvie Goutte), CH de Châlons en Champagne, Châlons en Champagne, France (Patrick Chillet, Anaïs Pitta, Barbara Darjent, Amandine Bruneau), CHU Angers, Angers, France (Sigismond Lasocki, Maxime Leger, Soizic Gergaud, Pierre Lemarie), CHU Grenoble Alpes, Grenoble, France (Nicolas Terzi, Carole Schwebel, Anaïs Dartel, Louis-Marie Galerneau), APHP - Hôpital Européen Georges Pompidou, Paris, France (Jean-Luc Diehl, Caroline Hauw-Berlemont, Nicolas Péron, Emmanuel Guérot), Hôpital Privé d'Antony, Antony, France (Abolfazl Mohebbi Amoli, Michel Benhamou, Jean-Pierre Deyme, Olivier Andremont), Institut Arnault Tzanck, Saint Laurent du Var, France (Diane Lena, Julien Cady, Arnaud Causeret, Arnaud De La Chapelle) ; Centre Hospitalier d' Angoulême, Angoulême, France (Christophe Cracco, Stéphane Rouleau, David Schnell) ; Centre Hospitalier de Cahors, Cahors, France (Camille Foucault), Centre hospitalier de Carcassonne, Carcassonne, France (Cécile Lory) ; CHU Nice – Hôpital L'Archet 2, Nice, France (Thibault Chapelle, Vincent Bruckert, Julie Garcia, Abdlazize Sahraoui) ; Hôpital Privé du Vert Galant, Tremblay-en-France, France (Nathalie Abbosh, Caroline Bornstain, Pierre Pernet) ; Centre Hospitalier de Rambouillet, Rambouillet, France (Florent Poirson, Ahmed Pasem, Philippe Karoubi) ; Hopitaux du Léman, Thonon les Bains, France (Virginie

Poupinel, Caroline Gauthier, François Bouniol, Philippe Feuchere), Centre Hospitalier Victor Jousselin, Dreux, France (Florent Bavoze, Anne Heron), Hôpital Sainte Camille, Brie sur Marne, France (Serge Carreira, Malo Emery, Anne Sophie Le Floch, Luana Giovannangeli), Hôpital d'instruction des armées Clermont-Tonnerre, Brest, France (Nicolas Herzog, Christophe Giacardi, Thibaut Baudic, Chloé Thill), APHP - Hôpital Pitié Salpêtrière, Paris, France (Said Lebbah, Jessica Palmyre, Florence Tubach, David Hajage) ; APHP - Hôpital Avicenne, Bobigny, France (Nicolas Bonnet, Nathan Ebstein, Stéphane Gaudry, Yves Cohen) ; Groupement Hospitalier la Rochelle Ré Amis, La Rochelle, France (Julie Noublanche, Olivier Lesieur) ; Centre Hospitalier Intercommunal de Mont de Marsan et du Pays des Sources, Mont de Marsan, France (Arnaud Sément, Isabel Roca-Cerezo, Michel Pascal, Nesrine Sma) ; Centre Hospitalier Départemental de Vendée, La-Roche-Sur-Yon, France (Gwenhaël Colin, Jean-Claude Lacherade, Gauthier Bionz, Natacha Maquigneau) ; Pôle Anesthésie-Réanimation, CHU Grenoble (Pierre Bouzat, Michel Durand, Marie-Christine Hérault, Jean-Francois Payen)

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KR, NH, LC, AF and NL declare no competing interests.

Data sharing statement

The data analyzed and presented in this study are available from the corresponding author on reasonable request, providing the request meets local ethical and research governance criteria after publication. Patient-level data will be anonymized and study documents will be redacted to protect the privacy of trial participants.

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ABSTRACT

Background. COVID-19 patients requiring mechanical ventilation are particularly at risk of developing ventilator-associated pneumonia (VAP). Risk factors and the prognostic impact of developing VAP during critical COVID-19 have not been fully documented.

Methods. Patients invasively ventilated for at least 48h from the prospective multicentre COVID-ICU database were included in the analyses. Cause-specific Cox regression models were used to determine factors associated with the occurrence of VAP. Cox-regression multivariable models were used to determine VAP prognosis. Risk factors and the prognostic impact of early vs. late VAP, and *Pseudomonas*-related vs. non-*Pseudomonas*-related VAP were also determined.

Main findings. 3388 patients were analysed (63 [55-70] years, 75.8% males). VAP occurred in 1523/3388 (45.5%) patients after 7 [5-9] days of ventilation. Identified bacteria were mainly *Enterobacteriaceae* followed by *Staphylococcus aureus* and *Pseudomonas aeruginosa*. VAP risk factors were male gender (Hazard Ratio (HR) 1.26, 95% Confidence Interval [1.09-1.46]), concomitant bacterial pneumonia at ICU admission (HR 1.36 [1.10-1.67]), PaO₂/FiO₂ ratio at intubation (HR 0.99 [0.98-0.99] per 10 mmHg increase), neuromuscular-blocking agents (HR 0.89 [0.76-0.998]), and corticosteroids (HR 1.27 [1.09-1.47]). VAP was associated with 90-mortality (HR 1.34 [1.16-1.55]), predominantly due to late VAP (HR 1.51 [1.26-1.81]). The impact of *Pseudomonas*-related and non-*Pseudomonas*-related VAP on mortality was similar.

Conclusion. VAP affected almost half of mechanically ventilated COVID-19 patients. Several risk factors have been identified, among which modifiable risk factors deserve further investigation. VAP had a specific negative impact on 90-day mortality, particularly when it occurred between the end of the first week and the third week of ventilation.

Keywords list: COVID-19, intensive care unit, invasive mechanical ventilation, mortality,
risk factors, ventilator-associated pneumonia.

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Abbreviation List:

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3	ARDS	Acute Respiratory Distress Syndrome
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5	C-VAP	COVID-19-related VAP
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8	COVID-19	COronaVirus (SARS-CoV-2)-related Disease
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11	HR	Hazard Ratio
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14	ICU	Intensive Care Unit
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17	IL	Interleukin
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19	IMV	Invasive Mechanical Ventilation
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22	NC-VAP	non COVID-19-related VAP
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25	NMBA	NeuroMuscular Blocking Agents
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27	VAP	Ventilator-Associated Pneumonia
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1. INTRODUCTION

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3 “Coronavirus disease 2019” (COVID-19), due to SARS-CoV-2 infection, primarily affects the
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5 lungs. From the beginning of the pandemic to early September 2022, approximately 615 million
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7 people have been diagnosed with COVID-19, among whom approximately 6.5 million died,
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9 worldwide [1]. Severe pneumonia and acute respiratory distress syndrome (ARDS) are the two
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11 most severe forms of COVID-19. High-flow oxygen therapy is the first-line treatment of
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13 COVID-19-related severe hypoxemia [2], however, more than half of critically ill COVID-19
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15 patients will require invasive mechanical ventilation (IMV). Ventilator-associated pneumonia
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17 (VAP) affects between 29% and 64% of COVID-19 patients [3–7]. VAP incidences of up to
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19 84% have even been reported in SARS-CoV-2 infected patients requiring ECMO [8]. To date,
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21 several pathophysiological hypotheses have been proposed to explain the particular
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23 vulnerability of COVID-19 patients to bacterial lung superinfection. However, the
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25 identification of risk factors of VAP, as well as the impact of VAP on the prognosis of severely
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27 SARS-CoV-2 infected patients is not fully documented. Previous reports based on small cohorts
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29 suggested that the male gender and the need for vasopressors are risk factors of VAP in COVID-
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31 19 [3,9]. Additionally, the occurrence of VAP in ventilated COVID-19 patients did not seem to
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33 affect mortality [9], mainly driven by VAP-induced septic shock and ARDS [4].
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43 Based on the analysis of the largest multicenter prospective cohort including 4929 critically-ill
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45 COVID-19 patients admitted into the ICU, the primary objectives of this study were to describe
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47 the incidence, characteristics, risk factors, and the prognosis of VAP in severe COVID-19
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49 pneumonia; and secondly to describe the risk factors and the prognosis of early vs. late VAP,
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51 and *Pseudomonas*-related vs. non-*Pseudomonas*-related VAP.
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2. PATIENTS AND METHODS

Study design

The multicenter prospective COVID-ICU cohort has previously been described [6]. Briefly, the study was conducted in 149 ICUs from 138 centers in France, Switzerland, and Belgium. Between February 25, 2020, and May 2, 2020, all consecutive patients over 16 years of age suffering from respiratory failure with laboratory-confirmed SARS-CoV-2 infection admitted to a participating ICU were prospectively included.

Inclusion and exclusion criteria

Were included in the current analysis all invasively mechanically ventilated (> 48h) patients of the COVID-ICU cohort. Were excluded patients who had been invasively ventilated for more than 24 hours prior to a transfer into one of the participating centers.

Data collection

Full data collection has been previously described [6]. Briefly, data were retrieved via an electronic form, completed daily. A particular focus on patients' respiratory support was made, regarding both the type of support and its settings. Records of additional treatments such as neuromuscular blocking agents (NMBA), corticosteroids, etc. were collected. Recorded outcomes included time of weaning from IMV, time of ICU and hospital discharge, vital status at ICU and at hospital discharge, and vital status 28 and 90 days after ICU admission.

VAP definition

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Only the first episode of bacterial VAP was considered when addressing the primary objectives. Regarding subgroup analyses, only the first episode of early and/or late VAP, and *Pseudomonas*-related and/or non-*Pseudomonas*-related VAP were considered. VAP diagnosis was based on: 1) clinical and radiological suspicion based on the European Center of Disease Control criteria [10]; 2) confirmed by one positive microbiological sample defined when culture recovered $\geq 10^6$ CFU.mL⁻¹ for tracheal aspirate, $\geq 10^4$ CFU.mL⁻¹ for broncho-alveolar lavage, and $\geq 10^3$ CFU.mL⁻¹ for distal protected brush or aspirate [10]; 3) leading the attending physician to initiate an antimicrobial therapy. In addition, VAP must have occurred at least 48h after the onset of IMV. Finally, pneumonia only related to *L. pneumophila*, mycoplasma, and chlamydia species, anaerobes, or isolated oro-pharyngeal flora were excluded from the analyses. Early and late VAP were defined as occurring $<$ and ≥ 5 days respectively after the onset of IMV [11].

Statistical analyses

Baseline characteristics of patients are described as counts (proportions) for categorical variables and median [1st-3rd quartiles] for quantitative variables.

Factors associated with the occurrence of VAP were identified using cause-specific Cox regression models, after checking the proportional-odds hypothesis and controlling for the competing risk of death. The at-risk period started 48h after the onset of IMV. Factors associated with early and late VAP were identified in independent analyses using the same models. For early VAP, all patients were censored on day 5 following the onset of invasive mechanical ventilation. For late VAP, the at-risk period started 5 days after the onset of IMV in all patients still requiring IMV, and the occurrence of an early VAP was considered as a covariate. In another analysis, only *Pseudomonas*-related VAPs were considered, using the

1 same statistical approach, with the occurrence of earlier non-*Pseudomonas*-related VAP
2 considered as a covariate.
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5 To determine whether the occurrence of VAP was associated with patients' prognosis, Cox
6 regression multivariable models were used to study the time to death or hospital/ICU discharge
7 alive, considering the occurrence of a VAP as a time-dependent variable. For length-of-stay
8 outcomes, death was considered as a competing event with the use of cause-specific models.
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10 For all regression analyses, a univariable analysis was conducted and a multivariable model for
11 variables deemed clinically relevant was built, regardless of the univariable significant
12 associations [12].
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23 All tests were two-tailed and interpreted at the 0.05 significance threshold. All analyses were
24 performed using the R statistical software version 4.0.3 (R Foundation for Statistical
25 Computing, Vienna, Austria).
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32 33 34 35 **IRB approval**

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38 The study was approved by the French Intensive Care Society ethical committee (CE-SRLF 20-
39 23). Due to the observational design and in accordance with French law [13], patients or next-
40 of-kin of ICU non-survivors were informed that anonymized data regarding their hospital stay
41 were collected in the database.
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52 **Reporting guidelines**

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55 This observational study follows the STROBE guidelines. STROBE checklist is provided as a
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3. RESULTS

Patients

Over the study period, 4929 patients were included in the COVID-ICU database. Complete follow-up data were available for 4676 out of the 4929 patients, including 473 (10.1%) patients exclusively treated with standard oxygen therapy, 381 (8.1%) with high-flow oxygen therapy, and 156 (3.3%) with non-invasive ventilation. Among the remaining 3666 patients, 278 were ventilated for more than 24h prior to admission into a participating ICU. Eventually, 3388 invasively ventilated patients were analyzed. According to the protocol, episodes only due to *Legionella pneumophila* (n=1), mycoplasma and chlamydia species (n=1), anaerobes (n=8), or isolated oro-pharyngeal flora (n=116) were not considered as VAP. Finally, 1523 (45.0%) patients fully analyzable presented at least one episode of VAP (**Figure 1**).

Characteristics of patients and their clinical and biological data at ICU admission are available in **Table 1**. The median age was 63 [55-70] years. There were 2545/3388 (75.1%) male patients. The most frequent comorbidities were hypertension (48.9%) and diabetes (27.5%). There were 352 (10.4%) immunocompromised patients. Median time between the first COVID-19 symptoms and ICU admission was 7 [4-10] days. At admission, SOFA and SAPS-II scores were 10 [8-12] and 39 [30-52], respectively. Concomitant bacterial pneumonia has been diagnosed in 245 (7.2%) SARS-CoV-2 infected patients. There was no relevant difference regarding co-morbidities, and characteristics at admission and during the first 24h following tracheal intubation between patients with and without subsequent VAP, except for the prevalence of diabetes and values of PaO₂/FiO₂ ratio (**Table 1**).

First VAP episode description and predictors

1 At least one episode of VAP occurred in 1523 (45.0%) patients, after a median of 7 [5-9] days
2 of IMV. The cumulative probability of developing VAP is presented in **Figure A.1**. Distribution
3 of the bacteria isolated during the first episode of VAP is presented in **Table 2**. VAP was
4 monomicrobial in 1263/1523 (82.9%) of cases. Among the 1814 bacterial species isolated,
5 *Enterobacteriaceae* were found the most frequently, followed by *Staphylococcus aureus* and
6 *Pseudomonas aeruginosa*.
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14 Univariable and multivariable analyses of COVID-19-related VAP (C-VAP) predictors are
15 reported in **Table 3**. After adjustment, variables independently associated with C-VAP were
16 male gender (HR 1.26 95%CI[1.09-1.46], $p = 0.002$), concomitant bacterial pneumonia at ICU
17 admission (HR 1.36 [1.10-1.67], $p = 0.004$), the severity of respiratory failure at the time of
18 IMV initiation (HR 0.99 [0.98-0.99] per 10 mmHg increase of the PaO₂/FiO₂ ratio, $p = 0.001$),
19 NMBA use (HR 0.89 [0.76-0.998], $p = 0.046$), and corticosteroid use (HR 1.27 [1.09-1.47], p
20 = 0.002).
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36 **Early and late VAP description and predictors**

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40 Among the 1523 patients that presented C-VAP, 491 (32.2%) patients presented an early VAP,
41 and 1313 (86.2%) had at least one episode of late VAP. Distribution of the bacterial species
42 isolated during early and late VAP is presented in **Table A.1**. *S. aureus*, *S. pneumoniae*, and *H.*
43 *influenzae* were isolated more frequently in early than in late VAP, while *P. aeruginosa* was
44 isolated more frequently in late than in early VAP.
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53 After adjustment, the only variable independently associated with early VAP was concomitant
54 bacterial pneumonia at ICU admission (HR 1.51 [1.03-2.22], $p = 0.04$) (**Table A.2**), while
55 variables independently associated with late VAP were male gender (HR 1.21 [1.03-1.44], $p =$
56 0.02), the severity of respiratory failure at the time of intubation (HR 0.99 [0.98-0.99] per 10
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1 mmHg increase of the PaO₂/FiO₂ ratio, $p = 0.002$), NMBA use (HR 0.84 [0.72-0.97], $p = 0.02$),
2 and a previous episode of early VAP (HR 3.11 [2.64-3.67], $p < 0.001$) (**Table A.3**).
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8 ***Pseudomonas*-related VAP description and predictors**

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11 Among the 1523 patients that presented C-VAP, 656 (43.1%) presented at least one episode of
12 *Pseudomonas*-related VAP. After adjustment, variables independently associated with
13 *Pseudomonas*-related VAP occurrence were the use of prone positioning (HR 1.25 [1.02-1.53],
14 $p = 0.03$) and a previous non-*Pseudomonas*-related VAP (HR 5.87 [4.74-7.27], $p < 0.001$)
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Patient outcomes and impact of VAP on prognosis

All VAP

Overall 28-day and 90-day mortality were 25.8% and 31.7%, respectively. Among survivors, the median length of IMV, ICU, and hospital stay were 17 [8-28], 19 [12-32], and 31 [19-49] days, respectively (**Table 2**). After adjustment for the other predictors of 90-day mortality of critically ill COVID-19 patients [6], the occurrence of at least one episode of VAP was significantly associated with poor outcome (HR 1.34 [1.16-1.55], $p < 0.001$) (**Table 4** and **Figure 2**). VAP was also associated with higher ICU and hospital length-of-stay among survivors (**Table 2** and **Figure A.2**).

Early and late VAP

After adjustment, late VAP was independently associated with 90-day mortality (HR 1.51 [1.26-1.81], $p < 0.001$), while early VAP was not (HR 1.10 [0.91-1.32], $p = 0.34$) (**Table A.5**).

***Pseudomonas*-related VAP**

The impact of *Pseudomonas*-related and non-*Pseudomonas*-related VAP on 90-day mortality was similar (HR 1.18 [0.99-1.40] and HR 1.18 [1.02-1.37], respectively) (**Tables A.6A&B**).

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4. DISCUSSION

VAP incidence and microbial ecology

In this prospective multicenter study, 45% of mechanically ventilated COVID-19 patients presented at least one episode of VAP. This result is in keeping with previous smaller reports, in which the incidence of C-VAP ranged from 30% to 60% [14]. However, this incidence is higher than reported in mixed non-COVID ICU patients, usually ranging from 10% to 25% [15,16], and reaches similar incidences to those reported in trauma or brain injury [17]. Taking into consideration the severity of lung injury, this incidence remains higher than reported in patients with severe ARDS due to other causes [18,19], including other viral ARDS [8,20,21]. This suggests the involvement of a specific mechanism related to COVID-19. It cannot be ruled out that the surge of severe patients, may have led to a decrease in vigilance and incomplete compliance with infection prevention measures [22]. Indeed, the surge of ICU patients led to work overload and understaffing (notably due to infection of healthcare workers), and consequently to hiring non-ICU nurses and increasing the patient-to-nurse ratio [23]. Moreover, nurses had to take care of more severe patients requiring more frequent invasive ventilation than before the first epidemic waves. In addition, closing the doors of patients' rooms, the need to wear highly protective equipment to get in (and their possible shortage), and the possible fear of staff contamination contributed to decreasing the number of daily visits to patients [24]. Finally, ICU workers experienced high levels of stress and psychological burden, decreasing their vigilance and compliance with bundles of care for VAP prevention [25].

However, other pathophysiological features related to SARS-CoV-2 itself or to the excessive host inflammatory response may contribute to this increased susceptibility to bacterial superinfection, such as a large production of Interleukin (IL)-6, IL-1 β , and IL-10 [26–28], lymphopenia [26,29], decreased B and dendritic cells activation [30], decreased HLA-DR expression on lung macrophages [31], or expansion of myeloid-derived suppressor cells [32].

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Despite this increased incidence, the bacterial ecology reported in C-VAP appears close to that of non-COVID-19-related VAP (NC-VAP) [15]. Indeed, *Enterobacteriaceae*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus* were the three main isolates, similar to the findings of a large European multicenter study [33]. Our results are also in keeping with those of previous smaller studies comparing bacterial ecology in C-VAP and NC-VAP [7,34,35]. Finally, we confirmed previous observations made both in NC-VAP [33] and C-VAP [9], reporting a greater proportion of *S. aureus*, *S. pneumoniae*, and *H. influenzae*, and less *P. aeruginosa* in early compared to late VAP.

VAP predictors

Among patient-related risk factors, only the male gender was independently associated with C-VAP in our study. This is in keeping with previous reports about NC-VAP [36–38] and C-VAP [3,9]. Conversely, chronic renal and heart failures, COPD, diabetes, and immunodeficiency, frequently cited as NC-VAP risk factors [15,39], were not associated with C-VAP. Regarding severity factors, we observed that the severity of hypoxemia at intubation was associated with a moderate additional risk of C-VAP, which is consistent with the previous identification of ARDS as a risk factor of NC-VAP [15,39]. In contrast with several small-size studies [40,41] and randomized controlled trials [42], steroids use was associated with C-VAP in this study, as previously suggested in NC-VAP [15]. However, due to the design of the study, we cannot rule out the participation of non-respiratory organ failure in this result, notably of associated septic shock, which is both a potential indication for hydrocortisone therapy and a risk factor of VAP [37,43]. In addition, the effect of steroids on the incidence of VAP may vary during ICU stay, with an increased risk being reported for patients hospitalized for at least 14 days in the ICU [44]. Conversely, NMBA use was associated with a reduced incidence of C-VAP in this study.

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This is an unexpected result as a large recent study showed a 2.5-fold increased risk of NC-VAP with NMBA use, even after adjustment for the severity of the ARDS [38]. Thus, further studies are needed to determine if early administration of NMBA could be a protective factor in C-VAP. NMBA may prevent patient self-induced lung injury (P-SILI) by removing the strong inspiratory efforts arising from the high respiratory drive frequently observed in COVID-19 patients [45], which may favor VAP by worsening lung injuries and prolonging the duration of IMV.

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Finally, the parameter associated with VAP with the highest hazard ratio was concomitant bacterial pneumonia at ICU admission, which occurred in 7.2% of patients. This incidence, lower than for other viral ARDS such as influenza-related ARDS, is consistent with previous reports [46,47]. The risk of VAP may in part be explained by a more dysregulated inflammation in case of bacterial co-infection, favoring subsequent superinfection. This is in keeping with the higher mortality observed in COVID-19 intubated patients suffering from concomitant bacterial infection [47], similar to that reported in other respiratory viral-bacterial co-infections [48].

VAP impact on the outcome

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The negative impact of VAP on mortality is established in general ICU patients [16,49] and in patients suffering from influenza pneumonia [50]. However, the impact of C-VAP on mortality is still a matter of debate. Nseir *et al.* reported a 1.7-fold increase in 28-day mortality due to C-VAP [50], while Gamberini *et al.* did not observe any significant excess in mortality either for early or late C-VAP [51]. The crude mortality rates of patients with and without VAP in our study must not be directly compared due to the immortal time bias leading to underestimating mortality in patients with VAP. The Cox regression analysis accounting for competing risk of death and time-varying history of VAP controlled this bias and confirmed that the occurrence

1 of C-VAP was associated with higher mortality (HR 1.34 [1.16-1.55]). These estimates are
2 somewhat smaller than those reported by Nseir *et al.* Moreover, we observed different results
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4 for early and late C-VAP, only the latter being significantly associated with increased 90-day
5 mortality. Gamberini *et al.* previously reported a detrimental impact of late rather than early C-
6 VAP on weaning from IMV, although no effect on mortality was observed, possibly due to a
7 lack of power. In addition, landmark analyses suggested that VAP-related excess in mortality
8 is of particular concern during the first 15 days following intubation. Indeed, the cumulative
9 probability of death at day 90 no longer differed between patients with and without C-VAP as
10 soon as VAP occurred 15 days or more after intubation, suggesting that beyond this time point
11 the adverse effect of VAP may be overcome by other factors affecting patients with a prolonged
12 ICU stay. Finally, we observed a similar impact on mortality of *Pseudomonas*-related and non-
13 *Pseudomonas*-related C-VAP, confirming in C-VAP the absence of specific risk due to
14 *Pseudomonas* recently reported in NC-VAP [49].
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36 **Strengths and limitations**

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38 To our knowledge, this study is the largest cohort of ICU COVID-19 patients with VAP. Thanks
39 to the detailed data available in the COVID-ICU database, we were able to perform a
40 comprehensive risk factor analysis and adjust prognostic analyses on a large number of
41 variables already known to impact COVID-19 patients' mortality. Moreover, the Cox
42 regression models used for prognostic analyses allowed us to estimate the specific association
43 of VAP with mortality independently of the ventilation time already elapsed at the time of VAP
44 onset. Thus, our study adds to current knowledge the identification of C-VAP risk factors and
45 definitely confirmed the link between developing VAP and over-mortality during critical
46 COVID-19.
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1 We acknowledge several limitations to our study. First, all patients were included during the
2 first epidemic wave of SARS-CoV-2 affecting Europe in the spring of 2020. Thus, it cannot be
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4 excluded that recent features including the acquisition of immunity following successive
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6 epidemic waves or vaccination, or the emergence of SARS-CoV-2 variants, may change some
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8 of our results. Second, collected data did not allow us to precisely describe the bacterial ecology
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10 of C-VAP, for instance regarding the distribution of species within the *Enterobacteriaceae*
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12 family, or to provide antibiotic susceptibility and resistance profiles. Finally, although this study
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14 was conducted in 149 ICUs from 138 centers, across three countries, our results were obtained
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16 from a west European population. Since genetic predispositions to VAP and ethnical
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18 quantitative and qualitative variations in immune function have been described [39], further
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20 large studies are needed to confirm our results in different populations.
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CONCLUSION

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3 Patients with critical COVID-19 requiring IMV are especially exposed to the risk of VAP, in
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5 particular if they are males, present a bacterial pneumonia concomitantly with COVID-19,
6
7 suffer from severe hypoxemic respiratory failure, and are treated with corticosteroids. C-VAP
8
9 is independently associated with 90-day mortality and ICU morbidity, mainly due to the effect
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11 of late-VAP occurring before the 3rd week of ICU stay. A potential protective effect of NMBA
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13 use at the early stage of ventilation of critical COVID-19 patients requiring IMV deserves
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15 further investigations.
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ADDITIONAL INFORMATION.

The additional Figures and Tables are available online in the appendices.

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TABLES

TABLE 1. Demographic, clinical, biological, and ventilatory support characteristics of the 3388 patients according to the occurrence of ventilator-associated pneumonia (VAP).

	No.	All patients (n=3388)	VAP (n=1523)	No VAP (n=1865)
Age, years	3387	63 [55-70]	63 [55-70]	63 [55-71]
Men, number (%)	3358	2545 (75.8%)	1195 (79%)	1350 (73.2%)
Body mass index, kg.m⁻²	3182	28.6 [25.6-32.5]	28.7 [25.7-32.7]	28.4 [25.6-32.4]
<18		18 (0.6%)	5 (0.3%)	13 (0.7%)
18-25		649 (20.4%)	292 (20.2%)	357 (20.5%)
25-30		1268 (39.8%)	565 (39.1%)	703 (40.4%)
>30		1247 (39.2%)	582 (40.3%)	665 (38.3%)
Active smoker, number (%)	3388	141 (4.2%)	58 (3.8%)	83 (4.5%)
Cardiovascular comorbidities				
Treated hypertension	3388	1656 (48.9%)	898 (48.2%)	758 (49.8%)
Coronary artery disease	3388	373 (11.0%)	173 (11.4%)	200 (10.7%)
Chronic heart failure	3388	115 (3.4%)	50 (3.3%)	65 (3.5%)
Respiratory comorbidities				
COPD	3388	206 (6.1%)	98 (6.4%)	108 (5.8%)
Asthma	3388	221 (6.5%)	97 (6.4%)	124 (6.6%)
Diabetes	3388	932 (27.5%)	450 (29.5%)	482 (25.8%)
Chronic renal failure	3388	310 (9.1%)	147 (9.7%)	163 (8.7%)
Chronic liver failure	3388	22 (0.6%)	10 (0.7%)	12 (0.6%)
Immunodeficiency		352 (10.4%)	160 (10.5%)	192 (10.3%)
Hematological malignancies	3388	97 (2.9%)	46 (3.0%)	51 (2.7%)
Active solid tumor	3388	50 (1.5%)	16 (1.1%)	34 (1.8%)
Solid organ transplant	3388	74 (2.2%)	40 (2.6%)	34 (1.8%)
Human Immunodeficiency Virus	3388	56 (1.7%)	24 (1.6%)	32 (1.7%)
Immunosuppressive therapy ^a	3388	145 (4.3%)	72 (4.7%)	73 (3.9%)
Long-term corticosteroids ^b	3388	135 (4.0%)	62 (4.1%)	73 (3.9%)
Clinical frailty score^c	3028	2 [2-3]	2 [2-3]	2 [2-3]
Time between first symptoms and ICU admission, days	3387	7 [4-10]	7 [4-10]	7 [4-10]
NSAID intake before ICU admission	2919	207 (7.1%)	96 (7.3%)	111 (7.0%)
At ICU admission				
SAPS II score	3107	39 [30-52]	39 [30-52]	40 [31-52]
SOFA score at ICU admission	2567	10 [8-12]	10 [8-12]	10 [7-12]
Patient origin	3373			
Direct admission from home/emergency medical ambulance		511 (15.1%)	237 (15.6)	274 (14.8%)
Emergency room		1521 (45.1%)	693 (45.6%)	828 (44.7%)

	Medical wards		1078 (32%)	463 (30.5%)	615 (33.2%)
	Other ICU		259 (7.7%)	125 (8.2%)	134 (7.2%)
	Operating theatre		4 (0.1%)	2 (0.1%)	2 (0.1%)
Concomitant bacterial pneumonia		3387	245 (7.2%)	140 (9.2%)	105 (5.6%)
Respiratory support, number (%)		3383			
	Standard oxygen therapy		448 (13.2%)	193 (12.7%)	255 (13.7%)
	High-flow oxygen		264 (7.8%)	106 (7%)	158 (8.5%)
	Non-invasive ventilation		88 (2.3%)	34 (2.2%)	54 (2.9%)
	Invasive mechanical ventilation		2583 (76.4%)	1190 (78.1%)	1393 (74.9%)

At intubation

Ventilator settings^d					
	VT, mL.kg ⁻¹ PBW	2997	6.2 [5.9-6.7]	6.1 [5.8-6.7]	6.2 [5.9-6.8]
	Set PEEP, cmH ₂ O	1306	12 [10-14]	12 [10-14]	12 [10-13]
	Plateau pressure, cmH ₂ O	2049	24 [21-27]	24 [21-27]	24 [21-27]
	Driving pressure, cmH ₂ O	1318	12 [10-14]	12 [9-14]	12 [10-14]
	Set FiO ₂	2823	0.50 [0.40-0.60]	0.50 [0.40-0.60]	0.50 [0.40-0.60]
	PaO ₂ /FiO ₂ , mmHg	2652	186 [146-243]	176 [140-225]	193 [150-247]
Biology^d					
	White blood cells, x10 ⁹ .L ⁻¹	3108	9.0 [6.8-11.9]	9.2 [6.9-12.3]	8.8 [6.7-11.7]
	Lymphocytes, x10 ⁹ .L ⁻¹	2745	0.8 [0.5-1.1]	0.8 [0.5-1.1]	0.8 [0.5-1.1]
	Hemoglobin, g.dL ⁻¹	3126	11.4 [10.1-12.6]	11.4 [10.1-12.6]	11.4 [10.2-12.6]
	Platelets, x10 ⁹ .L ⁻¹	3122	240 [183-311]	240 [182-309]	240 [184-313]
	Creatinine, μmol.L ⁻¹	3073	82 [61-125]	83 [63-124]	80 [60-125]
	Bicarbonates, mmol.L ⁻¹	3107	25 [23-28]	26 [23-28]	25 [23-28]
	C-reactive protein, mg.L ⁻¹	2067	195 [126-283]	201 [130-290]	190 [123-276]
	Procalcitonine, ng.mL ⁻¹	1571	0.58 [0.25-1.44]	0.60 [0.28-1.54]	0.54 [0.22-1.40]
	Fibrinogen, g.L ⁻¹	2138	6.9 [5.7-7.9]	6.9 [5.8-7.9]	6.8 [5.6-7.9]
	D-dimers, μg.L ⁻¹	1483	1860 [1047-4000]	1893 [1022-4099]	1830 [1060-3818]
	Lactate, mmol.L ⁻¹	3065	1.30 [1.00-1.70]	1.30 [1.00-1.70]	1.30 [1.00-1.70]

Results are expressed as n (%) or median [25th–75th percentiles]

^a except corticosteroids

^b daily intake above 20mg of prednisone equivalent

^c Clinical Frailty Score (CFS) as described by Rockwood et al. (A global clinical measure of fitness and frailty in elderly people. *CMAJ*. 2005;173:489–95). The validated French translation of the CFS was used in this study (Abraham et al. Validation of the clinical frailty score (CFS) in French language. *BMC Geriatr*. 2019 Nov 21;19(1):322)

^d worst value during the 24h following tracheal intubation

No.: number of available data; NSAID: non-steroidal anti-inflammatory drug; PBW: predicted body weight

TABLE 2. Treatments, VAP characteristics and outcomes of the 3388 patients according to the occurrence of ventilator-associated pneumonia (VAP).

	No.	All patients (n=3388)	VAP (n=1523)	No VAP (n=1865)
Treatments				
Neuromuscular blockers use^a	3076	2125 (69.1%)	1008 (70.8%)	1117 (67.6%)
Prone positioning use^a	3187	1209 (37.9%)	602 (41.8%)	607 (34.7%)
Systemic antibiotic use^a	3242	2080 (64.2%)	934 (63.9%)	1146 (64.4%)
Including beta-lactam antibiotics	3249	2049 (63.1%)	935 (63.8%)	1114 (62.4%)
Corticosteroid treatment	3388	815 (24.1%)	363 (23.8%)	452 (24.2%)
VAP characteristics				
Early VAP	1523	-	491 (32.2%)	-
Late VAP	1523	-	1313 (86.2%)	-
Monomicrobial VAP	1523	-	1263 (82.9%)	-
Polymicrobial VAP	1523	-	260 (17.1%)	-
Isolated pathogen^b				
<i>Pseudomonas aeruginosa</i>		-	286 (15.8%)	-
<i>Acinetobacter baumannii</i>		-	19 (1%)	-
<i>Haemophilus influenzae</i>		-	48 (2.6%)	-
Enterobacteriaceae and other GNB		-	1087 (59.9%)	-
<i>Staphylococcus aureus</i>		-	242 (13.3%) ^c	-
<i>Streptococcus pneumoniae</i>		-	35 (1.9%)	-
Enterococci		-	61 (3.4%)	-
Other streptococci		-	36 (2%)	-
Outcomes				
Subsequent VAP				
Second episode	1523	-	736 (48.3%)	-
Third episode	1523	-	174 (11.4%)	-
>3 episodes	1523	-	145 (9.5%)	-
28-day mortality^d	3388	874 (25.8%)	329 (21.6%)	545 (29.2%)
90-day mortality^d	3388	1074 (31.7%)	456 (29.9%)	618 (33.1%)
Length of mechanical ventilation^e, days	2389	17 [8-28]	25 [16-41]	10 [5-19]
ICU length-of-stay^e, days	2389	19 [12-32]	28 [19-43]	14 [8-21]
Hospital length-of-stay^e, days	2344	31 [19-49]	41 [28-60]	23 [15-37]

^a at least during 48h hours following intubation and before VAP diagnosis

^b total number of bacterial isolates, n=1814 in 1523 first VAP episodes

^c including 37 (2%) methicillin-resistant *Staphylococcus aureus*

^d crude mortality at 28 and 90 days could not be directly compared between patients with and without VAP due to immortal time bias. See Table 4 for multivariable analysis and text for interpretation.

^e among survivors

TABLE 3. Factors associated with ventilator-associated pneumonia (VAP) in mechanically ventilated adults with COVID-19.

	Univariable HR [95%CI]	p-value	Multivariable HR [95%CI]	p-value
Age, per 10 years	0.99 [0.95-1.04]	0.72	0.96 [0.91-1.02]	0.18
Male gender	1.22 [1.07-1.38]	0.002	1.26 [1.09-1.46]	0.002
Active smoking	0.90 [0.69-1.17]	0.44	0.83 [0.61-1.12]	0.22
Body mass index \geq 30 kg.m⁻²	1.04 [0.91-1.20]	0.57	1.05 [0.92-1.20]	0.45
Treated hypertension	1.08 [0.98-1.20]	0.12	1.00 [0.88-1.13]	0.97
Chronic heart failure	1.02 [0.77-1.35]	0.89	1.07 [0.78-1.49]	0.67
COPD	1.09 [0.83-1.44]	0.54	1.18 [0.92-1.50]	0.20
Diabetes	1.19 [1.07-1.33]	0.002	1.08 [0.94-1.23]	0.27
Chronic renal failure	1.19 [1.00-1.41]	0.05	1.10 [0.89-1.36]	0.37
Immunodeficiency	1.17 [1.00-1.38]	0.06	1.09 [0.89-1.34]	0.39
Concomitant bacterial pneumonia at admission	1.51 [1.28-1.78]	<0.001	1.36 [1.10-1.67]	0.004
Non-respiratory SOFA score at intubation, per point	1.04 [1.02-1.06]	<0.001	1.02 [1.00-1.05]	0.09
PaO₂/FiO₂ at intubation, per 10 mmHg	0.99 [0.98-0.995]	0.002	0.99 [0.98-0.99]	0.001
Leucopenia or hyperleucocytosis at intubation	1.10 [0.99-1.22]	0.08	1.07 [0.95-1.21]	0.24
Neuromuscular blockers^a	0.95 [0.85-1.07]	0.39	0.89 [0.76-0.998]	0.046
Prone positioning^a	1.14 [1.03-1.27]	0.02	1.11 [0.98-1.27]	0.10
Corticosteroids use^b	1.39 [1.23-1.57]	<0.001	1.27 [1.09-1.47]	0.002

^a at least during 48h hours following intubation and before VAP diagnosis

^b at least during 48h hours following intubation and before VAP diagnosis at a dose greater than or equal to 40 mg prednisone equivalent

TABLE 4. Factors associated with 90-day mortality in mechanically ventilated adults with COVID-19.

	Univariable HR [95%CI]	<i>p</i>-value	Multivariable HR [95%CI]	<i>p</i>-value
Age, per 10 years	1.49 [1.40-1.58]	<0.001	1.47 [1.37-1.58]	<0.001
Body mass index >30 kg.m⁻²	0.82 [0.72-0.94]	0.004	0.94 [0.81-1.09]	0.39
Diabetes	1.50 [1.32-1.70]	<0.001	1.30 [1.13-1.50]	<0.001
Immunodeficiency	1.74 [1.47-2.06]	<0.001	1.60 [1.33-1.96]	<0.001
Time between first symptoms and ICU admission, per day	0.96 [0.95-0.87]	<0.001	0.96 [0.95-0.98]	<0.001
Non-respiratory SOFA score at intubation, per one point	1.10 [1.07-1.13]	<0.001	1.09 [1.06-1.12]	<0.001
PaO₂/FiO₂ at intubation, per 10 mmHg	0.99 [0.98-0.998]	0.02	0.98 [0.98-0.99]	0.003
At least one episode of VAP	1.38 [1.20-1.58]	<0.001	1.34 [1.16-1.55]	<0.001

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Figure 1. Flow chart of the selection of patients included into the COVID-ICU database for analyses.

Figure 2. Landmark analyses of the cumulative probability of death for patients still alive and mechanically ventilated at day 5, day 10, day 15 and day 20, depending on the earlier occurrence of VAP.

APPENDICES

Supplementary Material Legends

Figure A.1. Cumulative probability of VAP occurrence across the duration of mechanical of ventilation. The at-risk period starts after the initial 48h gray area.

Figure A.2. Landmark analyses of the cumulative probability of discharge from the ICU for patients still alive and mechanically ventilated at day 5, day 10, day 15 and day 20, depending on the earlier occurrence of VAP.

Table A.1. Bacterial distribution of the first ventilator-associated pneumonia (VAP) episode, according to the occurrence of early and late VAP.

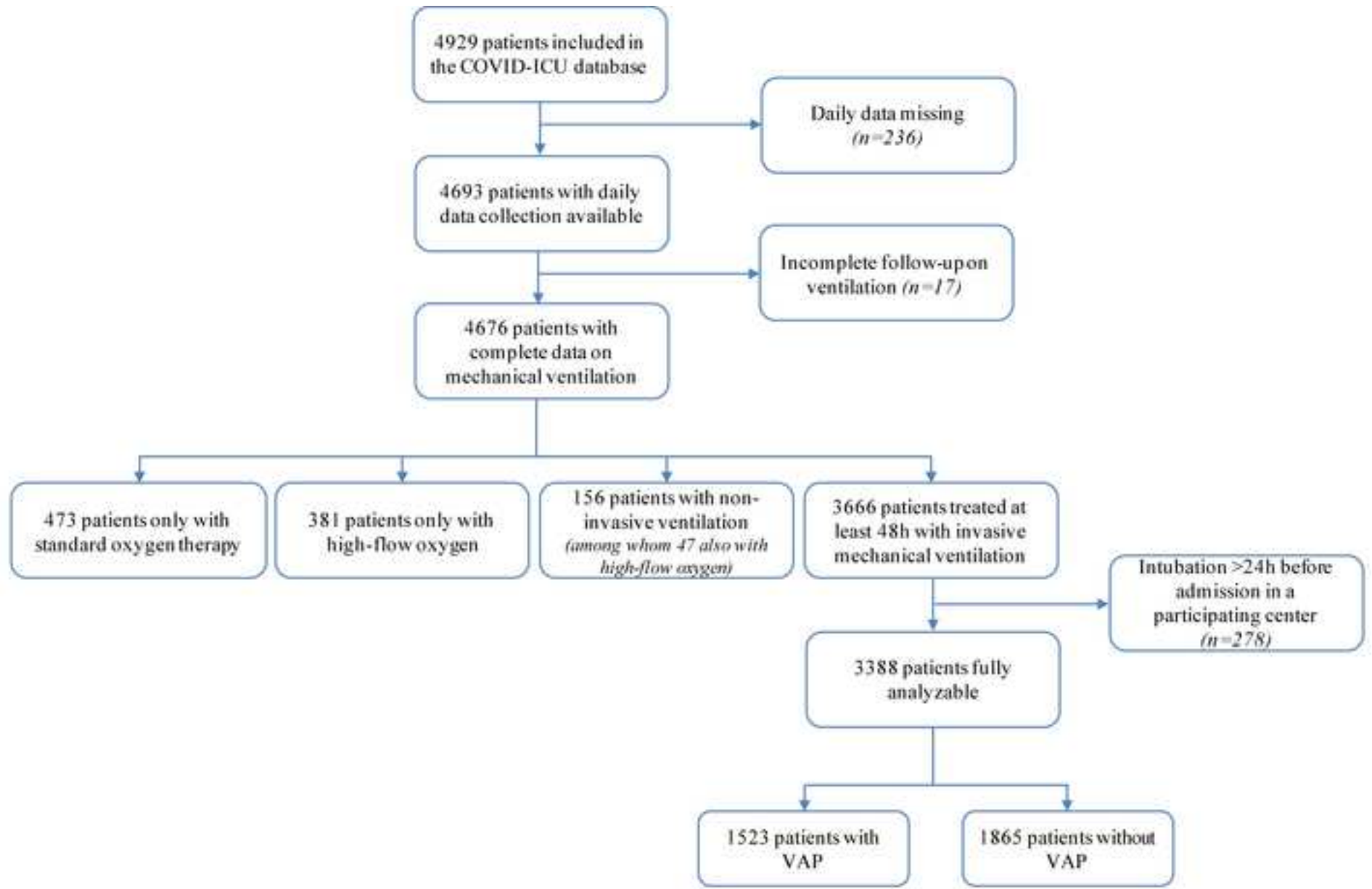
Table A.2. Factors associated with early ventilator-associated pneumonia (VAP) in mechanically ventilated adults with COVID-19.

Table A.3. Factors associated with late ventilator-associated pneumonia (VAP) in mechanically ventilated adults with COVID-19.

Table A.4. Factors associated with *Pseudomonas*-related ventilator-associated pneumonia (VAP) in mechanically ventilated adults with COVID-19.

Table A.5. Factors associated with 90-day mortality in mechanically ventilated adults with COVID-19, including early and late VAP.

Table A.6. Factors associated with 90-day mortality in mechanically ventilated adults with COVID-19, including *Pseudomonas*-related and non-*Pseudomonas*-related VAP.



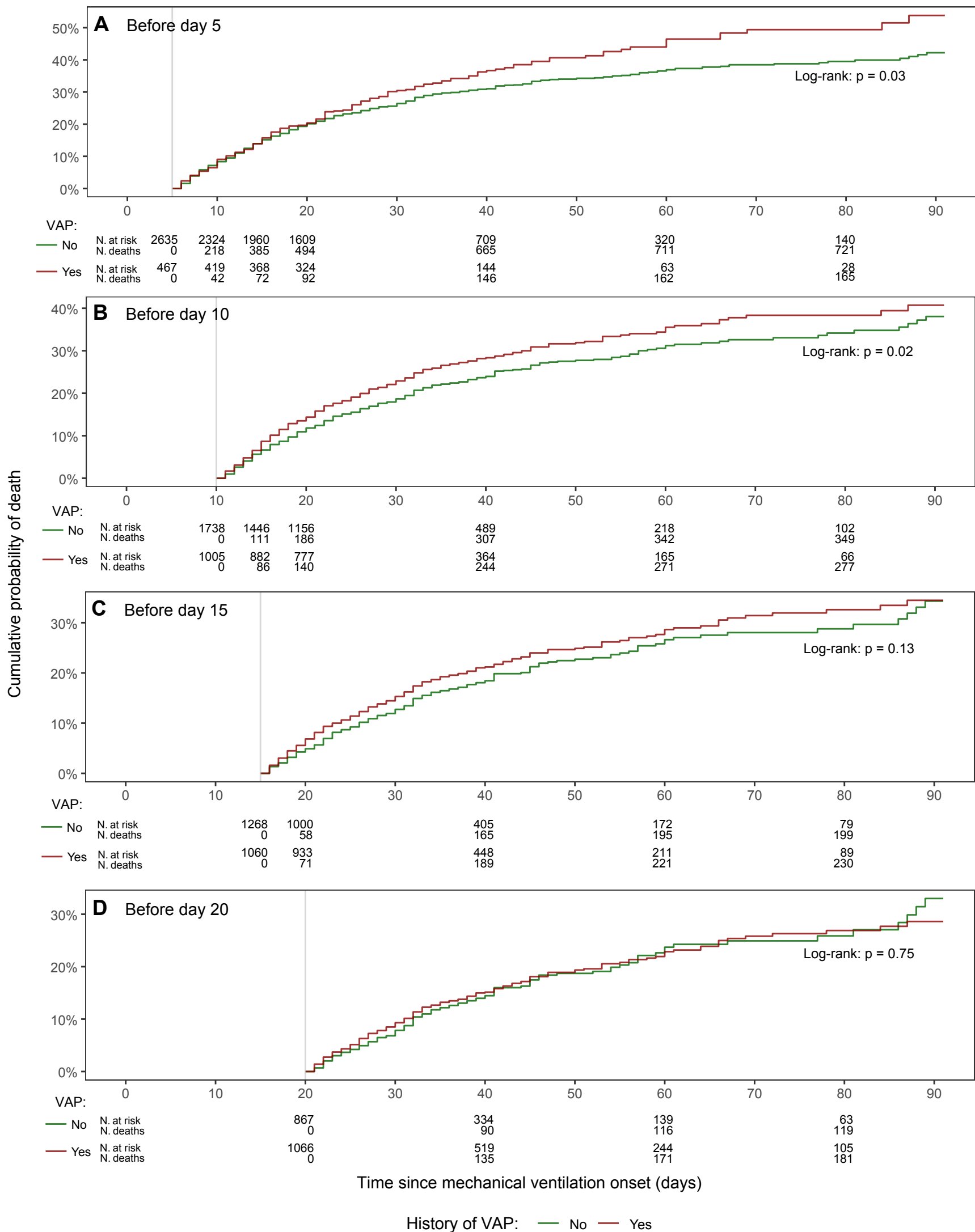


Table A.1. Bacterial distribution of the first ventilator-associated pneumonia (VAP) episode, according to the occurrence of early and late VAP

	All first VAP (n=1523)	First early VAP (n=491)	First late VAP (n=1313)	<i>p</i> -value
Monomicrobial VAP	1263 (82.9%)	413 (84.1%)	1080 (82.3%)	0.39
Polymicrobial VAP	260 (17.1%)	78 (15.9%)	233 (17.7%)	
Isolated pathogen^a				0.04
<i>Pseudomonas aeruginosa</i>	286 (15.8%)	76 (13.2%)	257 (16.3%)	
<i>Acinetobacter baumannii</i>	19 (1%)	6 (1%)	15 (1%)	
<i>Haemophilus influenzae</i>	48 (2.6%)	25 (4.3%)	42 (2.7%)	
Enterobacteriaceae and other GNB	1087 (59.9%)	338 (58.7%)	938 (59.6%)	
<i>Staphylococcus aureus</i>	242 (13.3%) ^b	87 (15.1%) ^b	212 (13.5%) ^b	
<i>Streptococcus pneumoniae</i>	35 (1.9%)	19 (3.3%)	26 (1.7%)	
Enterococci	61 (3.4%)	18 (3.1%)	52 (3.3%)	
Other streptococci	36 (2%)	7 (1.2%)	33 (2.1%)	

^a total number of bacterial isolates, n=1814 in 1523 first VAP episodes, n=576 in 491 first early VAP episodes, and n=1575 in 1313 first late VAP episodes

^b including 37 (2%), 14 (2.4%), and 34 (2.2%) methicillin-resistant *Staphylococcus aureus* for all first VAP, first early VAP, and first late VAP episodes, respectively

Table A.2. Factors associated with early ventilator-associated pneumonia (VAP) in mechanically ventilated adults with COVID-19

	Univariable HR [95%CI]	p-value	Multivariable HR [95%CI]	p-value
Age, <i>per 10 years</i>	0.98 [0.89-1.08]	0.68	0.95 [0.85-1.06]	0.34
Male sex	1.30 [0.98-1.71]	0.07	1.27 [0.94-1.72]	0.12
Active smoking	0.51 [0.24-1.08]	0.08	0.48 [0.22-1.05]	0.07
Body mass index ≥ 30 kg.m ²	0.95 [0.75-1.19]	0.65	0.94 [0.72-1.22]	0.63
Treated hypertension	1.09 [0.88-1.36]	0.42	1.06 [0.82-1.37]	0.66
Chronic heart failure	1.25 [0.72-2.19]	0.43	1.23 [0.67-2.25]	0.50
COPD	1.15 [0.737-1.79]	0.54	1.24 [0.77-2.00]	0.37
Diabetes	1.13 [0.89-1.44]	0.32	1.10 [0.85-1.44]	0.47
Chronic renal failure	1.18 [0.82-1.69]	0.37	1.09 [0.72-1.65]	0.37
Immunodeficiency	1.02 [0.71-1.46]	0.93	0.92 [0.60-1.41]	0.72
Concomitant bacterial pneumonia at admission	1.54 [1.07-2.22]	0.02	1.51 [1.03-2.22]	0.04
Non-respiratory SOFA score at intubation	1.01 [0.97-1.06]	0.59	1.01 [0.96-1.06]	0.66
PaO ₂ /FiO ₂ at intubation, <i>per 10 mmHg</i>	0.99 [0.97-1.00]	0.15	0.99 [0.97-1.00]	0.16
Leucopenia or hyperleucocytosis at intubation	1.10 [0.88-1.38]	0.40	1.06 [0.83-1.34]	0.66
Neuromuscular blockers ^a	0.97 [0.76-1.24]	0.79	0.90 [0.69-1.17]	0.43
Prone positioning ^a	1.13 [0.90-1.42]	0.30	1.13 [0.86-1.48]	0.37
Corticosteroids use ^b	1.41 [0.98-2.02]	0.06	1.35 [0.91-2.00]	0.14

^a at least during 48h hours following intubation and before VAP diagnosis

^b at least during 48h hours following intubation and before VAP diagnosis at a dose greater than or equal to 40 mg prednisone equivalent

HR: Hazard Ratio, 95%CI: 95% Confidence Interval

Table A.3. Factors associated with late ventilator-associated pneumonia (VAP) in mechanically ventilated adults with COVID-19

	Univariable HR [95%CI]	p-value	Multivariable HR [95%CI]	p-value
Age, per 10 years	0.99 [0.94-1.04]	0.73	0.97 [0.92-1.03]	0.37
Male sex	1.22 [1.06-1.40]	<0.01	1.21 [1.03-1.44]	0.02
Active smoking	0.96 [0.72-1.27]	0.77	0.95 [0.67-1.34]	0.75
Body mass index ≥ 30 kg.m ²	1.07 [0.95-1.19]	0.27	1.09 [0.95-1.26]	0.22
Treated hypertension	1.04 [0.93-1.16]	0.45	0.95 [0.82-1.09]	0.46
Chronic heart failure	1.04 [0.76-1.41]	0.82	1.05 [0.74-1.51]	0.77
COPD	1.12 [0.89-1.41]	0.334	1.06 [0.81-1.39]	0.68
Diabetes	1.15 [1.02-1.30]	0.03	0.99 [0.85-1.15]	0.85
Chronic renal failure	1.20 [0.99-1.45]	0.06	1.19 [0.94-1.52]	0.16
Immunodeficiency	1.20 [1.01-1.44]	0.04	1.14 [0.92-1.42]	0.25
Concomitant bacterial pneumonia at admission	1.51 [1.25-1.82]	<0.001	1.11 [0.89-1.38]	0.36
Previous episode of early VAP	3.46 [3.02-3.96]	<0.001	3.11 [2.64-3.67]	<0.001
Non-respiratory SOFA score at intubation	1.03 [1.00-1.05]	0.03	1.02 [0.99-1.05]	0.18
PaO ₂ /FiO ₂ at intubation, per 10 mmHg	0.99 [0.98-1.00]	<0.01	0.99 [0.98-0.99]	0.002
Leucopenia or hyperleucocytosis at intubation	1.10 [0.98-1.24]	0.09	1.04 [0.91-1.19]	0.56
Neuromuscular blockers ^a	0.91 [0.80-1.03]	0.15	0.84 [0.72-0.97]	0.02
Prone positioning ^a	1.17 [1.04-1.31]	<0.01	1.02 [0.88-1.18]	0.78
Corticosteroids use ^b	1.28 [1.13-1.46]	<0.001	1.17 [0.99-1.38]	0.06

^a at least during 48h hours following intubation and before VAP diagnosis

^b at least during 48h hours following intubation and before VAP diagnosis at a dose greater than or equal to 40 mg prednisone equivalent

HR: Hazard Ratio, 95%CI: 95% Confidence Interval

Table A.4. Factors associated with *Pseudomonas*-related ventilator-associated pneumonia (VAP) in mechanically ventilated adults with COVID-19

	Univariable HR [95%CI]	p-value	Multivariable HR [95%CI]	p-value
Age, per 10 years	1.00 [0.93-1.07]	0.97	1.00 [0.92-1.09]	0.97
Male sex	1.35 [1.10-1.66]	<0.01	1.19 [0.93-1.52]	0.18
Active smoking	0.88 [0.59-1.33]	0.55	0.83 [0.50-1.39]	0.49
Body mass index ≥ 30 kg.m ²	0.94 [0.80-1.11]	0.48	0.96 [0.78-1.18]	0.67
Treated hypertension	1.06 [0.90-1.24]	0.48	0.96 [0.78-1.18]	0.70
Chronic heart failure	1.26 [0.84-1.90]	0.27	1.37 [0.84-2.26]	0.21
COPD	1.10 [0.79-1.53]	0.57	1.14 [0.77-1.70]	0.52
Diabetes	1.16 [0.97-1.38]	0.10	0.99 [0.80-1.24]	0.96
Chronic renal failure	1.38 [1.07-1.78]	0.01	1.34 [0.97-1.85]	0.07
Immunodeficiency	1.11 [0.85-1.44]	0.46	1.03 [0.75-1.43]	0.84
Concomitant bacterial pneumonia at admission	1.52 [1.15-2.00]	<0.01	1.25 [0.92-1.71]	0.15
Previous episode of non- <i>Pseudomonas</i> VAP	6.23 [5.20-7.46]	<0.001	5.87 [4.74-7.27]	<0.001
Systemic antibiotic therapy ^a	1.97 [1.46-2.68]	<0.001	1.21 [0.82-1.77]	0.34
Non-respiratory SOFA score at intubation	1.02 [0.98-1.05]	0.34	1.00 [0.97-1.01]	0.92
PaO ₂ /FiO ₂ at intubation, per 10 mmHg	0.99 [0.98-1.01]	0.25	1.00 [0.99-1.01]	0.84
Leucopenia or hyperleucocytosis at intubation	1.28 [1.08-1.50]	<0.01	1.12 [0.92-1.35]	0.25
Neuromuscular blockers ^a	0.93 [0.78-1.11]	0.43	0.86 [0.69-1.06]	0.16
Prone positioning ^a	1.28 [1.08-1.50]	<0.01	1.25 [1.02-1.53]	0.03
Corticosteroids use ^b	1.33 [1.10-1.60]	<0.01	1.23 [0.98-1.55]	0.08

^a at least during 48h hours following intubation and before VAP diagnosis

^b at least during 48h hours following intubation and before VAP diagnosis at a dose greater than or equal to 40 mg prednisone equivalent

HR: Hazard Ratio, 95%CI: 95% Confidence Interval

Table A.5. Factors associated with 90-day mortality in mechanically ventilated adults with COVID-19, including early and late VAP.

	Univariable HR [95%CI]	p-value	Multivariable HR [95%CI]	p-value
<i>Age, per 10 years</i>	1.49 [1.40-1.58]	<0.001	1.50 [1.39-1.61]	<0.001
Body mass index >30 kg.m²	0.82 [0.72-0.94]	0.004	0.95 [0.80-1.11]	0.51
Diabetes	1.50 [1.32-1.70]	<0.001	1.30 [1.11-1.52]	0.001
Immunodeficiency	1.74 [1.47-2.06]	<0.001	1.65 [1.34-2.04]	<0.001
Time between first symptoms and ICU admission, per day	0.96 [0.95-0.87]	<0.001	0.96 [0.94-0.97]	<0.001
Non-respiratory SOFA score at intubation, per one point	1.10 [1.07-1.13]	<0.001	1.09 [1.06-1.12]	<0.001
PaO₂/FiO₂ at intubation, per 10 mmHg	0.99 [0.98-0.998]	0.02	0.98 [0.97-0.99]	0.002
Early VAP	1.11 [0.95-1.29]	0.178	1.10 [0.91-1.32]	0.34
Late VAP	1.62 [1.40-1.88]	<0.001	1.51 [1.26-1.81]	<0.001

HR: Hazard Ratio, 95%CI: 95% Confidence Interval

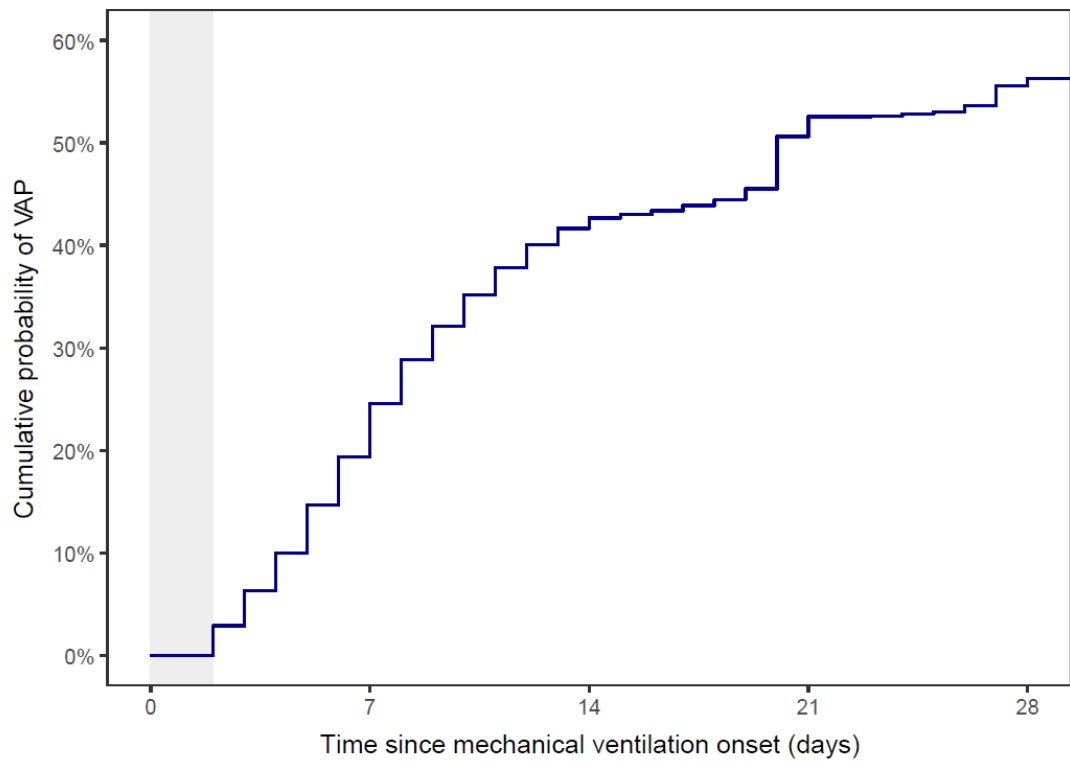
Table A.6A. Factors associated with 90-day mortality in mechanically ventilated adults with COVID-19, including *Pseudomonas*-related VAP.

	Univariable HR [95%CI]	<i>p</i> -value	Multivariable HR [95%CI]	<i>p</i> -value
Age, per 10 years	1.49 [1.40-1.58]	<0.001	1.47 [1.37-1.57]	<0.001
Body mass index >30 kg.m ²	0.82 [0.72-0.94]	0.004	0.97 [0.84-1.12]	0.65
Diabetes	1.50 [1.32-1.70]	<0.001	1.34 [1.17-1.53]	<0.001
Immunodeficiency	1.74 [1.47-2.06]	<0.001	1.61 [1.34-1.93]	<0.001
Time between first symptoms and ICU admission, per day	0.96 [0.95-0.87]	<0.001	0.97 [0.95-0.98]	<0.001
Non-respiratory SOFA score at intubation, per one point	1.10 [1.07-1.13]	<0.001	1.09 [1.06-1.12]	<0.001
PaO ₂ /FiO ₂ at intubation, per 10 mmHg	0.99 [0.98-0.998]	0.02	0.98 [0.98-0.99]	0.002
<i>Pseudomonas</i> -related VAP	1.23 [1.05-1.45]	0.01	1.18 [0.99-1.40]	0.06

Table A.6B. Factors associated with 90-day mortality in mechanically ventilated adults with COVID-19, including non-*Pseudomonas*-related VAP.

	Univariable HR [95%CI]	<i>p</i> -value	Multivariable HR [95%CI]	<i>p</i> -value
Age, per 10 years	1.49 [1.40-1.58]	<0.001	1.47 [1.37-1.57]	<0.001
Body mass index >30 kg.m ²	0.82 [0.72-0.94]	0.004	0.96 [0.82-1.11]	0.56
Diabetes	1.50 [1.32-1.70]	<0.001	1.34 [1.17-1.53]	<0.001
Immunodeficiency	1.74 [1.47-2.06]	<0.001	1.60 [1.33-1.92]	<0.001
Time between first symptoms and ICU admission, per day	0.96 [0.95-0.87]	<0.001	0.96 [0.95-0.98]	<0.001
Non-respiratory SOFA score at intubation, per one point	1.10 [1.07-1.13]	<0.001	1.09 [1.06-1.12]	<0.001
PaO ₂ /FiO ₂ at intubation, per 10 mmHg	0.99 [0.98-0.998]	0.02	0.98 [0.98-0.99]	0.003
Non- <i>Pseudomonas</i> -related VAP	1.22 [1.06-1.39]	<0.01	1.18 [1.02-1.37]	0.03

HR: Hazard Ratio, 95%CI: 95% Confidence Interval



N. at risk	3388	2049	938	451	244
N. VAP	0	804	1303	1479	1523

