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Evolución, manejo clínico y morbimortalidad de los pacientes con neumonía grave por virus pandémicos ingresados en la UCI

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Programa de Doctorado en Medicina
Departamento de Medicina

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Elisabeth Papiol Gallofré

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TESIS DOCTORAL

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Listado de abreviaturas

AB: Antibióticos

AKI: Acute Kidney Injury (Lesión renal aguda)

APACHE II: Acute Physiology and Chronic Health Evaluation II (Evaluación de la Fisiología Aguda y de la Salud Crónica II)

ARDS: Acute Respiratory Distress Syndrome (Síndrome de distrés respiratorio agudo)

BAL: Bronchoalveolar Lavage (Lavado broncoalveolar)

CDC: Centers for Disease Control and Prevention

CFU: Colony Forming Unit (Unidad formadora de colonias)

CLRT: Continuous Renal Replacement Therapy (Terapia renal sustitutiva continua)

COPD: Chronic Obstructive Pulmonary Disease (Enfermedad pulmonar obstructiva crónica)

COVID-19: Coronavirus Disease 2019

CPAP: Continuous Positive Airway Pressure (Presión positiva continua en la vía aérea)

CPK: Creatine Phosphokinase (Creatinfosfoquinasa)

CRP: C-Reactive Protein (Proteína C reactiva)

CT: Computed Tomography (Tomografía computarizada)

DD: Dímero D

EAT: Empirical Antibiotic Treatment (Tratamiento antibiótico empírico)

ELISA: Enzyme-Linked Immunosorbent Assay (Ensayo por inmunoabsorción ligado a enzimas)

EPOC: Enfermedad Pulmonar Obstructiva Crónica (COPD)

ERS: European Respiratory Society (Sociedad Europea de Respiratorio)

ESCMID: European Society of Clinical Microbiology and Infectious Diseases (Sociedad Europea de Microbiología Clínica y Enfermedades Infecciosas)

ESICM: European Society of Intensive Care Medicine (Sociedad Europea de Medicina Intensiva)

FiO_2: Fraction of Inspired Oxygen (Fracción inspiratoria de oxígeno)

FR: Factores de Riesgo

GAP_diagnosis_cut: Intervalo entre inicio de síntomas y diagnóstico

GAP_ICU_cut: Intervalo entre diagnóstico de infección por virus pandémico e ingreso en UCI

GLM: Generalized Linear Model (Regresión logística)

ICU: Intensive Care Unit (Unidad de Cuidados Intensivos)

IEAT: Inappropriate Empirical Antibiotic Treatment (Tratamiento Antibiótico Empírico Inadecuado)

IL-6: Interleukin-6

LDH: Lactate Dehydrogenase (Lactato deshidrogenasa)

ML: Machine Learning (Aprendizaje automático)

MDR: Multidrug-Resistant (Multirresistente)

MRSA: Methicillin-Resistant *Staphylococcus aureus (Staphylococcus aureus* resistente a meticilina)

MSSA: Methicillin-Sensitive *Staphylococcus aureus* (*Staphylococcus aureus* sensible a meticilina)

MV: Invasive Mechanical Ventilation (Ventilación mecánica invasiva)

NAVM: Neumonía asociada a ventilación mecánica

O_2: Oxígeno

OOB: Out-of-Bag (Error de bolsa de exclusión)

PCR: Polymerase Chain Reaction (Reacción en cadena de la polimerasa)

PCT: Procalcitonina

PROA: Programas de Optimización de Uso de Antibióticos

RF: Random Forest

ROC: Receiver Operating Characteristic

RT-PCR: Reverse Transcription Polymerase Chain Reaction

Rx-cutoff: Infiltrados en más de dos campos pulmonares en la radiografía de tórax

SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2 (Coronavirus del Síndrome Respiratorio Agudo Grave 2)

SDRA: Síndrome de Distrés Respiratorio Agudo

SEMICYUC: Sociedad Española de Medicina Intensiva, Crítica y Unidades Coronarias

SOFA: Sequential Organ Failure Assessment (Evaluación Secuencial de la Disfunción Orgánica)

TAVM: Traqueobronquitis asociada a ventilación mecánica

UCI: Unidad de Cuidados Intensivos

VAP: Ventilator-Associated Pneumonia (Neumonía asociada a ventilación)

WBC: White Blood Cells (Recuento de leucocitos)

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RESUMEN

Las pandemias virales representan uno de los mayores desafíos contemporáneos para la medicina intensiva, al provocar un aumento súbito de pacientes con neumonías graves que tensiona las UCI y exige respuestas clínicas rápidas en contextos de elevada incertidumbre. Esta presión asistencial y la variabilidad en la respuesta de los pacientes evidencian la necesidad de mejorar el abordaje inicial, optimizando tanto el diagnóstico como el tratamiento empírico desde el ingreso. La presente tesis tiene como objetivo profundizar en ese abordaje inicial mediante la identificación de factores de riesgo clínicos, microbiológicos y fisiopatológicos que condicionan la evolución, así como en la evaluación del impacto de las decisiones terapéuticas adoptadas en las primeras 24 horas. Al integrar datos de pacientes críticos con influenza A(H1N1)pdm09 y SARS-CoV-2, este trabajo se alinea con los principios de la medicina de precisión, y persigue ofrecer herramientas para estratificar el riesgo desde el primer momento, identificar precozmente a los pacientes con peor pronóstico, adecuar las intervenciones a las características individuales y formular estrategias dinámicas que mejoren los resultados clínicos y faciliten la toma de decisiones durante futuras emergencias sanitarias.

ABSTRACT

Viral pandemics represent one of the greatest contemporary challenges for critical care medicine, as they lead to a sudden surge of patients with severe pneumonia that overwhelms ICUs and demands rapid clinical responses under conditions of high uncertainty. This healthcare pressure and the variability in patients' responses highlight the need to improve the initial management by optimizing both diagnostic processes and empirical treatments from the moment of admission. The present thesis aims to enhance this early approach by identifying clinical, microbiological, and pathophysiological risk factors that influence patient outcomes, and by evaluating the impact of key therapeutic decisions made within the first 24 hours. By integrating data from critically ill patients with influenza A(H1N1)pdm09 and SARS-CoV-2, this work aligns with the principles of precision medicine and seeks to provide tools for early risk stratification, timely identification of patients with worse prognosis, personalized interventions tailored to individual characteristics, and the development of dynamic strategies to improve clinical outcomes and support decision-making in future public health emergencies.

1. Introducción

1.1 Generalidades

Desde el Neolítico, el ser humano ha convivido con epidemias que, en muchas ocasiones, han definido el rumbo de su historia. La sedentarización, el desarrollo de la agricultura y la domesticación animal incrementaron la densidad poblacional y facilitaron el contacto entre humanos y animales, propiciando la aparición de brotes epidémicos locales que, con el tiempo, evolucionaron hasta convertirse en fenómenos interregionales y globales (1). Pandemias como la peste negra en el siglo XIV, la viruela tras la llegada a América o las sucesivas oleadas gripales de los siglos XIX y XX ilustran no solo pérdidas demográficas masivas, sino también profundas transformaciones sociales, políticas y culturales. La Tabla 1 recoge las pandemias más relevantes de la historia documentada (2,3).

Tabla 1. Principales pandemias en la historia de la humanidad

Nombre de la Pandemia	Microorganismo Responsable	Período Histórico	Lugar de Origen	Mortalidad Estimada (número de personas fallecidas)
Peste de Atenas	Probable fiebre tifoidea o ébola	430 a.C.	Atenas, Grecia	~100,000
Plaga de Justiniano	Yersinia pestis	541-542 d.C.	Imperio Bizantino	~25-50 millones
Peste Negra	Yersinia pestis	1347-1351	Asia Central	~75-200 millones
Viruela en América	Variola virus	Siglo XVI	América	~50-100 millones
Gripe Española	Influenza A (H1N1)	1918-1919	Estados Unidos	~50 millones
Poliomielitis (brotes epidémicos)	*Poliovirus*	1940-1960	Europa/Estados Unidos	~3000/año (EEUU antes de la vacuna))
Gripe Asiática	Influenza A (H2N2)	1957-1958	China	~1-2 millones
Gripe de Hong Kong	Influenza A (H3N2)	1968-1969	Hong Kong	~1 millón
VIH/SIDA	Virus de la inmunodeficiencia humana	Desde 1981	África Central	~36 millones
Gripe A (H1N1)pdm09	Influenza A (H1N1)pdm09	2009-2010	México	~200,000
COVID-19	SARS-CoV-2	Desde 2019	Wuhan, China	>7 millones (OMS 2023)

La medicina moderna no dispuso de herramientas eficaces para afrontar estas crisis hasta el siglo XIX, cuando los descubrimientos de Pasteur y Koch y el nacimiento de la microbiología permitieron comprender los mecanismos de transmisión y los agentes

etiológicos. En el siglo XX, la introducción de vacunas, antibióticos y sistemas de salud pública supuso un punto de inflexión, reduciendo drásticamente la mortalidad de muchas enfermedades infecciosas. Sin embargo, fenómenos contemporáneos como la globalización, el cambio climático y la presión humana sobre ecosistemas naturales han favorecido la aparición de nuevos patógenos con capacidad de transmisión eficiente entre humanos (1,2).

En las últimas décadas, los virus respiratorios han ganado protagonismo como agentes emergentes. Epidemias previas por SARS-CoV-1 en 2003, MERS-CoV en 2012 y distintos subtipos de influenza aviar (H5N1, H7N9) pusieron de manifiesto la facilidad con la que los virus zoonóticos pueden adaptarse al ser humano y propagarse rápidamente (3–8). Entre ellos, dos pandemias recientes han tenido un impacto global extraordinario: la gripe A(H1N1)pdm09 de 2009 y la COVID-19 causada por el SARS-CoV-2, emergida a finales de 2019 (3–8).

Aunque ambos virus difieren en su estructura genética, mecanismos de transmisión y comportamiento epidemiológico, comparten rasgos clínicos fundamentales: transmisión por vía respiratoria (incluyendo gotas y aerosoles), potencial para inducir neumonía viral grave y SDRA, y una elevada tasa de ingreso en unidades de cuidados intensivos. Estas unidades se convirtieron no solo en escenarios de asistencia intensiva, sino también en focos de generación de conocimiento clínico durante ambas crisis sanitarias (9,10).

1.2. Infección por virus de la gripe A(H1N1)pdm09

1.2.1. Fisiopatología

El virus influenza A(H1N1)pdm09 es un ortomixovirus con genoma de ARN segmentado en ocho fragmentos, que codifican proteínas estructurales (hemaglutinina [HA], neuraminidasa [NA], M1/M2, nucleoproteína [NP]) y no estructurales (NS1, NS2). La HA permite la unión del virus a los residuos de ácido siálico en la superficie del epitelio respiratorio, facilitando la endocitosis. Tras la liberación del genoma viral en el núcleo, se inician los procesos de transcripción y replicación. La NA favorece la diseminación del virus al escindir los enlaces del ácido siálico y evitar la agregación de los nuevos viriones (2,9,10).

Este ciclo viral causa daño directo al epitelio respiratorio y desencadena una intensa respuesta inmunitaria innata. Las células presentadoras de antígeno, como los macrófagos y las células dendríticas, secretan interferones tipo I, TNF-α, IL-6 e IL-1β, atrayendo neutrófilos y linfocitos T $CD8^+$ al lugar de la infección. Si esta respuesta se desregula, puede provocar daño alveolar difuso, caracterizado histológicamente por exudados fibrinosos, formación de membranas hialinas y edema intersticial, configurando el cuadro clínico-patológico del síndrome de distrés respiratorio agudo (SDRA) (2,10).

1.2.2. Clínica, neumonía y SDRA

La infección suele iniciarse tras 1–3 días de incubación con fiebre alta, tos seca, odinofagia, cefalea, mialgias y malestar general. En algunos pacientes, especialmente aquellos con comorbilidades como obesidad, EPOC o cardiopatía, la infección progresa rápidamente a una neumonía viral primaria, con disnea progresiva, taquipnea e hipoxemia refractaria al oxígeno suplementario (2,9,10).

La radiografía y la tomografía computarizada (TC) de tórax suelen mostrar infiltrados pulmonares bilaterales, parcheados o difusos. El diagnóstico de SDRA se establece según los criterios de Berlín, que requieren una $PaO_2/FiO_2 \leq 300$ mmHg con PEEP ≥ 5 cmH_2O, presencia de infiltrados pulmonares bilaterales y ausencia de causa cardiogénica (11). Este cuadro aparece precozmente y se asocia a daño alveolar difuso, disminución de la

distensibilidad pulmonar, elevada mortalidad y necesidad frecuente de ventilación mecánica invasiva (12).

La aspergilosis pulmonar invasiva asociada a gripe (IAPA) es una complicación emergente en pacientes con neumonía grave causada por el virus influenza A(H1N1)pdm09 ingresados en UCI, incluso en ausencia de inmunosupresión clásica. Su incidencia se estima entre el 14 % y el 19 % en pacientes sometidos a ventilación mecánica, y suele manifestarse precozmente, durante los primeros 2–3 días tras la intubación. Se asocia a una mortalidad elevada, superior al 50 %. El diagnóstico requiere la combinación de hallazgos clínico-radiológicos y microbiológicos, que incluyen el cultivo de *Aspergillus* spp., la detección de galactomanano en suero o en lavado broncoalveolar (LBA) y la PCR fúngica. La positividad del galactomanano en suero es frecuente, lo que permite un diagnóstico más temprano y favorece el inicio precoz del tratamiento antifúngico en pacientes de alto riesgo (13).

1.2.3. Tratamiento

El tratamiento de la gripe A(H1N1)pdm09 grave se basa en tres pilares: soporte de órganos, terapia antiviral específica y tratamiento de la coinfección bacteriana.

El soporte respiratorio se adapta a la gravedad del cuadro. En pacientes con hipoxemia moderada, puede iniciarse oxigenoterapia de alto flujo o ventilación no invasiva. Si la hipoxemia se agrava o el trabajo respiratorio aumenta, se indica ventilación mecánica invasiva con estrategia de protección pulmonar (volumen corriente de 4–8 mL/kg de peso ideal, presión meseta $\leq$ 30 cmH_2O y PEEP individualizada), relajación neuromuscular y pronación en caso de $PaO_2/FiO_2 \leq 150$ mmHg. En situaciones de hipoxemia refractaria, puede considerarse el uso de ECMO en centros especializados (11). El resto del soporte orgánico (hemodinámico, renal, metabólico) debe individualizarse según la evolución clínica (14).

La terapia antiviral recomendada para los pacientes con neumonía grave es la administración de inhibidores de la neuraminidasa, siendo el oseltamivir (75 mg cada 12 horas durante 5 días) el fármaco de elección. Aunque su eficacia es mayor si se inicia en

las primeras 48 horas desde el comienzo de los síntomas, en pacientes críticos se recomienda su uso incluso más allá de ese periodo (12,15,16). En caso de sospecha de coinfección bacteriana, basada en la clínica, los hallazgos radiológicos o los biomarcadores inflamatorios, se debe iniciar una antibioterapia empírica ajustada a las guías locales y a la epidemiología del centro. Posteriormente, el tratamiento debe optimizarse conforme a la evolución clínica, los niveles de procalcitonina y los resultados microbiológicos, idealmente en el marco de un programa de optimización del uso de antimicrobianos (PROA) (17,18).

1.2.4. Prevención

La medida más eficaz para prevenir la gripe A(H1N1)pdm09 es la vacunación estacional, con una efectividad promedio del 60–70 % en la reducción de casos, hospitalizaciones y muertes (12,19). Tras la pandemia de 2009, la cepa A(H1N1)pdm09 se incorporó de forma permanente en las vacunas trivalentes y tetravalentes. Estas vacunas están especialmente recomendadas en grupos de riesgo, como las personas mayores de 65 años, los pacientes con enfermedades crónicas, las mujeres embarazadas y el personal sanitario (20). De forma complementaria, las medidas no farmacológicas como la higiene de manos, el uso de mascarillas y la ventilación de espacios cerrados, han demostrado ser eficaces para reducir la transmisión del virus y prevenir brotes, especialmente en entornos vulnerables o durante períodos de alta circulación viral (12).

1.3. Infección por SARS-CoV-2

1.3.1. Fisiopatología

El SARS-CoV-2 es un betacoronavirus de ARN monocatenario positivo de aproximadamente 30 kb que codifica cuatro proteínas estructurales (Spike, Envelope, Membrana y Nucleocápside) y varias proteínas no estructurales. La entrada viral se produce cuando la glicoproteína Spike (S) se une al receptor ACE2, ampliamente expresado en el epitelio alveolar, las células endoteliales, los miocitos cardíacos, las nefronas y los enterocitos. La activación de la proteasa celular TMPRSS2 facilita la

escisión de la proteína S, permitiendo la fusión de la membrana viral con la célula huésped y la liberación del genoma viral en el citosol.

Una vez dentro de la célula, el virus se replica y desencadena una respuesta inmunitaria bifásica. En la primera fase, la replicación viral directa induce citopatía y estimula la inmunidad innata, con liberación de interferones tipo I, TNF-α, IL-6 e IL-1β por parte de macrófagos y células dendríticas. Esta señalización promueve la activación y el reclutamiento de neutrófilos y linfocitos T $CD8^+$.

En los casos graves, esta respuesta inmunitaria se desregula, dando lugar a una segunda fase caracterizada por una hiperinflamación sistémica o "tormenta de citoquinas". Esta se manifiesta por concentraciones elevadas de IL-6, TNF-α, IL-1β, ferritina y dímero D, entre otros marcadores. El proceso inflamatorio favorece el daño endotelial, el estado protrombótico y la lesión alveolar difusa, con formación de membranas hialinas y edema intersticial, lo que puede desembocar en un síndrome de distrés respiratorio agudo (SDRA) y disfunción multiorgánica (1,5,21).

1.3.2. Clínica, neumonía y SDRA

La COVID-19 suele comenzar tras un periodo de incubación de 2 a 7 días con síntomas inespecíficos como fiebre, tos seca, astenia, mialgias, cefalea y, en algunos casos, anosmia o ageusia. En un subgrupo de pacientes, particularmente varones de edad avanzada o con comorbilidades como obesidad, EPOC o enfermedad cardiovascular, la infección progresa rápidamente a una neumonía viral primaria, caracterizada por disnea progresiva, taquipnea e hipoxemia persistente a pesar del oxígeno suplementario (6,9,22,23).

Las pruebas de imagen, como la radiografía o la tomografía computarizada (TC) de tórax, muestran opacidades en vidrio deslustrado bilaterales, difusas o parcheadas. El diagnóstico de SDRA se establece según los criterios de Berlín, que requieren una $PaO_2/FiO_2 \leq 300$ mmHg con PEEP ≥ 5 cmH_2O, presencia de infiltrados pulmonares bilaterales y ausencia de causa cardiogénica (11).

El SDRA suele aparecer entre los días 7 y 10 de evolución clínica. A diferencia del

SDRA clásico, algunos pacientes presentan un fenotipo atípico (fenotipo L), con hipoxemia severa y buena compliancia pulmonar, lo que ha motivado el desarrollo de estrategias ventilatorias adaptadas. En fases avanzadas, predomina el fenotipo H, caracterizado por baja distensibilidad, consolidaciones extensas y elevada mortalidad, que requiere frecuentemente ventilación mecánica invasiva (11,24).

La aspergilosis pulmonar invasiva asociada a COVID-19 (CAPA) es una complicación emergente en pacientes con neumonía grave por SARS-CoV-2 ingresados en UCI, especialmente en aquellos que requieren ventilación mecánica prolongada o tratamiento immunomodulador. Su incidencia oscila entre el 5 % y el 15 %, pudiendo alcanzar hasta el 30 % en cohortes con cribado sistemático. La CAPA suele desarrollarse entre los días 7 y 10 tras la intubación y se asocia a una mortalidad elevada, estimada entre el 45 % y el 70 %. El diagnóstico es complejo debido a la baja sensibilidad del galactomanano sérico, lo que obliga a integrar los hallazgos clínicos y radiológicos con el cultivo, el galactomanano o la PCR en lavado broncoalveolar. La sospecha precoz de CAPA es esencial ante un empeoramiento clínico no explicado o la aparición de nuevos infiltrados pulmonares durante la evolución del SDRA, ya que su identificación temprana permite iniciar un tratamiento antifúngico adecuado y mejorar el pronóstico (13).

1.3.3. Tratamiento

El abordaje terapéutico de la COVID-19 ha evolucionado significativamente desde el inicio de la pandemia. Durante la fase viral, el antiviral remdesivir ha demostrado un beneficio modesto al reducir el tiempo de recuperación en pacientes que requieren oxigenoterapia, pero no ventilación mecánica invasiva.

En la fase inflamatoria, la dexametasona a dosis bajas (6 mg diarios durante 10 días) ha evidenciado una reducción significativa de la mortalidad en pacientes con necesidad de oxígeno suplementario o ventilación mecánica (25), según el estudio RECOVERY (26). Asimismo, immunomoduladores como tocilizumab (anticuerpo anti-IL-6R) y baricitinib (inhibidor de JAK1/2) han mostrado beneficios en pacientes con inflamación sistémica persistente y deterioro respiratorio progresivo (23).
El soporte ventilatorio debe adaptarse al fenotipo clínico del SDRA, empleando

estrategias de ventilación protectora, sesiones prolongadas de decúbito prono y, en casos de hipoxemia refractaria, oxigenación por membrana extracorpórea (ECMO) en centros especializados (11,14). El uso de antibióticos debe reservarse exclusivamente para pacientes con sospecha clínica o confirmación microbiológica de coinfección bacteriana, de acuerdo con las recomendaciones de los programas de optimización del uso de antimicrobianos (PROA) (17,27).

1.3.4. Prevención

La vacunación frente al SARS-CoV-2 constituye la principal herramienta preventiva frente a la COVID-19. Las vacunas de ARNm y vector viral han demostrado una elevada eficacia para prevenir la enfermedad sintomática y, especialmente, para reducir el riesgo de formas graves y hospitalización, con tasas de efectividad que superan el 90 % tras la pauta completa en los estudios iniciales.

La vacunación está especialmente indicada en personas mayores de 60 años, pacientes con comorbilidades (enfermedades cardiovasculares, respiratorias, obesidad, diabetes, inmunodepresión) y profesionales sanitarios. De forma complementaria, las medidas no farmacológicas como el uso de mascarilla en espacios cerrados, el distanciamiento físico, la higiene de manos y la ventilación adecuada, han demostrado ser eficaces para reducir la transmisión viral en diferentes contextos epidemiológicos (23).

1.4. Factores de riesgo y mortalidad en la neumonía grave por virus pandémicos

La neumonía grave causada por virus pandémicos es una de las principales causas de ingreso en las Unidades de Cuidados Intensivos (UCI) durante los períodos epidémicos, generando una elevada morbimortalidad y una gran presión asistencial (4,28–30). En este contexto, la identificación precoz de los factores de riesgo asociados a una evolución desfavorable resulta fundamental para optimizar el manejo clínico, priorizar recursos y aplicar estrategias terapéuticas adecuadas desde las fases iniciales (31–33).

Sin embargo, los factores de riesgo descritos pueden variar según el agente viral, las características del paciente y el tipo de análisis utilizado. Esta heterogeneidad plantea dudas

sobre cuáles son los verdaderos determinantes de mortalidad (34–41). En los siguientes apartados se revisan los principales factores de riesgo identificados en pacientes críticos con infección por influenza A(H1N1) pdm09 o SARS-CoV-2, incluyendo los hallazgos más recientes obtenidos mediante técnicas de aprendizaje automático.

1.4.1 Gripe A(H1N1) pdm09

Durante la pandemia de gripe A(H1N1)pdm09 en 2009, la mayoría de los ingresos en UCI correspondieron a adultos jóvenes previamente sanos, en contraste con lo observado habitualmente en la gripe estacional. Los principales factores de riesgo descritos para una evolución desfavorable fueron el embarazo, la obesidad, la enfermedad respiratoria crónica (asma o EPOC), la diabetes, la inmunosupresión y las enfermedades cardiovasculares (26,32,42–45).

La mortalidad en UCI osciló entre el 25 % y el 40 %, siendo especialmente elevada en pacientes con síndrome de distrés respiratorio agudo (SDRA), coinfección bacteriana o disfunción multiorgánica. Diversos estudios han identificado la coinfección como un predictor independiente de mortalidad, lo que destaca la importancia de su diagnóstico precoz y de un tratamiento adecuado (29,43,46,47).

Aunque la mayoría de los estudios iniciales utilizaron modelos estadísticos clásicos, análisis posteriores aplicaron técnicas de aprendizaje automático, como árboles de decisión y Random Forest, para identificar factores de riesgo. Sin embargo, su rendimiento predictivo ha sido limitado y no han demostrado mejoras consistentes frente a la regresión logística. (29,39,40,47,48).

1.4.2 SARS-CoV-2 (COVID-19)

En el caso del SARS-CoV-2, los factores de riesgo asociados a una evolución clínica desfavorable han sido ampliamente caracterizados y se han mantenido relativamente consistentes a lo largo de las sucesivas olas pandémicas. Entre los principales destacan la edad avanzada, la obesidad, la hipertensión arterial, la diabetes mellitus, la enfermedad renal crónica, las enfermedades cardiovasculares, la inmunosupresión y el sexo masculino

(6,49). A nivel biológico, diversos biomarcadores inflamatorios y de daño tisular, como la linfopenia, el dímero D, la ferritina, la interleucina-6 (IL-6), la procalcitonina y la troponina, han demostrado una asociación independiente con una mayor probabilidad de complicaciones y mortalidad en pacientes con COVID-19 grave (38,49–51).

La mortalidad en UCI de estos pacientes ha oscilado entre el 30 % y el 45 %, siendo especialmente elevada en aquellos que desarrollan síndrome de distrés respiratorio agudo (SDRA), shock séptico o disfunción multiorgánica (35,52). A diferencia de lo observado en la pandemia por gripe A(H1N1)pdm09, donde la coinfección bacteriana se identificó como un factor pronóstico relevante, los estudios disponibles sobre COVID-19 no han demostrado una asociación consistente entre la presencia de coinfección o sobreinfección bacteriana y un aumento del riesgo de muerte. En los análisis multivariantes, estas variables no se han incluido como predictores independientes de mortalidad, lo que sugiere que podrían reflejar la gravedad clínica o complicaciones evolutivas más que actuar como determinantes causales directos (35,47).

La elevada heterogeneidad clínica observada en pacientes con COVID-19 grave ha impulsado el uso de herramientas analíticas más sofisticadas para mejorar la estratificación pronóstica. En este sentido, los modelos de aprendizaje automático (machine learning) han cobrado protagonismo al permitir la identificación de relaciones no lineales, interacciones complejas entre variables y patrones clínicos latentes que no emergen con los análisis tradicionales. Modelos como Random Forest, redes neuronales o SVM han mostrado rendimientos similares o superiores a la regresión logística multivariable, especialmente cuando se dispone de grandes volúmenes de datos clínicos, demográficos y analíticos recogidos al ingreso (33,36,39).

Un ejemplo destacado lo constituye un estudio multicéntrico español que aplicó técnicas de agrupamiento no supervisado para identificar fenotipos clínicos al ingreso en UCI (35). Los autores detectaron tres perfiles de pacientes con neumonía grave por COVID-19, cada uno con diferente riesgo de mortalidad, lo que respalda el valor añadido de los modelos no lineales en la identificación de subgrupos clínicos con distinto pronóstico. Este enfoque no

solo mejora la capacidad predictiva, sino que aporta una visión más personalizada del riesgo, ajustada a las características fisiopatológicas de cada paciente.

En este contexto, el presente trabajo se propone comparar los factores de riesgo de mortalidad identificados mediante un modelo estadístico tradicional (regresión logística) y un modelo de aprendizaje automático (Random Forest), utilizando una amplia cohorte nacional de pacientes críticos con infección por SARS-CoV-2 o gripe A(H1N1)pdm09. Este enfoque comparativo permite explorar si el tipo de modelo influye en los determinantes pronósticos detectados y si la combinación de ambos métodos puede contribuir a una estratificación del riesgo más precisa y clínicamente útil en escenarios de alta complejidad asistencial.

Tabla 2. Factores de riesgo de mortalidad en neumonía grave por Influenzavirus y SARS COV-2

Factor de riesgo	Gripe A (H1N1)pdm09	Gripe estacional	SARS-CoV-2 (COVID-19)	Comentario / relevancia clínica
Edad avanzada	Menor relevancia (<65 años)	↑ Alta relevancia (≥65 años)	↑ Alta relevancia (≥60–65 años)	Más determinante en gripe estacional y COVID-19
Sexo masculino	—	—	↑ OR ~1,3–1,5	Predominio claro en COVID-19
Embarazo / puerperio	↑ Riesgo significativo	Moderado (más complicaciones que mortalidad)	Evidencia limitada	Relevante sobre todo en H1N1
Obesidad (IMC ≥30)	↑ Asociación	↑ Asociación	↑ Asociación	Determinante mayor común
Diabetes mellitus	↑ Riesgo	↑ Riesgo	↑ Riesgo	Determinante mayor común
Hipertensión arterial	—	Variable según series	↑ Asociación independiente	Más relevante en COVID-19
Enf. respiratoria crónica (EPOC/asma)	↑ Riesgo	↑ Riesgo	Tendencia no consistente	Predominante en influenzas
Cardiopatía / IAM previo	↑ Riesgo	↑ Riesgo	↑ Riesgo	Determinante mayor común
Enfermedad renal crónica	Datos limitados	Datos limitados	↑ Asociación clara	Mayor relevancia en COVID-19
Insuficiencia renal aguda (AKI)	↑ Mortalidad asociada	↑ Mortalidad asociada	↑ Mortalidad asociada	Marcador de disfunción orgánica grave
Inmunosupresión	↑ Riesgo	↑ Riesgo	↑ Riesgo	Determinante mayor común

SDRA al ingreso	↑ Mortalidad asociada	↑ Mortalidad asociada	↑ Mortalidad asociada	Indicador de gravedad respiratoria
Shock séptico / fracaso multiorgánico	↑ Mortalidad asociada	↑ Mortalidad asociada	↑ Mortalidad asociada	Indicador de disfunción multiorgánica,

1.5. Coinfección bacteriana, tratamiento antibiótico y aparición de bacterias multirresistentes en neumonías por virus pandémicos

En pacientes críticos con neumonía grave causada por virus pandémicos, como la gripe A(H1N1)pdm09 y el SARS-CoV-2, uno de los principales desafíos clínicos consiste en diferenciar entre infección viral aislada y coinfección bacteriana (29,47). Esta distinción resulta fundamental, ya que condiciona decisiones clave sobre el inicio, la duración y la adecuación del tratamiento antibiótico empírico. El uso indiscriminado de antimicrobianos en pacientes sin infección bacteriana confirmada se asocia a un mayor riesgo de toxicidad, aparición de resistencias y desarrollo de bacterias multirresistentes (BMR) (14,53,54). En este contexto, los programas de optimización del uso de antimicrobianos (PROA) constituyen una herramienta esencial para racionalizar el uso antibiótico en unidades de cuidados intensivos (UCI) (17,55).

1.5.1. Características de la coinfección bacteriana en gripe y COVID-19

La coinfección bacteriana es más frecuente en la gripe A(H1N1)pdm09 que en la COVID-19 (29,47,56). En la gripe, su prevalencia al ingreso en UCI se sitúa entre el 16% y el 35%, y se asocia con una mayor gravedad clínica, necesidad de ventilación mecánica y mortalidad. Su fisiopatología incluye la destrucción del epitelio respiratorio, la disbiosis del microbioma y la colonización por patógenos típicos como *Streptococcus pneumoniae*, *Staphylococcus aureus* o *Haemophilus influenzae* (16,47,57,58).

En contraste, en pacientes con COVID-19 la coinfección bacteriana precoz es infrecuente (<5 %), aunque no exenta de impacto clínico (29,31,58,59). La estancia prolongada en UCI, la ventilación mecánica invasiva y el uso de corticoides o immunomoduladores favorecen infecciones bacterianas secundarias tardías, como la neumonía asociada a la ventilación mecánica (NAVM), la traqueobronquitis asociada (TAVM) y las bacteriemias

(57,58). Estas infecciones se caracterizan por una alta prevalencia de BMR como *Klebsiella pneumoniae* productora de carbapenemasa, *Pseudomonas aeruginosa* y *Acinetobacter baumannii* (56,58,60–62).

Tabla 3. Coinfección bacteriana en neumonía grave por Influenzavirus y SARS COV-2

Aspecto	Gripe A(H1N1) / Estacional	SARS-CoV-2 (COVID-19)	Implicación clínica
Prevalencia de coinfección al ingreso (≤48 h)	16–35%	3–20%	En gripe es más frecuente; en COVID la mayoría reciben antibiótico empírico sin confirmación.
Momento habitual de aparición	Coinfección temprana, concomitante a la neumonía viral	Coinfección temprana infrecuente; predominan infecciones secundarias tardías (NAVM, bacteriemias) tras ≥7 días en UCI	En gripe requiere vigilancia microbiológica precoz; en COVID, foco en prevención de NAVM.
Patógenos comunitarios frecuentes	Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae	Mismos patógenos clásicos, pero muy baja prevalencia (≤5%)	En gripe debe sospecharse coinfección bacteriana clásica; en COVID es menos probable.
Patógenos nosocomiales / MDR	Gramnegativos hospitalarios ocasionales	Alta carga de MDR: Klebsiella pneumoniae KPC, Acinetobacter baumannii, Pseudomonas aeruginosa; MDR en UCI ≈27%	Fundamental implantar PROA y medidas de aislamiento de contacto en COVID-19.
Biomarcadores al ingreso	PCT >0,29 ng/mL sugiere coinfección; PCT <0,25 ng/mL tiene VPN ≈92% para descartarla	PCT y CRP con AUC baja (0,57–0,60), pero valores bajos mantienen VPN >97%; combinación CRP ≥97 mg/L + PCT ≥0,12 ng/mL aumenta probabilidad	En gripe ayudan a decidir inicio/retirada de antibiótico; en COVID orientan sobre todo la desescalada.
Antibiótico empírico al ingreso	Recomendado (β-lactámico + macrólido) por alta prevalencia de coinfección	Muy extendido (~70–75% reciben antibiótico pese a <5% de coinfección)	En gripe se justifica su uso precoz; en COVID conviene confirmación microbiológica antes de mantenerlo.
Impacto en mortalidad	Coinfección incrementa riesgo (HR ≈2–3)	No es predictor independiente tras ajustar por gravedad	En gripe respalda inicio precoz de tratamiento; en COVID su beneficio es dudoso.
Diagnóstico rápido (PCR multiplex, panel respiratorio)	Útil pero con menor penetración	Ampliamente adoptado; facilita suspensión de antibióticos si negativo	Herramienta clave para optimizar el tratamiento y reducir resistencias.

NAVM: neumonía asociada a ventilación mecánica; MDR: patógenos multirresistentes; BMR: bacterias multirresistentes; PROA: Programas de Optimización del Uso de Antimicrobianos; PCT: procalcitonina; CRP: proteína C reactiva; VPN: valor predictivo negativo.

1.5.2. Técnicas microbiológicas rápidas

El diagnóstico etiológico de la coinfección bacteriana se basa clásicamente en cultivos de muestras respiratorias y hemocultivos. Sin embargo, estas técnicas presentan importantes limitaciones, como la baja sensibilidad, el retraso en la obtención de resultados y la dificultad de interpretación en pacientes colonizados o en tratamiento antibiótico previo.

La incorporación de técnicas de biología molecular, como los paneles multiplex de PCR, ha revolucionado el diagnóstico microbiológico rápido (63). Estas pruebas permiten la detección simultánea de múltiples patógenos virales y bacterianos, así como de genes de resistencia, a partir de una única muestra clínica y en pocas horas. Su uso ha demostrado un alto rendimiento diagnóstico y facilita decisiones clínicas más seguras respecto al inicio, la desescalada o la suspensión del tratamiento antibiótico. Aunque su implantación ha sido más frecuente durante la pandemia de COVID-19, también han mostrado utilidad en el contexto de la gripe (12,14,23,64,65).

1.5.3. Uso de biomarcadores: procalcitonina (PCT) y proteína C reactiva (PCR)

Los biomarcadores inflamatorios como la procalcitonina (PCT) y la proteína C reactiva (PCR) constituyen herramientas valiosas para diferenciar infección viral aislada de coinfección bacteriana. La PCT se eleva en respuesta a infecciones bacterianas, pero suele permanecer baja en infecciones víricas. En gripe, valores <0,25 ng/mL presentan alto valor predictivo negativo; en COVID-19, aunque su rendimiento es menor, sigue siendo útil para apoyar decisiones de suspensión antibiótica en pacientes con baja sospecha clínica (18,66–68).

La PCR, aunque menos específica, también se eleva en infecciones bacterianas, y su interpretación combinada con la PCT, los hallazgos clínicos y los resultados microbiológicos aumenta la capacidad de discriminación. Además, la monitorización seriada de la PCT permite evaluar la respuesta al tratamiento y optimizar la duración del mismo (31,67,69,70).

1.5.4. Tratamiento antibiótico empírico: una práctica extendida, pero controvertida

A pesar de la baja prevalencia documentada de coinfección bacteriana en pacientes con neumonía viral grave, tanto en la pandemia de gripe A(H1N1)pdm09 como en la de COVID-19, el uso de antibióticos empíricos al ingreso en UCI ha sido una práctica ampliamente adoptada. Esta estrategia ha estado respaldada por recomendaciones iniciales de diversas sociedades científicas y autoridades de salud pública, en un contexto de elevada incertidumbre diagnóstica y alta mortalidad viral (12,14,22,23,29,56,70).

Iniciar tratamiento antibiótico en el momento de la intubación puede parecer una decisión prudente en pacientes críticos, donde diferenciar una neumonía vírica pura de una coinfección bacteriana no es inmediato. Sin embargo, esta práctica empírica choca con los principios de la optimización antimicrobiana, que promueven un uso dirigido y ajustado del tratamiento antibiótico, basado en criterios clínicos, microbiológicos y biomarcadores objetivos (14,31,64,65,71).

La literatura científica actual ofrece resultados contradictorios sobre los beneficios del tratamiento antibiótico empírico (EAT) en pacientes críticos con neumonía viral. Algunos estudios han sugerido que su uso precoz podría estar asociado con una menor incidencia de complicaciones respiratorias o incluso con una reducción de la mortalidad, incluso en ausencia de coinfección bacteriana documentada (72). En cambio, otros trabajos encuentran un beneficio clínico solo en aquellos pacientes con coinfección confirmada, sin observar mejoras significativas en quienes no presentan infección bacteriana concomitante (31,56). Por otro lado, existe evidencia que plantea que ni siquiera en pacientes coinfectados el uso de antibióticos modifica el pronóstico, y que su administración se asocia a un mayor riesgo de neumonía asociada a la ventilación mecánica (NAVM), prolongación de la estancia y aparición de bacterias multirresistentes (29,56,61,62).

Esta incertidumbre pone de relieve la necesidad de estudios específicos que evalúen de forma comparativa y ajustada el impacto real del TAE en pacientes con neumonía viral grave, distinguiendo entre aquellos con y sin coinfección. Disponer de esta evidencia permitiría mejorar las decisiones clínicas, ajustar las recomendaciones terapéuticas y reforzar una estrategia más segura y sostenible en el manejo de estos pacientes en UCI.

1.5.5. Bacterias multirresistentes y programas PROA

El sobreuso de antibióticos en pacientes con neumonía viral grave ha contribuido a la emergencia de BMR, especialmente en las UCI durante la pandemia por SARS-CoV-2. En este contexto, diversos informes, como el registro ENVIN-COVID en España, han documentado un aumento de infecciones nosocomiales por *Klebsiella pneumoniae* productora de carbapenemasa, *Pseudomonas aeruginosa* y *Acinetobacter baumannii*, asociadas a un peor pronóstico y mayores dificultades terapéuticas (73).

Frente a este escenario, los programas de optimización del uso de antimicrobianos (PROA) ofrecen un enfoque estructurado basado en cinco ejes principales:

- Indicación adecuada basada en criterios clínicos, factores de riesgo, diagnóstico microbiológico rápido y biomarcadores (17)
- Desescalada precoz a las 48–72 h tres obtener cultivos definitivos, evolución clínica y de biomarcadores (31)
- Optimización de la posología y vía de administración (66)
- Duración limitada del tratamiento, generalmente 5 días sin coinfección bacteriana documentada y 7–10 días en neumonía bacteriana confirmada (64).
- Suspensión precoz cuando la evolución clínica y los biomarcadores lo permitan (66).

Aunque los PROA no constituyen el objetivo principal de esta tesis, su aplicación es clave para evitar el uso innecesario de antibióticos, reducir la aparición de resistencias y mejorar los resultados clínicos en pacientes críticos con neumonía viral.

2. Hipótesis

Hipótesis 1:

La identificación de los factores de riesgo asociados a la mortalidad en pacientes con neumonía grave por virus pandémicos ingresados en UCI mediante modelos avanzados de aprendizaje automático ofrece resultados divergentes respecto a los obtenidos mediante regresión logística.

Hipótesis 2:

La administración empírica de antibióticos (EAT) en pacientes con neumonía grave por virus pandémicos ingresados en UCI sin evidencia microbiológica de coinfección bacteriana, no se asocia con una menor incidencia de neumonía asociada a la ventilación mecánica (NAVM) ni con una reducción de la mortalidad en UCI.

Se postula que el uso de antibióticos en ausencia de infección bacteriana documentada no aporta beneficios clínicos relevantes y puede favorecer la aparición de bacterias multirresistentes y otras complicaciones nosocomiales.

2.1. Justificación

Las infecciones respiratorias causadas por virus pandémicos, como el virus Influenza A(H1N1) pdm09 y el SARS-CoV-2, representan una amenaza recurrente para la salud pública global y un desafío importante para los sistemas sanitarios. En su forma grave, estas infecciones pueden evolucionar rápidamente hacia neumonía viral y síndrome de distrés respiratorio agudo (SDRA), generando una elevada demanda de recursos asistenciales en las unidades de cuidados intensivos (UCI). Durante las pandemias de 2009 y 2020, estas patologías no solo duplicaron o triplicaron la ocupación habitual de las UCI, sino que también pusieron en evidencia importantes lagunas en la capacidad predictiva y en la toma de decisiones clínicas en escenarios de alta incertidumbre.

Frente a esta complejidad, resulta esencial mejorar la estratificación pronóstica de los pacientes críticos mediante modelos analíticos robustos. La aplicación de técnicas de aprendizaje automático (machine learning), como el algoritmo Random Forest, permite detectar interacciones no lineales y patrones clínicos que podrían pasar desapercibidos con

métodos estadísticos clásicos como la regresión logística. Sin embargo, la utilidad real de estos enfoques en la práctica clínica sigue siendo motivo de debate: ¿aportan información nueva o refuerzan conocimientos ya establecidos? Comparar de forma sistemática ambas metodologías en grandes cohortes de pacientes con neumonía grave por virus pandémicos puede ayudar a identificar qué factores de riesgo son verdaderamente determinantes, independientemente del enfoque analítico utilizado, y cuáles dependen del modelo aplicado.

En paralelo, las pandemias han reavivado la preocupación por el uso indiscriminado de antibióticos en pacientes con neumonía viral. Aunque la coinfección bacteriana al ingreso es poco frecuente, especialmente en la COVID-19 (<5%), la mayoría de los pacientes hospitalizados reciben TAE. Esta práctica conlleva riesgos significativos: toxicidad, prolongación de la estancia, desarrollo de resistencias, aparición de infecciones nosocomiales como la neumonía asociada a ventilación mecánica (NAVM) y aumento de costes. Diversos estudios y guías clínicas, incluyendo las recomendaciones de los programas PROA, insisten en la necesidad de una prescripción más racional, apoyada en técnicas de diagnóstico microbiológico rápido y en el uso de biomarcadores como la procalcitonina o la proteína C reactiva. Aun así, persiste una considerable incertidumbre sobre el impacto real de esta estrategia en la morbimortalidad de los pacientes sin coinfección documentada.

Ambos ejes, la mejora en la predicción del riesgo de mortalidad y la evaluación crítica del tratamiento antibiótico empírico, convergen en una misma necesidad: avanzar hacia una medicina intensiva más precisa, que integre datos clínicos, microbiológicos y analíticos con herramientas metodológicas sólidas. Profundizar en estas cuestiones, mediante el análisis de bases de datos multicéntricas y el contraste entre enfoques analíticos diversos, puede contribuir a optimizar tanto los modelos de decisión clínica como el uso de recursos en situaciones de alta presión asistencial como las epidemias estacionales y las pandemias.

3. Objetivos

Objetivo principal

1. Evaluar los determinantes pronósticos al ingreso en pacientes con neumonía grave por virus pandémicos (influenza A H1N1 y SARS-CoV-2), con el fin de mejorar la estratificación del riesgo y apoyar la toma de decisiones en medicina intensiva.

Objetivos secundarios

1. Comparar la capacidad predictiva de modelos estadísticos clásicos (regresión logística multivariable) con modelos de aprendizaje automático (Random Forest) y explorar si su análisis combinado mejora la capacidad pronóstica.

2. Analizar el impacto del tratamiento antibiótico empírico (EAT) sobre la neumonía asociada a ventilación mecánica (NAVM) y la mortalidad en pacientes con neumonía grave por virus pandémicos en relación a la presencia o ausencia de coinfección bacteriana documentada.

4. Compendio de publicaciones

4.1 Artículo 1

Papiol, E.; Ferrer, R.; Ruiz-Rodríguez, J.C.; Díaz, E.; Zaragoza, R.; Borges-Sa, M.; Berrueta, J.; Gómez, J.; Bodí, M.; Sancho, S.; et al. Machine Learning-Based Identification of Risk Factors for ICU Mortality in 8902 Critically Ill Patients with Pandemic Viral Infection. *J. Clin. Med.* 2025, *14*, 5383. https://doi.org/10.3390/jcm14155383

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Machine Learning-Based Identification of Risk Factors for ICU Mortality in 8902 Critically Ill Patients with Pandemic Viral Infection

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Abstract

Background/Objectives: The SARS-CoV-2 and influenza A (H1N1)pdm09 pandemics have resulted in high numbers of ICU admissions, with high mortality. Identifying risk factors for ICU mortality at the time of admission can help optimize clinical decision making. However, the risk factors identified may differ, depending on the type of analysis used. Our aim is to compare the risk factors and performance of a linear model (multivariable logistic regression, GLM) with a non-linear model (random forest, RF) in a large national cohort. **Methods**: A retrospective analysis was performed on a multicenter database including 8902 critically ill patients with influenza A (H1N1)pdm09 or COVID-19 admitted to 184 Spanish ICUs. Demographic, clinical, laboratory, and microbiological data from the first 24 h were used. Prediction models were built using GLM and RF. The performance of the GLM was evaluated by area under the ROC curve (AUC), precision, sensitivity, and specificity, while the RF by out-of-bag (OOB) error and accuracy. In addition, in the RF, the im-portance of the variables in terms of accuracy reduction (AR) and Gini index reduction (GI) was determined. **Results**: Overall mortality in the ICU was 25.8%. Model performance was similar, with AUC = 76% for GLM, and AUC = 75.6% for RF. GLM identified 17 independent risk factors, while RF identified 19 for AR and 23 for GI. Thirteen variables were found to be important in both models. Laboratory variables such as

procalcitonin, white blood cells, lactate, or D-dimer levels were not significant in GLM but were significant in RF. On the contrary, acute kidney injury and the presence of *Acinetobacter* spp. were important variables in the GLM but not in the RF. **Conclusions**: Although the performance of linear and non-linear models was similar, different risk factors were determined, depending on the model used. This alerts clinicians to the limitations and usefulness of studies limited to a single type of model.

Keywords: ICU mortality; pandemic viruses; mortality risk factors; random forest; generalized linear model

1. Introduction

Pandemics have historically been one of the greatest threats to public health, causing high mortality and exerting a significant impact on healthcare systems and society in general. Two recent pandemics have been particularly devastating: the influenza A (H1N1) virus, which emerged in 2009, and SARS-CoV-2, first identified in 2019. Both caused millions of deaths worldwide [1–4] and challenged the response capacities of healthcare systems, the pharmaceutical industry, and governments. They also exhibited ethical, economic, and social consequences that are still being felt today [5,6].

Despite the knowledge and advances in biomedicine, there are still limitations in the ability to predict the outcome of patients critically ill with pandemic viral infections. Early identification of patients at increased risk of mortality is essential to optimize intensive care unit (ICU) resources and improve clinical outcomes. Several authors [7–11] have identified a large number of risk factors associated with mortality in patients critically ill with influenza A (H1N1) and SARS-CoV-2 that differ or overlap, depending on the population studied, the country, or the method of analysis used. Traditionally, statistical models such as logistic regression have been used to quantify the association between confounding variables and the dependent variable in a linear fashion. However, this approach displays limitations in detecting non-linear relationships (perhaps the most common in medicine) and the complex interaction between multiple variables, which limits its predictive power in clinical scenarios with high-dimensional data [12].

In this context, new machine learning techniques have emerged as promising tools for predicting complex clinical outcomes. Among these, random forest, one of the most widely used techniques today, has shown significant advantages in identifying complex patterns in the data, without the need for parametric assumptions. This algorithm, based on the combination of multiple decision trees, offers greater predictive accuracy and robustness to the collinearity and heterogeneity of clinical data than those of linear models [13,14].

Our hypothesis is that different risk factors can be identified by applying different models of analysis. To test our hypothesis, the aim of our study is to identify risk factors associated with mortality in patients with severe pneumonia due to influenza A (H1N1) and SARS-CoV-2 infection by comparing the predictive ability of traditional logistic regression models with advanced machine learning techniques, specifically random forest. Our study aims to alert clinicians to the limitations of classical models and the need for more complex or multiple analyses to identify true risk factors and thus optimize decision making in the management of ICU patients.

2. Materials and Methods

2.1. Design

We conducted a secondary analysis of two prospective, multicenter cohort studies. The first dataset came from the GETGAG registry, a voluntary registry established by the Spanish Society of Intensive Care Medicine (SEMICYUC) in 2009 during the influenza A(H1N1)pdm09 pandemic. A total of 184 Spanish ICUs contributed data between June 2009 and June 2019 [15]. The Ethics Committee of Joan XXIII University Hospital (CEI no. 11809) and the ethics committees of all participating centers approved the study protocol. We did not obtain informed consent from patients because the study was observational, and all data were anonymized. The second dataset comes from the COVID-19 registry, a voluntary initiative created by SEMICYUC in 2020 during the SARS-CoV-2 pandemic. Seventy-four Spanish ICUs contributed data between 1 July 2020 and 31 December 2021 [15]. We retrospectively registered the study on ClinicalTrials.gov (NCT04948242) on 30 June 2021. The institution's Internal Review Committee (Research Ethics Committee on Medicinal Products (CEIm) at the Pere Virgili Health Research Institute (IISPV), IRB# CEIM/066/2020) waived the requirement for informed consent. Local researchers maintained contact with the study team, and each participating hospital obtained approval from its local ethics committee. We conducted the study in accordance with the principles of the Declaration of Helsinki and the European Clinical Trials Directive 2001/20/EC on Good Clinical Practice [16].

We presented the results following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [17].

2.2. Study Population

We included a total of 8902 consecutive patients who required ICU admission due to respiratory infections caused by influenza A (H1N1)pdm09, seasonal influenza A or B (n = 3702), or SARS-CoV-2 (n = 5200) during the respective study periods. We confirmed the presence of each virus by performing real-time polymerase chain reaction (rt-PCR) in each hospital, according to Infectious Diseases Society of America (IDSA) recommendations for influenza [18] and World Health Organization (WHO) recommendations for SARS CoV-2 [19]. We monitored each patient until confirmed ICU discharge or death, whichever occurred first.

2.3. Definitions

We considered co-infection in patients who presented with lower respiratory tract infection symptoms and radiographic evidence of pulmonary infiltrates unexplained by other causes [20]. We confirmed coinfection through laboratory testing based on the criteria established by the Centers for Disease Control and Prevention (CDC) [20,21]. Only respiratory infection microbiologically confirmed with a respiratory specimen or serology obtained within 2 days of ICU admission was considered community-acquired coinfection. The diagnosis of coinfection was considered "definitive" if respiratory pathogens were isolated from blood or pleural fluid and if serological tests confirmed a four-fold increase of atypical pathogens, including *Chlamydia* spp., *Coxiella burnetti*, and *Moraxella catarrhalis*. Only patients with confirmed microbiologic diagnosis were included in the present analysis.

We diagnosed acute kidney injury (AKI) based on the Acute Kidney Injury Network (AKIN) criteria, as defined in the international KDIGO guidelines [22].

We defined appropriate empiric antibiotic treatment (AEAT) as the administration of antibiotics at ICU admission before microbiological results were available, followed by adjustment according to pathogen susceptibility once results became known. The attending physician at each center determined whether treatment met these criteria.

We defined inappropriate empiric antibiotic treatment (IEAT) as antibiotic therapy started at ICU admission that was not adjusted to the pathogen's susceptibility once microbiological results became available. This definition also included the administration of antibiotics to patients without documented bacterial co-infection.

We defined GAP-UCI as the time elapsed between the diagnosis of the pandemic viral infection and ICU admission.

We defined GAP-Diagnosis as the time between the onset of clinical symptoms and the microbiological confirmation of the pandemic viral infection.

2.4. Study Variables

We collected demographic data, comorbidities, and clinical and laboratory findings within the first 24 h after ICU admission. We also recorded whether patients required invasive mechanical ventilation and whether they presented with shock upon arrival. We assessed disease severity using the Acute Physiology and Chronic Health Evaluation II (APACHE II) score [23] and the level of organ dysfunction using the SOFA score [24]. The variables included in the study are detailed in Table 1.

Table 1. Baseline characteristics of the 8902 patients included in the analysis, categorized by ICU outcome and variable cut-off.

Variable	Whole Population (n = 8902)	Survival (n = 6608)	Non-Survival (n = 2294)	*p*-Value
General				
Age, median (Q1–Q3) years	60 (49–70)	58 (48–68)	67 (57–74)	<0.001
Age cut-off > 58 years, n (%)	5177(58.1)	3473 (52.6)	1704 (74.3)	<0.001
Male sex, n (%)	5855 (65.8)	4248 (64,3)	1607 (70.1)	<0.001
APACHE II, median (Q1–Q3)	14 (10–19)	13 (10–17)	17 (13–22)	<0.001
APACHE II cut-off > 13, n (%)	5309 (59.6)	3536 (53.5)	1773 (77.3)	<0.001
SOFA score, median (Q1–Q3)	5 (3–7)	4(3–7)	6(4–9)	<0.001
SOFA cut-off > 4, n (%)	6274 (70.5)	4299 (65.1)	1975 (86.1)	<0.001
GAP UCI, median (Q1–Q3)	1 (1–3)	1 (1–3)	2 (0–4)	<0.001
GAP UCI cut-off > 1 day, n (%)	6804 (76.4)	5085 (77.0)	1719 (74.9)	0.053
GAP diagnosis, median (Q1–Q3)	4 (1–7)	3 (1–7)	4 (1–7)	0.012
GAP diagnosis cut-off > 3 days, n (%)	5413 (60.8)	3943 (59.7)	1470 (64.1)	<0.001
> 2 fields with infiltrations in chest X-ray, n (%)	5343 (60.0)	3775 (57.1)	1568 (68.4)	<0.001
Antiviral vaccine, n (%)	1333 (14.9)	885 (13.4)	448 (19.5)	<0.001
Shock at ICU admission, n (%)	3549 (39.9)	2286 (34.6)	1263 (55.1)	<0.001
Laboratory				
White blood cells count, median (Q1–Q3) $\times 10^3$	8.6 (5.7–12.5)	8.5 (5.7–12.1)	9.0 (5.8–13.7)	<0.001
White blood cells count cut-off < 8.5 $\times 10^3$, n (%)	4405 (49.5)	3351 (50.7)	1054 (45.9)	<0.001
Lactate dehydrogenase, median (Q1–Q3) U/L	542 (403–687)	524 (378–665)	590 (458–749)	<0.001
Lactate dehydrogenase cut-off > 500 U/L, n (%)	5157 (57.9)	3593 (54.4)	1564 (68.2)	<0.001
C-reactive protein, median (Q1–Q3) mg/dL	19.6 (9.8–34.7)	19.0(9.5–34.4)	21.1 (10.4–35.4)	0.001
C-reactive protein cut-off >20 mg/dL, n (%)	4387 (49.3)	3184 (48.2)	1203 (52.4)	<0.001
Procalcitonin, median (Q1–Q3) ng/mL	0.88 (0.20–5.67)	0.83 (0.20–5.08)	1.04 (0.23–8.20)	<0.001
Procalcitonin cut-off >0.80 ng/mL, n (%)	4606 (51.7)	3350 (50.7)	1256 (54.8)	0.001
Lactate, median (Q1–Q3) mmol/L	2.0 (1.4–3.3)	2.0 (1.3–3.2)	2.2 (1.4–3.8)	<0.001
Lactate cut-off > 2 mmol/L, n (%)	4660 (52.3)	3369 (51.0)	1291 (56.3)	<0.001
Creatinine, median (Q1–Q3) mg/dL	0.89 (0.7–1.2)	0.85 (0.68–1.12)	1.01 (0.75–1.50)	<0.001
Creatinine cut-off >0.85 mg/dL, n (%)	4841 (54.4)	3330 (50.4)	1511 (65.9)	<0.001
D-dimer, median (Q1–Q3) ng/mL	3071 (971–6604)	2716 (900–6000)	4180 (1200–8680)	<0.001
D-dimer cut-off > 2700 ng/mL, n (%)	4663 (52.4)	3314 (50.2)	1349 (58.8)	<0.001
creatine phosphokinase, median (Q1–Q3) U/L	216 (100–420)	210 (97–414)	234 (111–442)	0.001
Creatine phosphokinase cut-off > 200 U/L, n (%)	4707 (52.9)	3433 (52.0)	1274 (55.5)	0.003

Table 1. *Cont.*

Variable	Whole Population (n = 8902)	Survival (n = 6608)	Non-Survival (n = 2294)	*p*-Value
Comorbidities				
Diabetes mellitus, n (%)	1196 (13.4)	756 (11.4)	440 (19.2)	<0.001
Asthma, n (%)	698 (7.7)	556 (8.4)	142 (6.2)	0.001
COPD, n (%)	1281 (14.4)	936 (14.2)	345 (15.0)	0.32
Chronic heart disease, n (%)	623 (7.0)	418 (6.3)	205 (8.9)	<0.001
Chronic liver disease, n (%)	595 (6.7)	357 (5.4)	238 (10.4)	<0.001
Pregnancy, n (%)	480 (5.4)	399 (6.0)	81 (3.5)	<0.001
Obesity, n (%)	3046 (34.2)	2256 (34.1)	790 (34.4)	0.81
Human immunodeficiency virus, n (%)	144 (1.6)	107 (1.6)	37 (1.6)	1.00
Hematologic disease, n (%)	436 (4.8)	237 (3.6)	199 (8.7)	<0.001
Immunosuppression, n (%)	711 (8.0)	401 (6.0)	310 (13.5)	<0.001
Treatment				
Steroids, n (%)	5275 (59.2)	3746 (56.7)	1529 (66.7)	<0.001
Antibiotics (AB) at ICU admission, n (%)	7410 (83.2)	5428 (82.1)	1982 (86.4)	<0.001
Appropriate empiric AB treatment, n (%)	951 ((10.7)	671 (10.2)	280 (12.2)	0.007
High flow nasal cannula at admission, n (%)	1438 (16.1)	1138 (17.2)	300 (13.1)	<0.001
Invasive mechanical ventilation, n (%)	4252 (47.8)	2751 (41.6)	1501 (65.4)	<0.001
Most common aetiology of coinfection				
Coinfection, n (%)	1211 (100)	810 (12.3)	401 (17.5)	<0.001
Methicillin-sensitive *S. aureus* (MSSA), n (%)	172 (14.2)	111 (13.7)	61 (15.2)	0.47
Pseudomonas aeruginosa, n (%)	143 (11.8)	82 (10.1)	61 (15.2)	0.01
Klebsiella spp. N (%)	85 (7.0)	60 (7.4)	25 (6.2))	0.45
Aspergillus spp., n (%)	78 (6.5)	33 (4.0)	45 (11.2)	<0.001
E. coli, n (%)	69 (5.7)	43 (5.3)	26 (6.3)	0.40
Methicillin-resistant *S. aureus* (MRSA). n (%)	56 (4.6)	33 (4.0)	23 (5.7)	0.19
Acinetobacter spp., n (%)	17 (1.4)	4 (0.5)	13 (3.2)	<0.001
Outcomes				
ICU LOS, median (Q1–Q3) days	13 (6–23)	12 (6–23)	14 (7–24)	0.03
Acute kidney injury, n (%)	1435 (16.1)	855 (12.9)	580 (25.3)	<0.001

APACHE II: Acute Physiology and Chronic Health Evaluation; SOFA: sequential organ failure assessment; GAP-UCI: time from diagnosis to ICU admission; GAP-Diagnosis: time from symptoms onset to diagnosis; ICU: intensive care unit; LOS: length of stay.

2.5. Missing Data Management

We excluded continuous variables with more than 30% missing data from the database. For variables with fewer missing values, we applied imputation using the missForest package in R/CRAN. This method was used to impute missing values for D-dimer (18%), lactate dehydrogenase (15%), procalcitonin (15%), creatinine (14%), SOFA score (14%), APACHE II score (10%), and C-reactive protein (5%). Categorical data, including ICU mortality, were complete for all patients.

2.6. Analysis Plan and Statistical Analysis

Firstly, we calculated the crude ICU mortality rate for the overall population and compared patient characteristics based on outcomes. We expressed qualitative variables as percentages and summarized quantitative variables as medians with interquartile ranges (Q1–Q3). To assess differences between groups, we applied the Chi-square and Fisher's exact tests for categorical variables and the Student's *t*-test or Mann–Whitney U-test for quantitative variables.

Secondly, we applied a binary logistic regression model to identify variables independently associated with all-cause ICU mortality. We incorporated into the generalized linear model (GLM) all variables that were statistically significant ($p < 0.05$) in the bivariate

analyses. We developed the mortality prediction model using only variables available at the time of ICU admission. To improve model performance, we categorized continuous variables, defining cut-off points based on the median values observed in surviving patients. We expressed the results as odds ratios (OR) with 95% confidence intervals.

To validate the model internally, we randomly divided the population into a development set (training data) containing 70% of patients and a validation set (testing data) with the remaining 30%. We assessed model performance by calculating accuracy, precision, sensitivity, specificity, and the area under the ROC curve (AUC). We also examined collinearity among explanatory variables using variance inflation factors (VIF).

In addition, we performed k-fold cross-validation with k = 10. This approach involved splitting the original dataset into a training set and a validation set. We further divided the training data into ten subsets. Each subset served once as the test set, while the remaining nine subsets were used for model training. After completing all iterations, we calculated accuracy and error for each model. We then averaged these results across the ten folds to obtain the final accuracy and error estimates.

Thirdly, because of the significant imbalance between groups, e.g., only 25% of patients belonged to the deceased group, we considered that this class discrepancy could affect the model's performance in predicting mortality. To test whether class imbalance influenced the linear model's results, we applied the ROSE (random over-sampling examples) package. This statistical package generates balanced samples through a smoothed bootstrap approach, enabling reliable estimates of classifier accuracy when the minority class is rare. ROSE also provides traditional methods to address class imbalance and includes multiple metrics for assessing accuracy, which can be estimated via cross-validation, bootstrapping, or the holdout method [25,26]. We implemented the under option, which subsamples the majority class without replacement until either the specified sample size (N) is reached or the positive examples achieve a predefined probability (p). This method reduces the resulting sample size. We used the ROSE software (version 0.0-4) exclusively on the training subset, leaving the test subset unchanged. After developing the model on the training data, we applied it to the test set and evaluated its performance. We reported results as odds ratios (OR) with 95% confidence intervals, along with accuracy, sensitivity, specificity, and the area under the ROC curve (AUC).

Fourthly, to test our hypothesis, we developed a non-linear model using a random forest classifier (RFc). This technique is a powerful, tree-based machine learning approach. We configured our model to generate 500 random trees, each considering at least 15 variables. We evaluated model performance by calculating the out-of-bag (OOB) error, which estimates prediction error through bootstrap aggregation. Additionally, we assessed variable importance by examining the average loss of accuracy and the Gini index. The Gini index, reported as "MeanDecreaseGini", measures the degree of disorder: higher values indicate greater importance in the model because scores near 0 imply higher disorder, while those closer to 1 reflect lower disorder and more consistent contribution to the outcome. For internal validation, we randomly split the population into a training set (70% of patients) and a test set (30%). We determined model performance by measuring accuracy.

We performed all statistical analyses using R statistical software (version 4.4.1) from The R Project for Statistical Computing (r-project.org).

3. Results

3.1. Whole Population

We included a total of 8902 ICU patients in the study: 3702 (41.6%) were diagnosed with influenza, and 5200 (58.4%) with coronavirus disease 2019 (COVID-19). All diagnoses were confirmed by polymerase chain reaction (PCR). Table 1 shows the general character-

istics of patients by ICU outcome. The cohort was predominantly male (65.8%), with a mean age of 60 years. Disease severity was moderate, with mean APACHE II and SOFA scores of 14 and 5, respectively. The most common comorbidities were obesity, diabetes, and chronic obstructive pulmonary disease (COPD). The mean ICU stay was 13 days, and the crude ICU mortality rate reached 25.8%. Compared to survivors, non-survivors were older and exhibited more severe illness, greater systemic inflammation, more comorbidities, higher requirements for organ support, and longer ICU stays. Coinfection was also more frequent among non-survivors, with significant differences observed in pathogens such as *Pseudomonas aeruginosa*, *Aspergillus* spp., and *Acinetobacter* spp. (Table 1).

3.2. Factors Associated with Crude ICU Mortality According to General Linear Model (GLM)

We used multiple logistic regression to examine the associations between crude ICU mortality (the dependent variable) and various independent variables. The model included the following factors: sex (male), age cut-off, APACHE II cut-off, SOFA cut-off, ICU GAP cut-off, GAP diagnosis cut-off, shock, asthma, COPD, chronic heart disease, chronic kidney disease, hematological disease, pregnancy, obesity, diabetes, HIV, immunosuppression, steroid use, and antibiotic treatment at ICU admission. Additional variables included mechanical ventilation at ICU admission, myocardial dysfunction, acute kidney injury (AKI), more than two areas of infiltration on chest X-ray, lactate dehydrogenase (LDH) cut-off, creatine phosphokinase (CPK) cut-off, white blood cell (WBC) cut-off; C-reactive protein (CRP) cut-off; procalcitonin (PCT) cut-off; lactate cut-off; D-dimer (DD) cut-off; presence of *Klebsiella* spp., *Acinetobacter* spp., *Streptococcus pneumoniae*, methicillin-sensitive *Staphylococcus aureus* (MSSA), *E. coli*, methicillin-resistant *S. aureus* (MRSA), *Pseudomonas aeruginosa*, and *Aspergillus* spp.; and administration of an antiviral vaccine. Among these, 17 variables were independently associated with all-cause ICU mortality. The significant factors are detailed in Figure 1 and Table 2.

Table 2. Variables associated with ICU mortality in the linear multivariate analysis (GLM) and non-linear multivariate analysis (random forest). Significant variables in the linear model and those with a significance greater than 10% for the decrease in accuracy or greater than 50% for the decrease in Gini in the non-linear model are shown.

	GLM Model		Random Forest Model	
Variable	**OR**	**95%CI**	**Decreased Accuracy**	**Decreased Gini**
Age ≥ 58 years	2.03	1.74–2.36	34.9%	79.2%
APACHE II ≥ 13 points	1.72	1.48–2.02	19.1%	88.1%
SOFA ≥ 4 points	1.47	1.23–1.76	26.0%	65.1%
Shock	1.27	1.09–1.47	16.4%	77.4%
Hematologic disease	1.67	1.26–2.22	19.5%	39.4%
Obesity	1.16	1.01–1.32	-----	92.4%
Diabetes	1.37	1.14–1.65	16.5%	60.6%
Immunosuppression	1.92	1.53–2.42	18.9%	53.0%
Steroids	1.54	1.34–1.77	12.7%	81.6%
Mechanical ventilation	1.94	1.67–2.25	33.0%	88.1%
Myocardial dysfunction	3.27	2.53–4.28	47.2%	63.6%
Acute kidney injury	1.29	1.07–1.55	----	-----
>2 fields with infiltrations in chest X-ray	1.54	1.34–1.77	16.8%	81.3%
LDH ≥ 500 U/L	1.41	1.22–1.63	11.5%	79.7%
Creatinine ≥ 0.85 mg/dL	1.33	1.14–1.55	13.3%	73.8%
Acinetobacter spp.	9.95	2.61–47.8	----	----
Aspergillus spp.	2.45	1.39–4.33	11.2%	----
Procalcitonin ≥2 ng/mL	----	----	23.0%	68.1%
D-dimer ≥ 2700 ng/mL	----	----	21.7%	75.9%

Table 2. *Cont.*

	GLM Model		Random Forest Model	
Variable	**OR**	**95%CI**	**Decreased Accuracy**	**Decreased Gini**
Lactate $\geq$ 2 mmol/L	----	----	18.1%	79.5%
COPD	----	----	17.4%	61.3%
CPK $\geq$ 200 U/L	----	----	13.1%	90.6%
GAP-Diagnosis $\geq$ 3 days	----	----	----	96.9%
WBC count < 8.5×10^3	----	----	----	93.3%
Male	----	----	----	81.3%
GAP-ICU $\leq$ 1 day	----	----	----	77.1%

Abbreviations: OR: odds ratio; CI: confidence interval; APACHE II: Acute Physiology and Chronic Health Evaluation; SOFA: sequential organ failure assessment; LDH: lactate dehydrogenase; GAP-ICU: time from diagnosis to ICU admission; GAP-Diagnosis: time from symptoms onset to diagnosis; ICU: intensive care unit; COPD: chronic obstructive pulmonary disease; CPK: creatine phosphokinase; WBC: white blood cells.

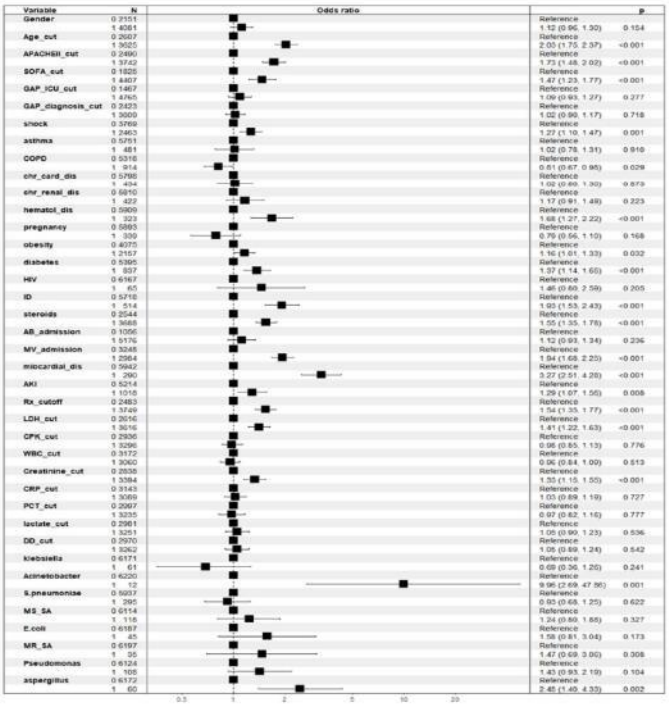

Figure 1. Odds ratio (OR) plot of variables associated with ICU crude mortality in linear multivariate analysis (GLM). Abbreviations: cut: cut-off; APACHE II: Acute Physiology and Chronic Health Evaluation; SOFA: sequential organ failure assessment; AB: antibiotics; CPK: creatine phosphokinase; DD: D-dimer; MR_SA: methicillin-resistant *S. aureus*; MV: invasive mechanical ventilation; WBC: white blood cells; COPD: chronic obstructive pulmonary disease; dis: disfunction; Chr_Card_dis; chronic cardiac disease; HIV: human immunodeficiency virus; AKI: acute kidney injury; CRP: C-reactive protein; GAP_ICU_cut: time elapsed between diagnosing pandemic viral infection and admission to ICU; Chr_renal_dis: chronic renal disease; ID: immunosuppression; Rx-cutoff: > 2 fields with infiltrations in chest X-ray; PCT: procalcitonin; MS_SA: methicillin-sensitive *S. aureus*; GAP_diagnsosis_cut: time from symptoms onset to diagnosis; hematol_dis: hematologic disease; LDH: lactate dehydrogenase.

3.3. Linear Model (GLM) Validation

When we applied the developed model to the test subset, it performed acceptably, achieving an accuracy of 76%, a sensitivity of 61%, and a specificity of 79% (see Supplementary Table S1). The area under the curve (AUC) was 0.76 (95% CI, 0.74–0.78; see Supplementary Figure S1). We did not detect collinearity among the included variables (see Supplementary Table S2). Cross-validation with k = 10 did not improve overall accuracy (which remained at 76%) but increased sensitivity to 94% while reducing specificity to 26% (see Supplementary Table S3).

3.4. Development of the GLM Model with Correction of Class Imbalance

When we applied the ROSE package to the training set, the number of patients decreased from 6232 to 3152. Among these, 1606 died, resulting in an estimated mortality rate of 50.9%, which was double the actual rate of 25%. Developing the linear GLM model with this balanced dataset did not improve performance, yielding an AUC-ROC of 76% (95% CI, 74–78%) and an accuracy of 68%. Supplementary Figures S2 and S3 and Table S4 provide details of the model development. Because this approach did not optimize results and reduced the sample size substantially, we decided to retain the original GLM model despite the class imbalance, as it did not appear to affect performance.

3.5. Factors Associated with ICU Mortality According to No-Linear Model (Random Forest)

We developed a random forest classifier (RFc) model to analyze the impact of confounding variables on ICU mortality in a non-linear manner. To enable comparison, we included the same independent variables used in the GLM. The RFc model yielded an out-of-bag (OOB) error rate of 25.3%.

Nineteen variables reduced model precision by more than 10% (Table 2 and Figure 2). Notably, obesity, acute kidney injury (AKI), and the presence of *Acinetobacter* spp. were important predictors in the GLM but did not contribute significantly to precision in the RFc model. In contrast, COPD, lactate, procalcitonin, D-dimer, and CPK were relevant for accuracy in the RFc model but not in the GLM.

Additionally, twenty-three variables were associated with a reduction in Gini greater than 50% in the non-linear analysis. AKI, *Acinetobacter* spp. and *Aspergillus* spp. were significant in the GLM but not relevant to Gini reduction. Conversely, GAP diagnosis, GAP ICU, male sex, and WBC count were important contributors to Gini decrease in the RF model (see Table 2 and Figure 2).

3.6. Non-Linear Model (RFc) Validation

We applied the developed model to the test subset, where it achieved an acceptable accuracy of 75.6%. This performance closely matched that of the linear GLM model, despite differences in the covariates used.

3.7. Patient Classification by Model

Of the 2670 patients in the test set, the GLM correctly classified 2035 (76.2%), and the random forest (RF) correctly classified 2018 (75.6%) (see Figure 3 and Supplementary Figure S4A,B). Both models agreed on the classification of 1872 patients (70.1%), and 489 patients were misclassified (18.3%). Figure 4 illustrates the probability distributions generated by each model (Class) compared to the actual outcomes (Real).

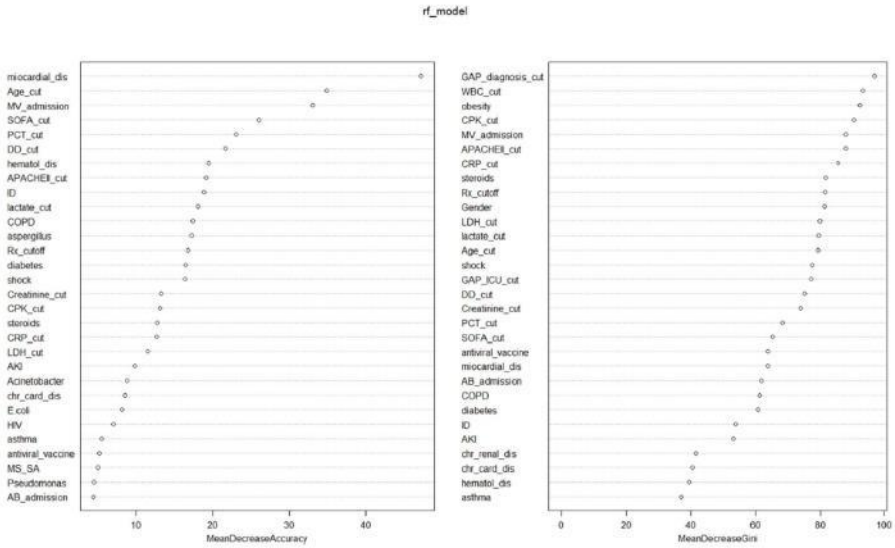

Figure 2. Contribution of each confounding variable according to the random forest (RF) model for variables associated with all-cause ICU mortality. Abbreviations: cut: cut-off; APACHE II: Acute Physiology and Chronic Health Evaluation; SOFA: sequential organ failure assessment; AB: antibiotics; CPK: creatine phosphokinase; DD: D-dimer; MR_SA: methicillin-resistant *S. aureus*; MV: invasive mechanical ventilation; WBC: white blood cells; COPD: chronic obstructive pulmonary disease; dis: disfunction; Chr_Card_dis; chronic cardiac disease; HIV: human immunodeficiency virus; AKI: acute kidney injury; CRP:C-reactive protein; GAP_ICU_cut: time elapsed between diagnosing pandemic viral infection and admission to ICU; Chr_renal_dis: chronic renal disease; ID: immunosuppression; Rx-cutoff: > 2 fields with infiltrations in chest X-ray; PCT: procalcitonin; MS_SA: methicillin-sensitive *S. aureus*; GAP_diagnsosis_cut: time from symptoms onset to diagnosis; hematol_dis: hematologic disease; LDH: lactate dehydrogenase).

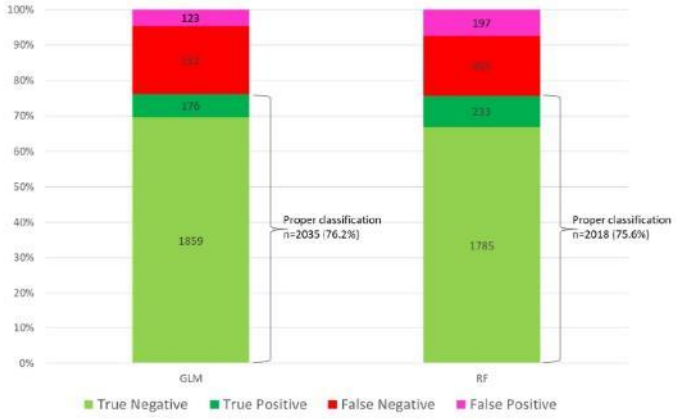

Figure 3. Classification of patients according to the linear (generalized linear model—GLM) and non-linear (random forest—RF) models.

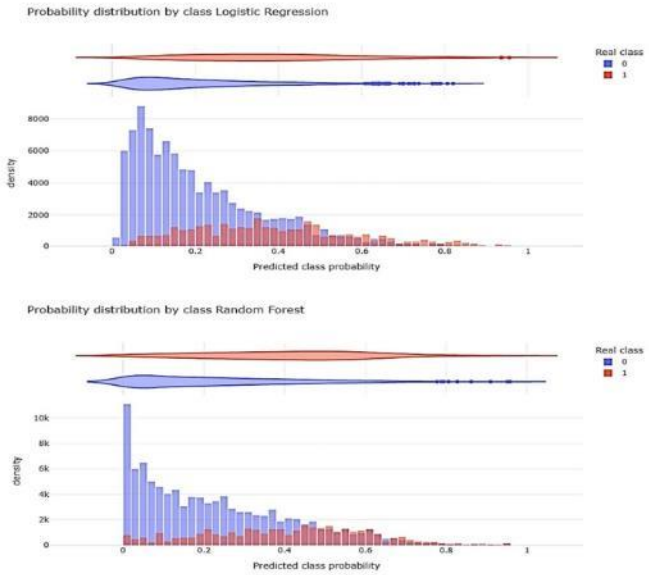

Figure 4. Distribution of the probability generated by each model (Class) with respect to the observed results (Real); (0 = survivors; 1 = non-survivors).

4. Discussion

To the best of our knowledge, this is the first study to use machine learning techniques for a large number of critically ill patients affected by pandemic viruses. Our main finding was that generating mortality prediction models using either a linear technique (GLM) or a non-linear technique (RF) was associated with similar performance, with an accuracy close to 80%.

However, the risk factors identified differed according to the type of analysis used. While factors such as age, severity, degree of organ dysfunction, and need for mechanical ventilation were important in both models (major determinants), other laboratory variables such as procalcitonin, D-dimer, and lactate levels were only identified in the RF model (minor determinants). Conversely, acute kidney injury (AKI) and the presence of *Acinetobacter* spp. were significant only in the GLM (minor determinants). These findings should alert clinicians to the limitations and implications of studies that rely exclusively on one methodological approach to identify prognostic factors.

The influenza A (H1N1) and SARS-CoV-2 pandemics have put enormous pressure on healthcare systems around the world, highlighting the urgent need for reliable and accurate methods to predict patient outcomes in order to manage resources appropriately. Although pandemics may seem to be a thing of the past, each winter, hospitals are overwhelmed by patients with respiratory failure due to viral infections, generating seasonal surges in ICU admissions and demand for resources.

The early identification of high-risk patients with viral infections is essential. It allows for rapid triage, targeted intensive care, and optimized resource allocation, all of which can ultimately improve patient outcomes. Against this backdrop, our study sought to evaluate and compare the performance of traditional statistical and machine learning models in predicting mortality, as well as exploring how each method identifies different clinical predictors of outcome.

Several authors have used different types of machine learning (ML) analysis to identify risk factors and develop predictive models for patients with SARS-CoV-2, while we did not find any studies involving influenza A H1N1. Additionally, most studies included hospitalized patients, with few critically ill patients. Huang et al. [27] reported an AUC of 94.4%, a sensitivity of 94.1%, and a specificity of 90.2% when using ML, but the population considered comprised only 127 patients, of whom 33 were critically ill. Meanwhile, Zhu et al. [28] examined 127 patients with confirmed cases of SARS-CoV-2 (16 of whom were severely ill), Gong et al. [29] examined 372 patients with confirmed cases of SARS-CoV-2 who were hospitalized, Aloisio et al. [30] examined 427 patients with confirmed cases of SARS-CoV-2, and Liu et al. [31] examined 336 severely ill patients with confirmed cases of SARS-CoV-2 (34 of whom died). All of these studies showed excellent performance (AUC > 90%) using linear logistic regression models. The small number of patients included in these studies limits the strength and generalizability of the results.

In line with our research, Reina-Reina et al. [32] conducted a sophisticated study on a population of 1200 patients with confirmed cases of SARS-CoV-2. The study assessed the risk of death and ICU admission using various machine learning (ML) techniques, including support vector machine (SVM), logistic regression (LR), k-nearest neighbors, decision tree, Gaussian naive Bayes, multi-layer perceptron (MLP), and ensemble methods such as AdaBoost and bagging. The authors found no significant differences in classification accuracy (>88%) between the different ML techniques. However, they opted for logistic regression (LR) as the algorithm for optimization due to the interpretability of the model, which is crucial in the medical field, despite random forest (RF) achieving slightly better average results. The model identified the most important variables as COPD, which increases the probability of death by 575%; age, which increases the probability by 145% every 10 years; and acute respiratory failure, which increases the probability by 513%. However, the authors do not report the differences between the predictor variables identified by each model, and only a small percentage of patients were critical.

Pourhomayoun et al. [33] applied various machine learning (ML) models (support vector machine (SVM), neural networks (NN), random forest (RF), decision tree, and logistic regression (LR)) to predict severity in a large cohort of more than 2,670,000 patients with SARS-CoV-2 infection. The original dataset contained 32 data points for each patient, including demographic and physiological data. The NN algorithm achieved the best performance and accuracy, with an area under the curve (AUC) of 89.98%, compared to 87.93% for random forest (RF) and 87.91% for logistic regression (LR). However, the authors did not conduct a statistical comparison of the AUCs to determine significance, nor did they compare the predictive factors of the different models, only presenting the NN factors in the form of a heat map. Furthermore, the severity of the patients' disease was not reported.

In an excellent review of machine learning (ML) techniques used for prognosis in patients with SARS-CoV-2 infection, Alballa et al. [34] note that the most commonly used algorithm for diagnostic and prognostic models is logistic regression (LR), followed by XGBoost and finally, support vector machine (SVM). The authors point out that most of the studies included in the review used unbalanced datasets. In these studies, the majority of records in the training dataset represent the negative class (survivors), while the positive class (non-survivors) is under-represented. Consequently, the performance of various ML algorithms applied in the context of COVID-19 may be biased. In such cases, a high accuracy score could be attributed to the model's ability to accurately identify negative samples and erroneously exclude all positive cases. In our study, we recognized and addressed this bias by applying subsampling to the majority class. However, this did not improve the performance of the balanced model compared to that of the unbalanced model, showing that class imbalance does not affect model reliability. This may be because the

mortality rate among our critically ill patients is 25%, whereas in most published studies, it is around 10–15% [8,32,35] due to the absence of critically ill patients.

As our study revealed, the linear model performs similarly to non-linear models when it comes to predicting mortality in patients with COVID-19, a finding that has been corroborated by several other studies [32–35]. However, despite the structural flexibility of machine learning models for predicting outcomes in patients with this disease, there are limitations to their practical use. These include high heterogeneity between patients' clinical profiles and small sample sizes, which may reduce the external validity and generalizability of the data. Most studies describe different risk factors and performances depending on which factors are included. This is consistent with studies [32,35–37] reporting the modest performance of machine learning (ML) models when trained exclusively with baseline clinical data collected at the time of intensive care unit (ICU) admission. The most successful predictive models, such as those of Wang et al. [38] and Karasneh et al. [39], incorporate dynamic, therapeutic, or immunological variables that significantly improve model performance. However, these variables are not available during the initial hours of care for critically ill patients, limiting their applicability to clinical practice.

We would like to highlight the strengths of our study. Firstly, the large number of critically ill patients included (n = 8902), of whom more than 3000 were affected by influenza A (H1N1)pdm09, makes it unique in its results. As it is a national multicenter study involving more than 148 ICUs in Spain, its results can be generalized to the whole country. Furthermore, it reports not only on the performance of the developed models, but also on the different risk factors identified and how patients are classified by each model. Based on these findings, we can classify risk factors as either major or minor determinants, depending on whether they are important in both models or only one. Recognizing these risk factors could be valuable in clinical practice for determining the prognosis of critically ill patients with a pandemic virus infection. Finally, our study alerts clinicians to the limitations of using models developed using a single method of analysis.

However, our study reflects limitations that need to be recognized. Firstly, despite the large number of patients and the study's multicenter nature, these findings cannot be extrapolated to other populations (non-critical), health systems, or continents without local validation. Secondly, while the potential bias due to class imbalance has been addressed, other biases cannot be ruled out, such as those related to ethnicity or other confounding variables, as these variables are not included in our data. Thirdly, including data on ICU evolution in the models could potentially improve performance. However, our aim was to identify early risk factors for mortality that could be modified by clinicians to improve prognosis.

5. Conclusions

Our study highlights the continued relevance of linear models (GLM) for predicting mortality in the era of machine learning analysis. However, it alerts clinicians to the need for a complementary approach combining linear and non-linear analysis in order to identify all the major and minor determinants of mortality, with the ultimate goal of improving the prognosis of this critical patient group.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm14155383/s1, Table S1: Performance of multivariate linear model (GLM) for ICU mortality; Table S2: Collinearity study by VIF (variance inflation factors) determination; Table S3: Cross-validation of multivariate linear (GLM) model; Table S4: Performance of balanced linear model; Figure S1: Area under ROC curve (AUC) for multivariate lineal model for ICU mortality; Figure S2: Forest plot with the variables included in the balanced linear model, along

with the odds ratio; Figure S3: area under ROC curve of balanced mortality linear model; Figure S4: Category profiles according to the model (A = linear model; B = no linear model).

Author Contributions: Conceptualization, E.P., R.F., J.C.R.-R., E.D., R.Z., M.B.-S., J.G., M.B., S.S., B.S., S.T. and A.R.; data curation, S.T.; formal analysis, E.P., R.F., J.C.R.-R., E.D., M.B.-S., J.B., J.G., M.B., S.S., B.S., S.T. and A.R.; investigation, E.P., E.D., R.Z., J.B., J.G., S.S. and B.S.; methodology, E.P., R.F., J.C.R.-R., E.D., R.Z., M.B.-S., J.B., J.G., M.B., B.S., S.T. and A.R.; project administration, E.P.; resources, S.T. and A.R.; software, J.B., J.G. and A.R.; validation, E.P., J.C.R.-R., M.B.-S., J.B., J.G., M.B., S.S., S.T. and A.R.; writing—original draft, E.P., R.F., J.C.R.-R., E.D., R.Z., M.B.-S., M.B., S.S., B.S. and A.R.; writing—review and editing, E.P., R.F., J.C.R.-R. and A.R. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The Ethics Committee of Joan XXIII University Hospital (CEI no. 11809) and each participating center approved the GETGAG registry. Due to the observational design and guaranteed data anonymity, informed consent was not obtained from patients. The COVID-19 registry was retrospectively registered on ClinicalTrials.gov (NCT04948242) on 30 June 2021.

Informed Consent Statement: The Institution's Internal Review Committee (Comitè Ètic d'Investigació amb Medicaments [CEIm] of the Institut d'Investigació Sanitària Pere Virgili [IISPV], IRB# CEIM/066/2020) waived the need for informed consent. Local investigators maintained contact with the study team, and participating hospitals secured local ethics committee approval. Both studies complied with the Declaration of Helsinki and the Clinical Trials Directive 2001/20/EC of the European Parliament on Good Clinical Practice.

Data Availability Statement: The corresponding author (A.R.) had full access to all study data and assumes responsibility for data integrity and accuracy of analyses. All authors approved the final manuscript. The views expressed are those of the authors and do not necessarily reflect those of SEMICYUC. The data supporting the conclusions are available from the Spanish Society of Critical Care (SEMICYUC) under authorization and are not publicly accessible. Researchers can request the data from the corresponding author (A.R.), with SEMICYUC's permission.

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4.2 Artículo 2

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Article

Does Empirical Antibiotic Use Improve Outcomes in Ventilated Patients with Pandemic Viral Infection? A Multicentre Retrospective Study

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Abstract: Background: During the influenza A(H1N1) and COVID-19 pandemics, empirical antibiotic treatment (EAT) was widely administered to critically ill patients despite low rates of confirmed bacterial co-infection (COI). The clinical benefit of this practice remains uncertain and may contradict antimicrobial stewardship principles. **Objective:** To evaluate whether EAT at ICU admission reduces ventilator-associated pneumonia (VAP) incidence or ICU mortality in critically ill patients with pandemic viral pneumonia, stratified by presence of COI. **Methods:** This retrospective analysis combined two national multicentre ICU registries in Spain, including 4197 adult patients requiring invasive mechanical ventilation for influenza A(H1N1) or COVID-19 between 2009 and 2021. Primary outcomes were ICU mortality and VAP incidence. Analyses were stratified by microbiologically confirmed bacterial COI. Propensity score matching, Cox regression, General Linear (GLM), and random forest models were applied. **Results:** Among patients without COI (n = 3543), EAT was not associated with lower ICU mortality (OR = 1.02, 95%CI 0.81–1.28, $p = 0.87$) or VAP (OR = 1.02, 95%CI 0.79–1.39, $p = 0.89$). In patients with confirmed COI (n = 654), appropriate EAT was associated with reduced VAP (17.4% vs. 36.3%, $p < 0.001$) and ICU mortality (38.4% vs. 49.6%, OR = 1.89, 95%CI 1.13–3.14, $p = 0.03$) compared to inappropriate EAT. **Conclusions:** EAT was not associated with a lower incidence of VAP or higher survival rates

and could be harmful if administered incorrectly. These findings support a more targeted approach to antibiotic use, guided by microbiology, biomarkers and stewardship principles.

Keywords: empirical antibiotic treatment; pandemic viral pneumonia; ventilator-associated pneumonia; ICU mortality; antimicrobial stewardship

1. Introduction

The influenza A(H1N1) and COVID-19 pandemics placed enormous pressure on health systems and were responsible for significant global mortality [1–4]. Although these pandemics occurred a decade apart, both were marked by widespread empirical use of antibiotics, largely encouraged by recommendations from scientific societies and public health authorities [5–10]. This practice persisted despite the consistently low prevalence of confirmed bacterial co-infection (COI)—reported in only 6% to 15% of cases—which raised serious concerns about the appropriateness of antimicrobial use and the resulting contribution to antibiotic resistance [10–16].

In viral pneumonias, antibiotic therapy is generally not indicated unless there is clear evidence of COI [17]. However, clinical uncertainty often complicates early decision-making, particularly in critically ill patients. In the absence of definitive diagnostic information, many clinicians initiate empirical antibiotic treatment (EAT) at the time of intubation as a precautionary measure. While this approach may appear clinically justifiable, it challenges the principles of antimicrobial stewardship, which emphasize minimizing unnecessary antibiotic use and discontinuing therapy as soon as bacterial infection is reasonably excluded [5,7].

The literature to date offers conflicting perspectives. Some studies suggest that EAT at intubation in COVID-19 patients may be associated with lower rates of pulmonary superinfection and mortality [18]. However, the generalizability of these findings remains uncertain, and other studies have not observed similar benefits [9,19,20]. In fact, some have reported an increased incidence of ventilator-associated pneumonia (VAP) associated with empirical antimicrobial use [21–23], reinforcing the need for a more cautious and evidence-based approach.

With dozens of viruses capable of causing pneumonia in humans, differentiating viral from bacterial pneumonia in clinical practice using traditional diagnostic methods can be very difficult. Our group [6,14,15] and others [9,16,24] have investigated the value of procalcitonin (PCT) in determining the presence of COI in pandemic viral pneumonia. Although PCT performs better in influenza than in COVID-19, it has been shown to be useful in aiding the diagnosis of COI and optimizing antimicrobial therapy [6,8,14,15,23]. Rather than recommending indiscriminate antimicrobial use in viral pneumonia, a real effort should be made to determine whether or not bacterial COI is present in patients with pandemic viral infection. In this context, the use of PCT and new rapid molecular diagnostic techniques could be a valid tool for optimizing EAT. In our opinion, antibiotics should be used with caution and discontinued unless the patient's true need has been established. While the administration of EAT in patients with bacterial COI should be appropriate and early, it is important to ensure that EAT is given to those who really need it and used with extreme caution.

We hypothesized that the administration of EAT in this population is not associated with a reduced incidence of VAP or lower ICU mortality, once COI has been reasonably excluded. To address our hypothesis, we conducted a retrospective study using two large multicentre Spanish ICU databases, encompassing 4197 patients who required mechanical

ventilation for acute respiratory failure due to either influenza A(H1N1) or COVID-19. Our primary objective was to evaluate the association between EAT and both VAP occurrence and ICU all-cause mortality, while the secondary objective was to assess the consistency of these findings across the two pandemic contexts and to explore the robustness of the results using both conventional statistical approaches and machine learning techniques.

2. Materials and Methods

2.1. Study Design

This was a secondary, retrospective observational analysis based on two prospective, multicentre cohort studies conducted in Spain. The analysis followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [25].

2.2. Setting

Data were obtained from two national registries coordinated by the Spanish Society of Intensive Care Medicine (SEMICYUC). The first dataset, the GETGAG registry [26,27], included patients admitted to 184 ICUs with influenza A(H1N1)pdm09 between June 2009 and June 2019. The second dataset, the COVID-19 registry [15,28], involved 74 ICUs and enrolled patients with SARS-CoV-2 infection between 1 July 2020 and 31 December 2021. Ethical approval was obtained for both registries, with appropriate waivers for informed consent due to the observational nature of the study.

2.3. Participants

Eligibility criteria: all adult patients admitted to the ICU for acute respiratory failure due to confirmed influenza A(H1N1) pdm09 or SARS-CoV-2 infection requiring invasive mechanical ventilation on admission were eligible.

Exclusion criteria: patients without invasive mechanical ventilation (IMV) on ICU admission and those with microbiologically confirmed fungal co-infection were excluded.

Final cohort: a total of 4197 patients met inclusion criteria and were included in the analysis.

Follow-up: patients were followed until ICU discharge or death.

2.4. Variables

Demographic data, comorbidities, and clinical and laboratory findings were collected during the first 24 h after ICU admission. In addition, the need for IMV and the presence of shock upon ICU admission were recorded. Disease severity was determined using the Acute Physiology and Chronic Health Evaluation II (APACHE II) score [29], while the level of organ dysfunction was determined using the SOFA score [30]. The variables controlled for in the study can be seen in Table 1.

Definitions: co-infection (COI), ventilator-associated pneumonia (VAP), empiric antibiotic treatment (EAT), appropriate EAT (AEAT), inappropriate EAT (IEAT), multidrug resistance (MDR), acute kidney injury (AKI), shock and immunosuppression were defined using standardized criteria (CDC, ERS/ESICM/ESCMID/ALAT, KDIGO) [1,14,31–34]. The exact meanings of these variables can be found in the Supplementary Materials.

Table 1. Characteristics of 4197 ventilated patients included in the study according to diagnosis of bacterial coinfection at ICU admission.

Variables #	*Whole Population (n = 4197)*			*Coinfection Patients (n = 654)*			*No Coinfection Patients (n = 3543)*		
	Total	*No EAT (n = 495)*	*EAT (n = 3702)*	*Total*	*No EAT (n = 28)*	*EAT (n = 626)*	*Total*	*No EAT (n = 467)*	*EAT (n = 3076)*
General characteristics									
Age, years	60 (49–69)	60 (46–69)	60(49–69)	59 (48–70)	62 (53–69)	59 (48–70)	60 (49–69)	60 (45–69)	60 (49–69) *
Male sex	2746 (65.4)	310 (62.6)	2436 (65.8)	433 (66.2)	19 (67.9)	414 (66.1)	2313	291 (62.3)	2022 (65.7)
APACHE II score	16 (12.21)	15(12–18)	16(12–21) ***	18 (13–24)	14 (10–18)	18 (13–24) ***	15 (12–20)	15 (12–18)	15 (12–21) *
SOFA score	6 (4–8)	5 (4–7)	6 (4–8) ***	7 (5–10)	5 (3–7)	7(5–10) ***	6 (4–8)	5 (4–7)	6 (4–8) ***
Gap-ICU, days	1 (1–3)	2(1–4)	1(1–43) ***	1 (0–2)	1.4 (0–4)	1.0 (0–2)	1 (1–3)	2 (1–4)	1 (1–3) ***
Chest X-ray cutoff	2646 (63.0)	317 (74.9)	2329 (62.9) ***	360 (55.0)	23 (82.1)	337 (53.8) ***	2340 (66.0)	348 (74.5)	1992 (64.8) ***
COVID	2139 (51.4)	279 (56.4)	1880 (50.8) **	191 (29.2)	20 (71.4)	171 (27.3) ***	1968 (55.5)	259 (55.5)	1709 (55.6)
Influenza	2038 (48.5)	216 (43.6)	1822 (49.2) **	463 (70.8)	8 (28.6)	455 (72.7) ***	1575 (44.4)	208 (44.5)	1367 (44.4)
Laboratory									
WBC × 10^3	8.7 (5.6–13.0)	8.6 (6.4–11.6)	8.8 (5.4–13.1)	8.5 (4.2–13.6)	8.3 (3.3–11.7)	8.6 (4.2–13.7)	8.8 (5.8–12.8)	8.6 (6.5–11.5)	8.8 (5.7–13.0)
LDH U/L	597 (454–763)	600 (487–722)	597 (450–768)	600 (460–745)	556 (467–628)	600 (458–749)	597 (454–766)	600 (490–725)	590 (450–770)
C-RP mg/mL	22.7 (11.5–40.0)	21.1 (9.6–33.0)	23.0 (11.8–42.9) ***	30.2 (16.5–80.4)	13 (6.7–29.0)	31 (17.7–82.5) ***	21.3 (10.8–35.8)	21.4 (10.0–33.1)	21.4 (11.0–37.0)
PCT ng/mL	1.4 (0.30–8.90)	0.84 (0.22–3.35)	1.50 (0.32–10.1) ***	5.3 (1.0–22.3)	0.73 (0.21–2.80)	5.99 (1.2–22.6) ***	1.08 (0.27–3.38)	0.87 (0.22–4.48)	1.14 (0.29–7.11) ***
Creatinine mg/dL	0.92 (0.70–1.32)	0.95 (0.73–1.25)	0.91 (0.70–1.34)	1.1 (0.7–1.8)	0.92 (0.65–1.41)	1.11 (0.77–1.81)	0.90 (0.70–1.26)	0.95 (0.72–1.25)	0.90 (0.70–1.27)
CPK	265 (119–485)	280 (124–487)	263 (119–485)	318 (138–589)	213 (142–358)	326 (138–602)	253 (117–473)	288 (124–497)	248 (115–469)
Lactate mmol/L	2.2 (1.5–3.6)	1.9 (1.4–2.8)	2.3 (1.5–3.7) ***	3.1 (2.0–4.6)	2.0 (1.4–2.5)	3.2 (2.0–4.7) ***	2.1 (1.4–3.9)	1.9 (1.4–2.8)	2.1 (1.4–3.5) **
D-dimer	4343 (1560–8170)	3316 (1360–6200)	4560 (1600–8400) ***	6400 (3080–11,131)	2030 (980–6270)	6685 (3290–11,230) ***	4000 (1470–7620)	3327 (1404–6200)	4111 (1480–7770) ***
Comobidities									
COPD	613 (14.6)	66 (13.3)	547 (14.8)	126 (19.3)	4 (14.3)	122 (19.5)	487 (13.7)	62 (13.3)	425 (13.8)
Asthma	302 (7.2)	37 (7.4)	265 (7.1)	41 (6.3)	2 (7.1)	39 (6.2)	261 (7.3)	35 (7.5)	226 (7.3)
Chr. Heart Dis	271 (6.4)	21 (4.2)	250 (6.7)	57 (8.7)	1 (3.5)	56 (8.9)	214 (6.0)	20 (4.3)	194 (6.3)
Chr.Renal Dis.	260 (6.2)	32 (6.4)	228 (6.1)	52 (7.9)	1 (3.5)	51 (8.1)	208 (5.8)	31 (6.6)	177 (5.7)
Hematologic Dis.	215 (5.1)	27 (5.4)	188 (5.0)	42 (6.4)	2 (7.1)	40 (6.4)	173 (4.8)	25 (5.3)	148 (4.8)
Pregnancy	200 (4.8)	14 (2.8)	186 (5.0) *	53 (8.1)	0 (0.0)	53 (8.4)	147 (4.1)	14 (3.0)	133 (4.3)
Obesity	1471 (35.0)	195 (39.4)	1276 (34.5) *	183 (28.0)	9 (32.1)	174 (27.8)	1288 (36.3)	186 (39.8)	1102 (35.8)
Diabetes	493 (11.7)	83 (16.8)	410 (11.1)	57 (8.7)	5 (17.9)	52 (8.3)	436 (12.3)	78 (16.7)	358 (11.6)
Immunosuppression	349 (8.3)	33 (6.6)	316 (8.5)	77 (11.8)	1 (3.5)	76 (12.1)	272 (7.6)	32 (6.8)	240 (7.8)

Table 1. *Cont.*

Variables #	*Whole Population (n = 4197)*			*Coinfection Patients (n = 654)*			*No Coinfection Patients (n = 3543)*		
	Total	*No EAT (n = 495)*	*EAT (n = 3702)*	*Total*	*No EAT (n = 28)*	*EAT (n = 626)*	*Total*	*No EAT (n = 467)*	*EAT (n = 3076)*
Treatments and complications									
Bacterial coinfection	654 (15.6)	28 (5.6)	626 (16.9)	NA	NA	NA	NA	NA	NA
AEAT	541 (12.9)	0 (0.0)	541(86.4)	541 (82.7)	0 (0.0)	541 (86.4)	NA	NA	NA
Corticosteriods	2424 (57.8)	237 (47.9)	2187 (59.1) ***	400 (61.2)	20 (32.1)	380 (60.7)	2024 (57.1)	217 (46.5)	1807 (58.7) ***
VAP	743 (17.7)	88 (17.8)	655 (17.7)	135 (20.6)	10 (35.7)	125 (20.0)	608 (17.1)	78 (16.7)	530 (17.2)
AKI	821 (19.6)	63 (12.7)	758 (20.5) ***	220	6 (21.4)	214 (34.2)	601 (16.9)	57 (12.2)	544 (17.7) **
Myocardial dysfunction	216 (5.1)	19 (3.8)	197(5.3)	131	1 (17.9)	130 (20.8)	201 (5.6)	18 (3.8)	183 (5.9)
Shock	2721 (64.8)	276 (55.8)	2445 (66.0) ***	41	2 (7.1)	39 (6.2)	2223 (62.7)	263 (56.3)	1960 (63.7) **
Outcomes									
LOS ICU, days	16 (9–27)	16 (11 -25)	16 (9–27)	16 (9–29)	19 (12–37)	16 (8–29)	16 (10–27)	16 (11–24)	16 (9–27)
LOS Hospital, days	26 (16–40)	26 (18–35)	26 (16–40)	26 (14–44)	26 (17–47)	26 (14–44)	26 (16–39)	25 (18–35)	26 (16–40)
IMV days	12 (5–22)	8 (1–20)	12 (6.23) ***	13 (7–25)	15 (7–35)	13 (7–25)	12 (5–22)	8 (1–20)	12 (6–22) ***
ICU mortality	1466 (34.9)	159 (32.1)	1307 (35.3)	264 (40.4)	16 (57.1)	248 (39.6)	1202 (33.9)	143 (30.6)	1059 (34.4)

Continuous variables are shown as median values and percentiles Q1–Q3. Categorical variables are shown as number of cases (n) and percentage (%). (LDH: Lactate dehydrogenase; C-RP: C-reactive protein; CPK: creatine phosphokinase; PCT: procalcitonin; VAP: ventilator associated pneumonia; AKI: acute kidney injury; LOS length of stay; ICU: intensive care units; Gap-ICU: time in days from hospital admission to ICU admission; chest X-ray cutoff: more than 2 lung fields occupied by infiltrates on chest X-ray; MDR: multi-drug resistant bacteria; EAT: empiric antibiotic treatment; AEAT: appropriate empiric antibiotic treatment). For comparisons within each subgroup * $p < 0.05$; ** $p < 0.01$ and *** $p < 0.001$. Primary outcome: All-cause ICU mortality. Secondary outcomes: incidence of ventilator-associated pneumonia (VAP), isolation of multidrug-resistant (MDR) organisms, ICU /hospital length of stay (LOS), duration of mechanical ventilation (IMV), acute kidney injury (AKI), and appropriateness of empirical antibiotic therapy. Exposures: receipt of empirical antibiotic treatment at ICU admission.

2.5. Data Sources and Measurement

Viral infections were confirmed via rt-PCR per IDSA [35] and WHO [36] recommendations. Coinfections were confirmed using CDC microbiological criteria. Standardized forms were used for data collection within each registry. Data consistency and integrity were maintained across participating centres. Diagnostic definitions and laboratory standards were harmonized within each registry.

2.6. Bias

To mitigate confounding, propensity score matching was applied for comparisons between groups with and without EAT. Multivariate regression and non-linear modelling (random forest) were used to control for known confounders. Definitions were standardized to reduce classification bias.

2.7. Analysis Plan and Statistical Analysis (Figure 1)

First, we performed a descriptive analysis distinguishing between patients with and without EAT on ICU admission. Continuous variables are presented as median and quantiles (Q1–Q3) and categorical variables as numbers (n) and percentages. Chi-square and U-Mann–Whitney tests were used to compare between groups.

Second, we performed a descriptive analysis differentiating patients with and without the presence of COI. Within each of these subgroups, we differentiated between those with and without EAT.

Third, within the subgroup of patients with COI, we examined the impact of appropriate EAT on mortality, development of VAP, ICU and hospital LOS, and IMV days. For this analysis, patients with inappropriate EAT (IEAT) were those with IEAT according to microbiological sensitivity and those without EAT on ICU admission.

Fourth, within the subgroup of patients without COI, to analyse the impact of EAT on the study objectives, and to convert an observational study into a quasi-randomized study, a propensity score matching was performed. After matching, the effect of EAT on all-cause ICU mortality and on the development of VAP was examined by Kaplan–Meier plot and differences were determined by Log Rang test.

In addition, a Cox proportional hazards (COX) and GLM model was used to determine whether EAT was a factor associated with VAP or ICU mortality in multivariate adjusted analysis. The results are expressed as hazard ratio (HR) and its 95% confidence interval (CI) for COX model and as Odds ratio (OR) and its 95%CI for GLM.

Fifth, in addition, to evaluate the impact of EAT on patients without COI, a non-linear regression analysis (random forest-RF) was performed to study whether there are non-linear associations between EAT use and crude mortality or the development of VAP that cannot be evidenced by linear analysis (GLM). The performance of the RF model was evaluated using out-of-bag (OOB) error. We also plotted the importance of the different variables for the model, which is related to the average loss of accuracy and the Gini index for the classification model.

Complete information on the statistical analysis is available in the Supplementary Materials.

Statistical analysis was performed with R statistical software (v 4.4.1) R: The R Project for Statistical Computing (r-project.org).

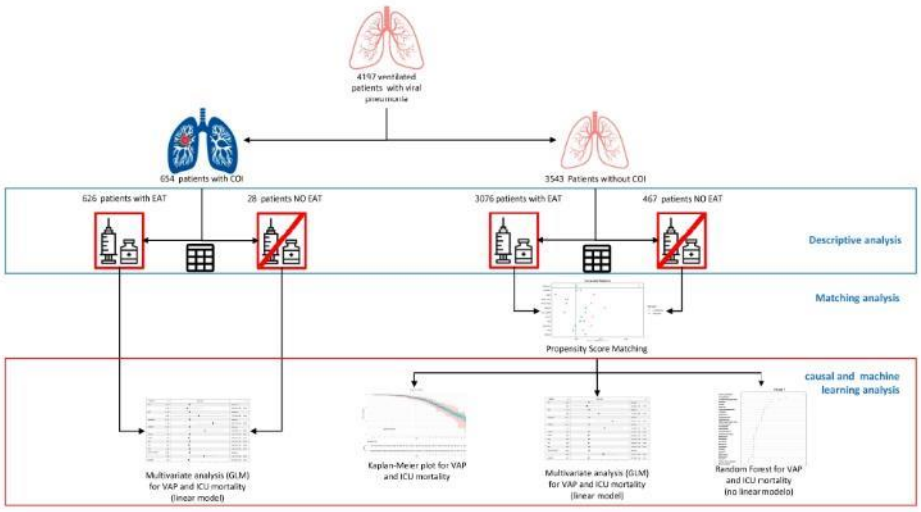

Figure 1. Schematic representation of the statistical analysis performed. A comparative analysis was performed between patients with and without empirical antibiotic treatment (EAT) in the coinfection subgroup (COI). A multivariate analysis was then conducted to identify factors associated with ventilator-associated pneumonia (VAP) and ICU mortality. In the subgroup without COI, a comparative analysis was performed between patients with and without EAT. Propensity score matching was then used to adjust the variables. The impact of EAT on VAP and ICU mortality was then evaluated over time using K-Meier and Cox regression, as a dichotomous variable using linear (GLM) and non-linear (random forest) models.

3. Results

3.1. Whole Population

A total of 4197 ventilated patients were included in the study (Figure S1). Of these, 3702 (88.2%) received EAT on admission to the ICU. Patients receiving EAT had higher severity of illness, higher levels of inflammation and higher levels of hypoperfusion. They also had a higher incidence of AKI, shock and more days with IMV than those who did not receive EAT. However, there were no significant differences in all-cause ICU mortality or in the incidence of VAP (Table 1).

3.2. Patients with Bacterial Coinfection (COI)

Of the 4197 patients, 654 (15.6%) had a microbiologically confirmed COI. The most frequently isolated microorganisms are shown in Table S1 (Supplementary Materials). A total of 704 microorganisms were isolated from 654 patients. Fifty-four patients (8.2%) and four patients (0.6%) had two and three microorganisms isolated simultaneously. *Streptococcus pneumoniae* (n = 217, 33.2%), methicillin-sensitive *Staphylococcus aureus* (n = 107, 16.4%) and *Pseudomonas aeruginosa* (n = 88, 13.4%) were the most commonly isolated microorganisms.

Twenty-eight patients (4.5%) did not receive EAT despite COI. Patients with COI without EAT had lower severity, lower systemic inflammation and lower hypoperfusion. However, these patients had a higher incidence of VAP and higher mortality than patients with EAT, although this was not significant, possibly due to a type 1 alpha error.(Table 1).

Of the 626 patients with COI and EAT, 85 (13.6%) received IEAT according to microbiological results. The general characteristics of patients with COI and EAT distinguishing

appropriate from inappropriate antibiotic treatment are shown in Table 2. Patients with IEAT were older, occurred more frequently during the COVID-19 pandemic period and had a higher incidence of VAP, more days of IMV, longer ICU and hospital stay. The presence of MDR microorganisms was more common in this group and, as expected, a higher crude ICU mortality was observed compared to those who received AEAT.

Table 2. The general characteristics of 626 patients with coinfection (COI) and empiric antibiotic treatment distinguishing appropriate (AEAT) from inappropriate (IEAT) empiric antibiotic treatment.

Variables #	IEAT (n = 85)	AEAT (n = 541)	*p*-Value
General Characteristics			
Age, years	62 (56–72)	59 (47–70)	0.009
Male sex	55 (64.7)	359 (66.4)	0.86
APACHE II score	18 (13–21)	19 (14–24)	0.17
SOFA score	7 (5–9)	7 (5–10)	0.04
Gap-ICU, days	1 (1–2)	1 (0–2)	0.18
Chest X-ray cutoff	51 (60.0)	286 (52.9)	0.26
COVID	48 (56.5)	123 (22.7)	<0.001
Influenza	37 (43.5)	418 (77.3)	<0.001
Laboratory			
WBC $\times 10^3$	8.0 (4.9–11.6)	8.7 (3.9–13.9)	0.60
LDH U/L	630 (473–830)	600 (458–745)	0.29
C-RP mg/mL	22.4 (13.0–33.3)	33.4 (19.7–91.3)	<0.001
PCT ng/mL	1.44 (0.24–8.26)	7.86 (1.55–24.0)	<0.001
Creatinine mg/dL	0.87 (0.70–1.48)	1.14 (0.79–1.86)	0.01
CPK	218 (119–399)	338 (151–647)	0.001
Lactate mmol/L	2.3 (1.6–3.6)	2.3 (2.2–4.8)	<0.001
D-dimer	3940 (1179–7200)	6800 (3780–11,700)	
Comorbidities			
COPD	11 (12.9)	111 (20.5)	0.13
Asthma	8 (9.4)	31 (5.7)	0.28
Chr. Heart Dis	4 (4.7)	52 (9.6)	0.20
Chr.Renal Dis.	7 (8.2)	44 (8.1)	1.0
Hematologic Dis.	4 (4.7)	36 (6.6)	0.65
Pregnancy	2 (2.3)	51 (9.4)	0.04
Obesity	34 (40.0)	140 (25.9)	0.01
Diabetes	13 (15.3)	39 (7.2)	0.02
Immunosuppression	8 (9.4)	68 (12.6)	0.51
Treatment and complications			
Corticosteroids	57 (67.1)	323 (59.7)	0.24
Presence of MDR bacteria	69 (81.2)	98 (18.1)	<0.001
VAP	31 (36.5)	94 (17.4)	<0.001
AKI	20 (23.5)	194 (35.9)	0.03
Myocardial dysfunction	4 (4.7)	10 (1.8)	0.10
Shock	61 (71.8)	424 (78.4)	0.22
Outcomes			
LOS ICU, days	22 (12–37)	16 (8–28)	0.001
LOS Hospital, days	30 (21–50)	25 (12–42)	0.008
IMV days	15 (10–30)	12 (6–24)	0.01
ICU mortality	40 (47.1)	208 (38.4)	0.16

Continuous variables are shown as median values and percentiles Q1–Q3. Categorical variables are shown as number of cases (n) and percentage (%). (LDH: Lactate dehydrogenase; C-RP: C-reactive protein; CPK: creatine phosphokinase; PCT: procalcitonin; VAP: ventilator associated pneumonia; AKI: acute kidney injury; LOS length of stay; ICU: intensive care units; Gap-ICU: time in days from hospital admission to ICU admission; Chest X-ray cutoff: more than 2 lung fields occupied by infiltrates on chest X-ray; MDR: multi-drug resistant bacteria; EAT: empiric antibiotic treatment; AEAT: appropriate empiric antibiotic treatment).

When patients who did not receive EAT (n = 28) are also considered within inappropriate EAT, a total of 113 (17.3%) patients meet IEAT criteria (global IEAT). The incidence of VAP (36.3% vs. 17.4%, $p < 0.001$) and crude ICU mortality (49.6% vs. 38.4%, $p = 0.03$) were higher in this subgroup compared to those with AEAT.

Of the 654 patients with COI, 135 (20.6%) developed VAP. The characteristics of patients according to the development of VAP or not are shown in Table 3. Strikingly, patients with VAP had lower severity and lower inflammation on ICU admission. The incidence of EAT and crude ICU mortality did not differ between patients with and without VAP. However, AEAT was more common in patients without VAP.

Table 3. Patients with bacterial coinfection (COI) according to whether or not they developed ventilator-associated pneumonia (VAP).

Variables #	No VAP (n = 519)	VAP (n = 135)	*p*-Value
General Characteristics			
Age, years	59 (47–70)	61 (52–71)	0.09
Male sex	337 (64.9)	96 (71.1)	0.21
APACHE II score	19 (14–25)	17 (12–21)	<0.001
SOFA score	7 (5–10)	7 (4–10)	0.44
Gap-ICU, days	1 (0–2)	1 (0–2)	0.55
Chest X-ray cutoff	268 (51.6)	92 (68.1)	0.001
Laboratory			
WBC $\times 10^3$	8.3 (3.7–13.7)	9.0 (5.0–13.3)	0.64
LDH U/L	600 (450–757)	590 (480–720)	0.62
C-RP mg/mL	33.0 (19.1–85.0)	22.6 (12.6–40.0)	<0.001
PCT ng/mL	7.0 (1.5–24.0)	1.5 (0.4–10.1)	<0.001
Creatinine mg/dL	1.1 (0.7–1.8)	0.9 (0.7–1.4)	0.01
CPK	338 (138–657)	268 (141–400)	0.01
Lactate mmol/L	3.2 (1.2–4.8)	2.3 (1.6–3.7)	<0.001
D-dimer	6667 (3900–11,220)	4000 (1000–9940)	<0.001
Comorbidities			
COPD	109 (21.0)	17 (12.6)	0.03
Asthma	32 (6.1)	9 (6.7)	0.98
Chr. Heart Dis	47 (9.0)	10 (7.4)	0.66
Chr.Renal Dis.	41 (7.9)	11 (8.1)	1.00
Hematologic Dis.	34 (6.5)	8 (5.9)	0.94
Pregnancy	46 (8.8)	7 (5.2)	0.22
Obesity	134 (25.8)	49 (36.3)	0.02
Diabetes	34 (6.5)	23 (17.0)	<0.001
Immunosuppression	65 (12.5)	12 (8.9)	0.30
Treatment and complications			
Corticosteroids	310 (59.7)	90 (66.7)	0.16
EAT	501 (96.5)	125 (92.6)	0.07
AEAT	451 (86.9)	98 (72.6)	<0.001
Global IEAT	72 (13.9)	41 (30.4)	<0.001
AKI	188 (36.2)	32 (23.7)	0.008
Myocardial dysfunction	10 (1.9)	5 (3.7)	0.20
Shock	403 (77.6)	95 (70.4)	0.09

Table 3. *Cont.*

Variables #	No VAP (n = 519)	VAP (n = 135)	*p*-Value
	Outcomes		
LOS ICU, days	14 (7–23)	31 (19–48)	<0.001
LOS Hospital, days	23 (12–36)	44 (27–59)	<0.001
IMV days	10 (6–19)	27 (17–41)	<0.001
ICU mortality	208 (40.1)	56 (41.5)	0.84

Continuous variables are shown as median values and percentiles Q1-Q3. Categorical variables are shown as number of cases (n) and percentage (%). (LDH: Lactate dehydrogenase; C-RP: C-reactive protein: CPK: creatine phosphokinase; PCT: procalcitonin; VAP: ventilator associated pneumonia; AKI: acute kidney injury; LOS length of stay; ICU: intensive care units; Gap-ICU: time in days from hospital admission to ICU admission; Chest X-ray cutoff: more than 2 lung fields occupied by infiltrates on chest X-ray; MDR: multi-drug resistant bacteria; EAT: empiric antibiotic treatment; AEAT: appropriate empiric antibiotic treatment, Global IEAT: includes patients with IEAT and those without EAT).

The variables included in the multivariate GLM model for VAP were as follows: AKI, EAT, global IEAT, diabetes, D-dimer, lactate, PCT, CRP, chest X-ray cutoff, and APACHE II according to the significance in Table S3 (Supplementary Materials). Only IEAT (OR = 2.23, 95%CI 1.31–3.73) and chest X-ray cutoff (OR = 1.62, 95%CI 1.07–2.42) were variables associated with the development of VAP (Figure S2, Supplementary Materials).

A total of 264 patients with COI died. Patients who died were older, had a higher degree of severity and inflammation, and had more comorbidities and complications (Table S3 in the Supplementary Materials). However, EAT (96.9% vs. 93.3%, $p = 0.09$) and AEAT (86.2% vs. 80.7%, $p = 0.07$) were not different between survivors and non-survivors. In addition, global IEAT was more common in non-survivors (21.2% vs. 14.6%, $p = 0.03$).

The variables included in the multivariate GLM model for crude ICU mortality were myocardial dysfunction, AKI, EAT, global IEAT, immunosuppression, hematologic disease, chronic heart disease, D.dimer, lactate, PCT, chest X-ray cutoff, GAP-UCI, SOFA, APACHE II and age according to significance in Table S4 (Supplementary Materials). Global IEAT (OR = 1.89, 95%CI 1.13–3.14) but not EAT (OR = 0.58, 95%CI 0.23–1.46) was associated with ICU mortality (Figure S3, Supplementary Materials).

3.3. Patients Without Bacterial Coinfection (No-COI)

Of the 3543 patients without COI, 3076 (86.8%) received EAT. Patients with EAT had higher levels of organ dysfunction and inflammation, received more steroids and had a higher incidence of shock on admission compared to patients without EAT. VAP and all-cause mortality in the ICU did not differ between groups (Table 1).

The impact of EAT on outcome can only be causally assessed in a randomised clinical trial. As this is not possible, and in an attempt to address the bias of an observational study, propensity score matching was applied to the non-COI population. For this purpose, the MatchIt package [37] of the R program was used with a "full" method and a caliper of 0.2 (more detailed information on propensity matching can be found in the Supplementary Materials).

After propensity score matching, there was a loss of only 23 patients who could not be matched. Finally, the matched cohort (n = 3520) has 467 controls and 3053 cases receiving EAT. The summary of balance for all data and matched data are shown in Table S5 and in Figures S4 and S5 in the Supplementary Materials.

No impact of EAT was observed on the development of VAP (Figure 2) or on 28-day mortality in the ICU (Figure 3).

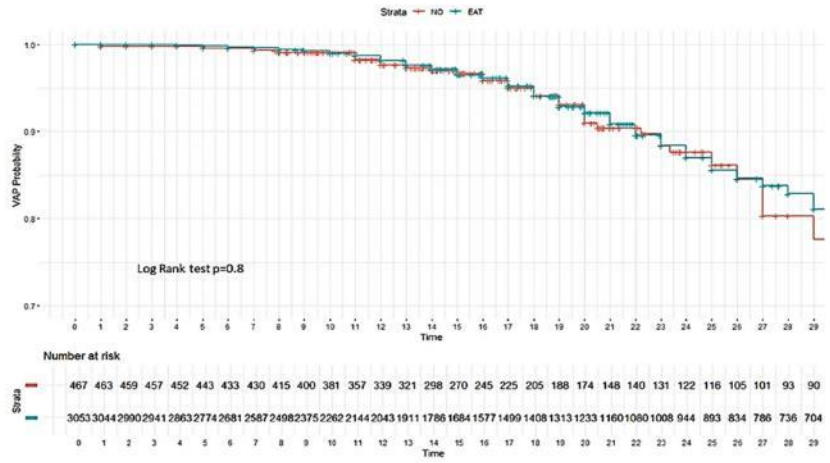

Figure 2. Kaplan–Meier plot for development of ventilator-associated pneumonia (VAP) according to whether or not patients without bacterial co-infection received empiric antibiotic treatment (EAT). As can be seen, there are no significant differences in the probability of developing VAP between the group with EAT (blue line) and the group without EAT (red line) (log rank test $p = 0.8$).

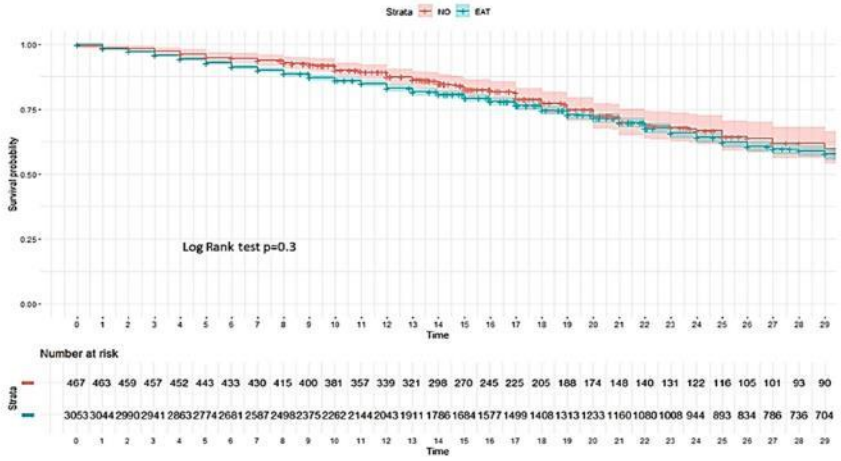

Figure 3. Kaplan–Meier plot for development of all-cause ICU mortality according to whether or not patients without bacterial co-infection received empiric antibiotic treatment (EAT). As can be seen, there are no significant differences in the survival probability between the group with EAT (blue line) and the group without EAT (red line) (log rank test $p = 0.3$).

3.4. Linear Models in Matched Cohort of Patients Without Coinfection

3.4.1. Risk Factors Associated with the Development of Ventilator-Associated Pneumonia (VAP)

The characteristics of patients in the matched cohort according to whether they developed VAP or not are shown in Table S6 in the Supplementary Materials. Patients with VAP had a higher mean age (62 vs. 60; $p < 0.001$) years, a higher degree of hypoperfusion (lactate

2.8 mmol/L vs. 2.2 mmol/L; $p < 0.001$) and a higher incidence of myocardial dysfunction (9.9% vs. 4.8%; $p < 0.001$). In addition, diabetes (17.5% vs. 11.2%; <0.001) and steroid use (71.1% vs. 54.3%; $p < 0.001$) were more common in this group. However, EAT was not associated with VAP on univariate analysis.

There was also no effect of EAT on the proportional hazard of VAP (HR = 1.00, 95%CI 0.78–1.27) when Cox regression was performed adjusting the model for age, chest X-ray cutoff, steroids, diabetes, obesity and lactate with a Shoenfeld global test of 0.35 (Figure 4 and Table S7 in the Supplementary Materials).

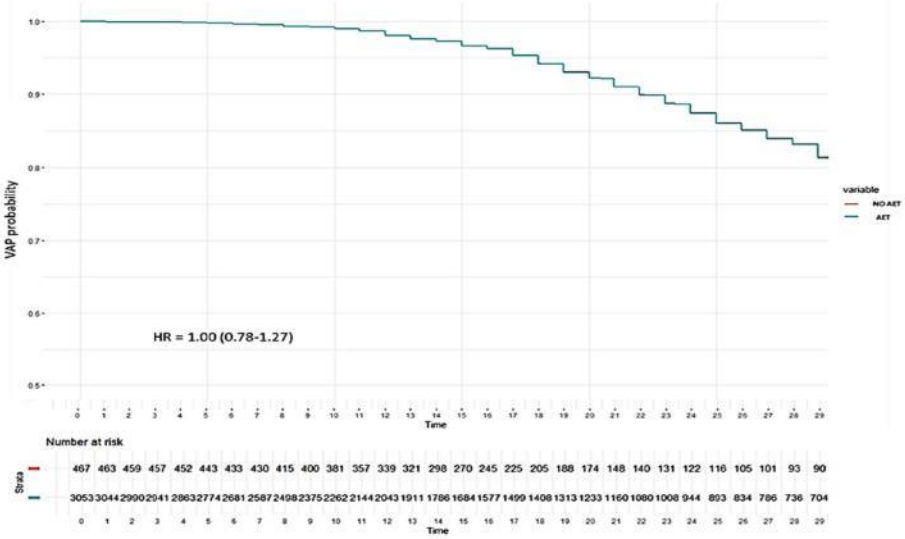

Figure 4. Cox Hazard regression plot for VAP probability according to received empiric antibiotic treatment (EAT) or not in matched cohort of patients without coinfection. As can be seen, the lines are almost superimposed, given that there are no significant differences in the proportional daily risk of developing VAP between the group with (blue line) and without (red line) EAT (HR = 1.0).

EAT was also not associated with the development of VAP in the logistic regression model (OR = 1.02, 95%CI 0.79–1.39). More than 2 infiltrated lung fields (OR = 1.63, 95%CI 1.34–2.0) and steroid administration (OR = 1.97, 95%CI 1.62–2.40) were the variables independently associated with an increased risk of VAP (Figure S6, Supplementary Materials).

3.4.2. Risk Factors Associated with All-Cause ICU Mortality

Of the 3520 patients in the matched cohort, 1192 (33.8%) died. As expected, the deceased patients were older (66 years vs. 58 years, $p < 0.001$), had higher APACHE II (17 vs. 14, $p < 0.001$) and SOFA (7 vs. 6, $p < 0.001$) severity, and higher levels of inflammation. In addition, chronic kidney disease, haematological disease, diabetes and immunosuppression, as well as the presence of AKI, shock and myocardial dysfunction were more common in non-surviving patients (Table S8 in the Supplementary Materials). However, EAT did not appear to be associated with ICU mortality in the univariate analysis.

There was also no effect of EAT on the proportional hazard of ICU mortality (HR = 1.02, 95%CI 0.85–1.22) when Cox regression analysis was performed adjusting the model for age, chest X-ray cut-off, AKI, myocardial dysfunction, VAP, steroids, immunodepression, diabetes, haematological disease, chronic kidney disease, shock, D-dimer, lactate, PCT,

WBC, LDH, SOFA, APACHEII, GAP_ICU and sex according to significance in univariate analysis. The Schoenfeld global test was $p < 0.001$ (Figure 5 and Table S9 in the Supplementary Materials).

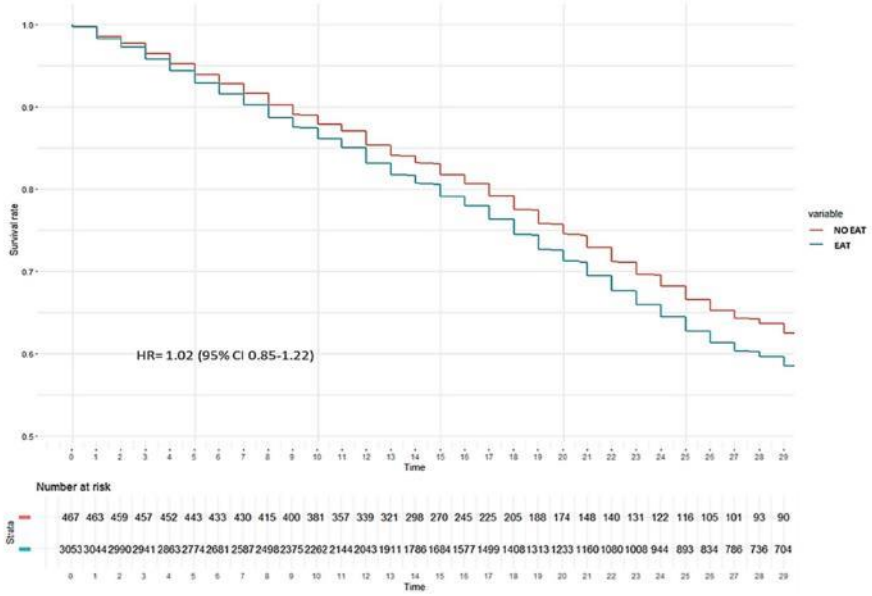

Figure 5. Cox Hazard regression plot for all-cause ICU mortality according to received empiric antibiotic treatment (EAT) or not in matched cohort of patients without coinfection. As can be seen, no significant differences in the proportional daily risk ICU survival between the group with (blue line) and without (red line) EAT was observed (HR = 1.02).

EAT was also not associated with all-cause ICU mortality in the logistic regression model (OR = 1.02, 95%CI 0.81–1.28). (Figure S7, Supplementary Materials).

3.5. Non-Linear Analysis–Random Forest Model (RF)

3.5.1. Factors Associated with VAP According to Non-Linear Model

A random forest classifier (RF) model was developed to study the contributions of confounding variables to the dependent variable (VAP) in a non-linear way. All independent variables were included in the RF model and a non-linear relationship with VAP was found. The RF model for VAP had an OOB error rate estimate of 16.0%.

Twelve variables had an impact of more than 10% on the reduction in model accuracy, and twelve variables were associated with a >50% reduction in GINI in the RF model (Figure 6A and Table S8 in the Supplementary Materials). However, AET was not an important variable for VAP development in the RF model.

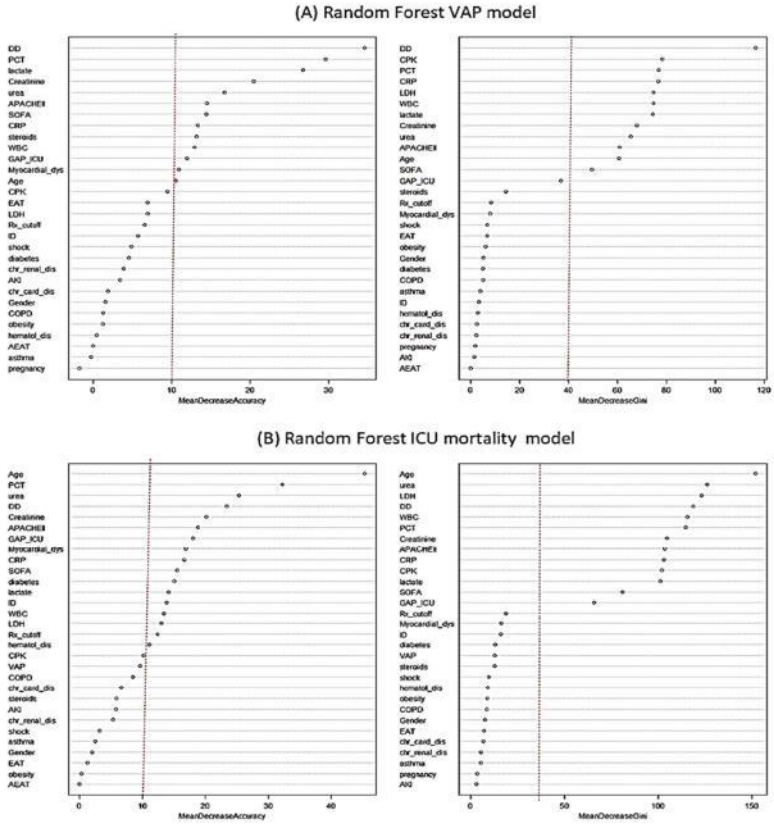

Figure 6. Contribution of each confounding variable according to the random forest (RF) model for variables associated with the development of ventilator-associated pneumonia (VAP) (**A**) and all-cause ICU mortality (**B**). As can be seen in the figure, the empiric antibiotic treatment (EAT) variable is below the cut-off points considered to determine which variables are important in the model (dotted red line) for the development of VAP (**A**) and for ICU mortality (**B**). Abbreviations: cut: cut-off; APACHE II: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential organ failure assessment; EAT: Empiric antibiotic treatment; VAP: ventilator-associated pneumonia; AEAT: Adecuate empiric antibiotic treatment; CPK: creatine phosphokinase; DD: D dímer; WBC: White blood cells; COPD: chronic obstructive pulmonary disease; dis: disfunction; Chr_Card_dis; chronic cardiac disease; AKI: acute kidney injury; CRP:C-reactive protein; GAP_ICU_cut: time elapsed between diagnosing pandemic viral infection and admission to ICU; Chr_renal_dis: Chronic renal disease; ID: immunosuppression; Rx-cutoff: >2 fields with infiltrations in chest X-ray; PCT: procalcitonin; Hematol-dis: Hematologic disease; LDH: Lactate dehydrogenase.

3.5.2. Factors Associated with All-Cause ICU Mortality According to No-Linear Model

A random forest classifier (RF) model was developed to study the contributions of confounding variables to the dependent variable (non-survivors) in a non-linear way. All independent variables were included in the RF model and non-linear relationship with ICU mortality was found. The RF model for VAP had an OOB error rate estimate of 27.8%.

Seventeen variables had an impact of more than 10% on the reduction in model accuracy, and thirteen variables were associated with a >50% reduction in GINI in the RF model (Figure 6B and Table S9 in the Supplementary Materials). However, AET was not an important variable for all-cause ICU mortality in the RF model.

4. Discussion

In this large multicentre cohort of critically ill patients with pandemic viral pneumonia (influenza A[H1N1] and COVID-19), our main conclusion is that empirical antibiotic treatment administered at ICU admission was not associated with a reduction in ventilator-associated pneumonia or ICU mortality in patients without microbiologically confirmed bacterial co-infection. This finding remained consistent after adjusting for confounders using propensity score matching and was confirmed by both traditional multivariate models (Cox and GLM) and non-linear approaches (random forest), reinforcing the robustness of the results.

In contrast, among patients with confirmed bacterial co-infection, EAT was associated with a lower incidence of VAP and ICU mortality, underscoring the importance of timely and appropriate antibiotic administration when bacterial pathogens are present. This highlights a key clinical distinction: while early antibiotics are warranted in patients with confirmed or strongly suspected bacterial infections, their indiscriminate use in all cases of viral pneumonia may be unjustified and potentially harmful.

Evidence regarding the impact of EAT in viral respiratory infections remains limited and heterogeneous [18,23,38,39]. Previous studies have varied widely in terms of population, design, and definitions of co-infection, limiting comparability [19]. Notably, a large international study of 3200 critically ill patients [21] found no effect of EAT on ventilator-associated lower respiratory tract infection, although that analysis did not adjust for baseline differences. A follow-up study evaluating PCT for detecting co-infection also failed to demonstrate a survival benefit from EAT in COVID-19 patients [9]

Other observational studies raise additional concerns. Hovind et al. [40] observed in 3979 patients hospitalized for a viral respiratory infection (influenza virus H3N2, H1N1, influenza B, respiratory syncytial virus [RSV], human metapneumovirus [hMPV] or severe acute respiratory syndrome coronavirus-2 [SARS-CoV-2]) that 67.7% received EAT. When EAT was initiated on admission, it was associated with increased in-hospital mortality (OR = 2.25, 95%CI 1.26–4.02). In addition, patients with EAT had a longer hospital stay. However, the number of critically ill patients in this study is very small (<2%).

Moretto et al. [20] studied the effect of EAT on in-hospital mortality using Cox hazard regression with propensity-matched variable adjustment. Of the 222 patients included, an adverse event (death or ICU transfer) was observed in 60 patients (34%) in the antibiotic group compared with 4 patients (8%) in the no antibiotic group (HR = 2.94 [95%CI: 1.07–8.11]; $p = 0.04$). After propensity score matching, there was no significant association be-tween antibiotic use and outcome (HR = 1.238; 0.77–2.00, $p = 0.37$).

Yin et al. [41], in hospitalized patients with moderate COVID-19, found that during the 30-day follow-up period, 375 (27.3%) of the 1373 patients admitted with non-severe COVID-19 progressed to severe disease. The proportion of patients who progressed to severe COVID-19 was higher in the EAT group compared to the non-EAT group (31.74% vs. 21.94%; $p < 0.0001$). In the Cox model, early antibiotic use was associated with a higher likelihood of progression to severe COVID-19 [aHR = 1.5; 95%CI 1.2–1.9]. After propensity matching, the results remained consistent, showing a higher risk of progression to severe COVID-19 in the EAT group (adjusted HR 1.416, 95%CI 1.069–1.876). Finally, the meta-analysis by Lansbury et al. [19] with over 3800 patients, evidences a low proportion of patients with COVID-19 presenting with COI, whereby the authors conclude that these

findings do not support the routine use of antibiotics in the treatment of confirmed COVID-19 infection.

Among critically ill patients, available evidence remains sparse. A small study by Buetti et al. [42] found no benefit of EAT in ICU patients, while a larger study by Saseedharan et al. [38] supported prophylactic antibiotics without comparative data. The study by Wendel–García et al. [18] with a large number of critically ill patients in a Spanish multicentre study concludes, after adjusting covariates by propensity matching, that the administration of EAT is associated with a lower incidence of respiratory superinfection and lower mortality. These conclusions are in contrast to our results, also developed in a Spanish multicentre database, but methodological differences limit comparison. The main difference between the studies is that our population includes not only patients with COVID-19 but also with influenza A (H1N1). Other differences between the studies relate to the inclusion of patients with confirmed fungal infections, the use of broader definitions of respiratory superinfection (including VAP and ventilator-associated tracheobronchitis), and the use of a 24 h time limit from intubation to define empirical antibiotic treatment, which could introduce misclassification bias. In addition, our most inclusive cohort (comprising both SARS-CoV-2 and influenza A [H1N1]) had a higher coinfection rate (15% versus 4%), which is likely to reflect differences in pathogen biology. Notably, influenza A (H1N1) carries a higher risk of bacterial coinfection than SARS-CoV-2, and there are significant differences in the epidemiology of coinfecting bacteria. This could affect prescribing patterns and observed outcomes.

Because viral and bacterial pneumonias share overlapping clinical features and biomarkers, clinicians frequently initiate EAT to avoid undertreatment—an approach widely endorsed by professional societies [5,7,17,35]. Yet, our findings argue for a more selective, evidence-based strategy. Tools such as PCT [9,14,15,24,43] and rapid molecular diagnostics [31,44,45] may help identify true co-infections and enable early antibiotic de-escalation. Notably, PCT performs better in influenza than in COVID-19 [8,9]. Unnecessary broad-spectrum antibiotic use during the COVID-19 pandemic likely contributed to increased antimicrobial resistance [10,11,13,46,47], and over 80% of COVID-19 patients received EAT despite low confirmed co-infection rates [9,19,20,38,40]. Spanish registry data showed VAP incidence more than doubled during the pandemic [48].

Our results strongly indicate that empirical antibiotic treatment should not be used for patients with respiratory infections caused by pandemic viruses in the absence of bacterial co-infection. Therefore, rather than adopting EAT as standard practice, the clinical approach should focus on identifying which patients have COI and would benefit most from antibiotics. Antibiotics should be administered promptly in cases of confirmed or highly suspected bacterial infection, but discontinued early if not justified.

Our study has several limitations. The observational design precludes causal inference. Residual confounding is possible. Data on timing of VAP onset were unavailable, limiting early/late stratification. Differences in co-infection rates and diagnostic approaches across centres may affect generalizability. Nonetheless, the use of robust statistical methods, including propensity score adjustment and machine learning, strengthens the reliability of our findings.

5. Conclusions

Our findings suggest that empirical antibiotic treatment should be initiated promptly when there is a high probability of bacterial co-infection. However, empirical antibiotic treatment at ICU admission did not reduce VAP incidence or ICU mortality in critically ill patients with viral pneumonia who lacked confirmed bacterial co-infection. Our findings

support a more targeted approach to antibiotic use, guided by microbiology, biomarkers and stewardship principles.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/antibiotics14060594/s1, Figure S1: Flow chart of included patients; Figure S2: Variables associated with the development of ventilator-associated pneumonia (VAP) in multivariate logistic regression model (GLM); Figure S3: Variables associated with the crude ICU mortality in multivariate logistic regression model (GLM); Figure S4: Histograms of propensity scores before and after matching; Figure S5: Plot of mean differences between unadjusted (no matched) and adjusted (matched) covariates; Figure S6: Variables independently associated with VAP in logistic regression model; Figure S7: Variables independently associated with all-cause ICU mortality in logistic regression model; Table S1: Microorganisms isolated (in order of frequency) in 654 patients with bacterial co-infection; Table S2: Patients with COI according to ICU outcome; Table S3: Summary of balance for all data (no-matched) and matched data; Table S4: Characteristics of matched cohort of patients without Coinfection according to ventilator associated pneumonia; Table S5: Variables associated with VAP in the Cox Hazard regression analysis; Table S6: Characteristics of matched cohort patients according to all-cause ICU mortality in patients without bacterial coinfection; Table S7: Variables associated with all-cause ICU mortality in the Cox Hazard regression analysis; Table S8: Importance of variables for VAP according to random forest model; Table S9: Importance of variables for all-cause ICU mortality according to random forest model.

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Institutional Review Board Statement: GETGAG (Grupo Español de Trabajo Gripe A Grave) registry was approved by the Ethics Committee of the of the Joan XXIII University Hospital (CEI no. 11809) and by each of the participating centres. COVID-19 Registry was retrospectively registered on ClinicalTrials.gov (NCT 04948242) on 30 June 2021.

Informed Consent Statement: The need for informed consent was waived by the Institution's Internal Review Committee (Comitè Ètic d'Investigació amb Medicaments [CEIm] del Institut d'Investigació Sanitària Pere Virgili [IISPV]IRB# CEIM/066/2020). Local researchers maintained contact with a study team member, and participating hospitals obtained local ethics committee approval. Both studies were carried out according to the principles of the Declaration of Helsinki and the Clinical Trials Directive 2001/20/EC of the European Parliament relating to the Good Clinical Practice guidelines.

Data Availability Statement: The corresponding author (AR) had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors approved the final version of the manuscript. The views expressed in this article are those of the authors and not necessarily those of the SEMICYUC. The data supporting the conclusions of this study are available from the Spanish Society of Critical Care (SEMICYUC), but restrictions apply to the availability of these data, which were used under SEMICYUC authorization for the present study and are therefore not publicly available. However, the data can be obtained from the corresponding author (AR) upon reasonable request and with the permission of SEMICYUC.

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5. Resumen global de los resultados

5.1 Determinantes pronósticos al ingreso en pacientes con neumonía grave por virus pandémicos (influenza A H1N1 y SARS-CoV-2)

Para identificar los factores de riesgo de mortalidad se realizó un primer trabajo donde se analizaron 8.902 pacientes en 184 unidades de cuidados intensivos españolas con neumonía grave causada por virus pandémicos, incluyendo gripe A (41,6 %) y COVID-19 (58,4 %). La cohorte presentó una mediana de edad de 60 años y predominó el sexo masculino (65,8 %). El perfil clínico inicial reflejaba una gravedad intermedia, con valores medianos de APACHE II de 14 y SOFA de 5. Las comorbilidades más prevalentes fueron obesidad, diabetes y EPOC. La mortalidad en UCI alcanzó el 25,8 %, y los pacientes que fallecieron eran significativamente mayores, con mayor puntuación en escalas de gravedad, y mayor frecuencia de shock, disfunción orgánica, coinfección bacteriana y uso de soporte vital avanzado (ver tabla 4).

Tabla 4 (Tabla 1 del artículo 1): Características basales de los 8902 pacientes incluidos en el análisis, categorizados según el desenlace en UCI y el punto de corte de las variables.

Variable	Whole population (n= 8,902)	Survival (n=6,608)	Non-survival (n=2,294)	p-value
General				
Age, median (Q1-Q3) years	60 (49-70)	58 (48-68)	67 (57-74)	<0.001
Age cut-off ≥ 58 years, n (%)	5177(58.1)	3473 (52.6)	1704 (74.3)	<0.001
Male sex, n (%)	5855 (65.8)	4248 (64,3)	1607 (70.1)	<0.001
APACHE II, median (Q1-Q3)	14 (10-19)	13 (10-17)	17 (13-22)	<0.001
APACHE II cut-off ≥ 13, n (%)	5309 (59.6)	3536 (53.5)	1773 (77.3)	<0.001
SOFA score, median (Q1-Q3)	5 (3-7)	4(3-7)	6(4-9)	<0.001
SOFA cut-off ≥ 4, n (%)	6274 (70.5)	4299 (65.1)	1975 (86.1)	<0.001
GAP UCI, median (Q1-Q3)	1 (1-3)	1 (1-3)	2 (0-4)	<0.001
GAP UCI cut-off ≥ 1 day, n (%)	6804 (76.4)	5085 (77.0)	1719 (74.9)	0.053
GAP Diagnosis, median (Q1-Q3)	4 (1-7)	3 (1-7)	4 (1- 7)	0.012
GAP diagnosis cut-off ≥ 3 days, n (%)	5413 (60.8)	3943 (59.7)	1470 (64.1)	<0.001
> 2 fields with infiltrations in chest X-ray, n (%)	5343 (60.0)	3775 (57.1)	1568 (68.4)	<0.001
Antiviral vaccine, n (%)	1333 (14.9)	885 (13.4)	448 (19.5)	<0.001
Shock at ICU admission, n (%)	3549 (39.9)	2286 (34.6)	1263 (55.1)	<0.001
Laboratory				
White blood cells count, median (Q1-Q3) $x10^3$	8.6 (5.7-12.5)	8.5 (5.7-12.1)	9.0 (5.8-13.7)	<0.001
White blood cells count cut-off ≤ 8.5 $x10^3$, n (%)	4405 (49.5)	3351 (50.7)	1054 (45.9)	<0.001
Lactate dehydrogenase, median (Q1-Q3) U/L	542 (403-687)	524 (378-665)	590 (458-749)	<0.001
Lactate dehydrogenase cut-off ≥ 500 U/L, n (%)	5157 (57.9)	3593 (54.4)	1564 (68.2)	<0.001
C reactive protein, median (Q1-Q3) mg/dL	19.6 (9.8-34.7)	19.0(9.5-34.4)	21.1 (10.4-35.4)	0.001
C reactive protein cut-off ≥20 mg/dL, n (%)	4387 (49.3)	3184 (48.2)	1203 (52.4)	<0.001
Procalcitonin, median (Q1-Q3) ng/mL	0.88 (0.20-5.67)	0.83 (0.20-5.08)	1.04 (0.23-8.20)	<0.001
Procalcitonin cut-off ≥0.80 ng/mL, n (%)	4606 (51.7)	3350 (50.7)	1256 (54.8)	0.001
Lactate, median (Q1-Q3) mmol/L	2.0 (1-4-3.3)	2.0 (1.3-3.2)	2.2 (1.4-3.8)	<0.001
Lactate cut-off ≥ 2mmol/L, n (%)	4660 (52.3)	3369 (51.0)	1291 (56.3)	<0.001
Creatinine, median (Q1-Q3) mg/dL	0.89 (0.7-1.2)	0.85 (0.68-1.12)	1.01 (0.75-1.50)	<0.001
Creatinine cut-off ≥0.85 mg/dL, n (%)	4841 (54.4)	3330 (50.4)	1511 (65.9)	<0.001
D dimer, median (Q1-Q3) ng/mL	3071 (971-6604)	2716 (900- 6000)	4180 (1200-8680)	<0.001
D dimer cut-off ≥ 2700 ng/mL, n (%)	4663 (52.4)	3314 (50.2)	1349 (58.8)	<0.001
creatine phosphokinase, median (Q1-Q3) U/L	216 (100-420)	210 (97-414)	234 (111-442)	0.001
creatine phosphokinase cut-off ≥ 200 U/L, n (%)	4707 (52.9)	3433 (52.0)	1274 (55.5)	0.003
Comorbidities				
Diabetes mellitus, n (%)	1196 (13.4)	756 (11.4)	440 (19.2)	<0.001
Asthma, n (%)	698 (7.7)	556 (8.4)	142 (6.2)	0.001
COPD, n (%)	1281 (14.4)	936 (14.2)	345 (15.0)	0.32
Chronic heart disease, n (%)	623 (7.0)	418 (6.3)	205 (8.9)	<0.001
Chronic liver disease, n (%)	595 (6.7)	357 (5.4)	238 (10.4)	<0.001
Pregnancy, n (%)	480 (5.4)	399 (6.0)	81 (3.5)	<0.001
Obesity, n (%)	3046 (34.2)	2256 (34.1)	790 (34.4)	0.81
Human immunodeficiency virus, n (%)	144 (1.6)	107 (1.6)	37 (1.6)	1.00
Hematologic disease, n (%)	436 (4.8)	237 (3.6)	199 (8.7)	<0.001
Immunosuppression, n (%)	711 (8.0)	401 (6.0)	310 (13.5)	<0.001
Treatment				
Steroids, n (%)	5275 (59.2)	3746 (56.7)	1529 (66.7)	<0.001
Antibiotics (AB) at ICU admission, n (%)	7410 (83.2)	5428 (82.1)	1982 (86.4)	<0.001
Appropriate empiric AB treatment, n (%)	951 ((10.7)	671 (10.2)	280 (12.2)	0.007
High flow nasal cannula at admission, n (%)	1438 (16.1)	1138 (17.2)	300 (13.1)	<0.001
Invasive mechanical ventilation, n (%)	4252 (47.8)	2751 (41.6)	1501 (65.4)	<0.001
Most common aetiology of coinfection				
Coinfection, n (%)	1211 (100)	810 (12.3)	401 (17.5)	<0.001
Methicillin- sensitive *S. aureus* (MSSA), n (%)	172 (14.2)	111 (13.7)	61 (15.2)	0.47
Pseudomonas aeruginosa, n (%)	143 (11.8)	82 (10.1)	61 (15.2)	0.01
Klebsiella spp. N (%)	85 (7.0)	60 (7.4)	25 (6.2))	0.45
Aspergillus spp, n (%)	78 (6.5)	33 (4.0)	45 (11.2)	<0.001
E. coli, n (%)	69 (5.7)	43 (5.3)	26 (6.3)	0.40
Methicillin- resistant *S. aureus* (MRSA). n (%)	56 (4.6)	33 (4.0)	23 (5.7)	0.19
Acinetobacter spp, n (%)	17 (1.4)	4 (0.5)	13 (3.2)	<0.001
Outcomes				
ICU LOS, median (Q1-Q3) days	13 (6-23)	12 (6-23)	14 (7-24)	0.03
Acute Kidney injury, n (%)	1435 (16.1)	855 (12.9)	580 (25.3)	<0.001

Las variables continuas se muestran como valores medianos y percentiles Q1–Q3. Las variables categóricas se presentan como número de casos (n) y porcentaje (%). (LDH: lactato deshidrogenasa; C-RP: proteína C reactiva; CPK: creatincinasa; PCT: procalcitonina; VAP: neumonía asociada a la ventilación mecánica; AKI: lesión renal aguda; LOS: duración de la estancia; ICU: unidades de cuidados intensivos; Gap-ICU: tiempo

en días desde el ingreso hospitalario hasta el ingreso en UCI; Chest x-ray cutoff: más de 2 campos pulmonares ocupados por infiltrados en la radiografía de tórax; MDR: bacterias multirresistentes; EAT: tratamiento antibiótico empírico; AEAT: tratamiento antibiótico empírico adecuado.)

Para identificar aquellas variables independientes para la mortalidad se diseñaron dos modelos multivariados distintos, uno lineal por regresión logística multivariable, y uno no lineal, Random Forest. La regresión logística identificó 17 factores con asociación independiente a la mortalidad, siendo los más relevantes la infección por *Acinetobacter spp.* (OR 9,95), disfunción miocárdica (OR 3,27) y edad superior a 58 años (OR 2,03). Otros predictores significativos incluyeron inmunosupresión, ventilación mecánica, puntuaciones elevadas de APACHE II y SOFA, y niveles elevados de LDH.

El modelo de Random Forest identificó un conjunto parcialmente diferente de variables importantes, incluyendo edad, APACHE II, SOFA, ventilación mecánica, shock e inmunosupresión como los factores más determinantes. Además, otorgó relevancia pronóstica a biomarcadores como lactato (>2 mmol/L), procalcitonina (>2 ng/mL), dímero-D (>2.700 ng/mL), CPK (>200 U/L) y presencia de EPOC, variables que no alcanzaron significación en el modelo lineal.

En total, trece variables fueron compartidas por ambos enfoques, destacando edad, sexo masculino, gravedad al ingreso, presencia de shock, ventilación mecánica, inmunosupresión, diabetes, enfermedad hematológica, disfunción miocárdica, LDH y creatinina elevada, y hallazgos radiológicos compatibles con neumonía extensa. En cambio, el GLM dio mayor peso a la lesión renal aguda y a la presencia de *Aspergillus* o *Acinetobacter*, mientras que Random Forest destacó biomarcadores inflamatorios y tiempos de acceso al diagnóstico y tratamiento (ver Tabla 5).

Tabla 5 (Tabla 2 del artículo1): Variables asociadas a la mortalidad en UCI en el análisis multivariante lineal (GLM) y el análisis multivariante no lineal (Random Forest). Se muestran las variables significativas en el modelo lineal y aquellas con una importancia superior al 10% en la disminución de la precisión o superior al 50% en la disminución del índice GINI en el modelo no lineal.

	GLM Model		**Random Forest Model**	
Variable	OR	95%CI	Decrease Accuracy	Decrease Gini
Age ≥ 58 years	2.03	1.74-2.36	34.9%	79.2%
APACHE II ≥ 13 points	1.72	1.48-2.02	19.1%	88.1%
SOFA ≥ 4 points	1.47	1.23-1.76	26.0%	65.1%
Shock	1.27	1.09-1.47	16.4%	77.4%
Hematologic disease	1.67	1.26-2.22	19.5%	39.4%
Obesity	1.16	1.01-1.32	-----	92.4%
Diabetes	1.37	1.14-1.65	16.5%	60.6%
Immunosuppression	1.92	1.53-2.42	18.9%	53.0%
Steroids	1.54	1.34-1.77	12.7%	81.6%
Mechanical ventilation	1.94	1.67-2.25	33.0%	88.1%
Myocardial dysfunction	3.27	2.53-4.28	47.2%	63.6%
Acute kidney injury	1.29	1.07-1.55	----	-----
> 2 fields with infiltrations in chest X-ray	1.54	1.34-1.77	16.8%	81.3%
LDH ≥ 500 U/L	1.41	1.22-1.63	11.5%	79.7%
Creatinine ≥ 0.85 mg/dL	1.33	1.14-1.55	13.3%	73.8%
Acinetobacter spp.	9.95	2.61-47.8	----	----
Aspergillus spp.	2.45	1.39-4.33	11.2%	----
Procalcitonin ≥2ng/mL	----	----	23.0%	68.1%
D-dimer ≥ 2700 ng/mL	----	----	21.7%	75.9%
Lactate ≥ 2 mmol/L	----	----	18.1%	79.5%
COPD	----	----	17.4%	61.3%
CPK ≥ 200 U/L	----	----	13.1%	90.6%
GAP-Diagnosis ≥ 3 days	----	----	----	96.9%
WBC count < 8.5 $x10^3$	----	----	----	93.3%
Male	----	----	----	81.3%
GAP-ICU ≤ 1day	----	----	----	77.1%

Abreviaturas**:** OR: razón de momios (Odds Ratio); IC: intervalo de confianza; APACHE II: Evaluación Fisiológica Aguda y de Salud Crónica II; SOFA: Evaluación Secuencial de Fallo Orgánico; LDH: lactato deshidrogenasa; GAP-UCI: tiempo desde el diagnóstico hasta el ingreso en UCI; GAP-Diagnóstico: tiempo desde el inicio de los síntomas hasta el diagnóstico; UCI: Unidad de Cuidados Intensivos; EPOC: enfermedad pulmonar obstructiva crónica; CPK: creatincinasa; WBC: leucocitos totales (recuento de glóbulos blancos).

5.2 Capacidad predictiva de modelos estadísticos clásicos (regresión logística multivariable) en comparación a modelos de aprendizaje automático (Random Forest) en la predicción de mortalidad

En el primer trabajo se aplicaron dos modelos predictivos a la cohorte de 8.902 pacientes con neumonía grave por virus pandémicos: un modelo estadístico lineal (regresión logística multivariable, GLM) y un modelo de aprendizaje automático no lineal (Random Forest, RF). Ambos mostraron un rendimiento muy similar: el GLM alcanzó un área bajo la curva (AUC) de 0,76 (IC 95 %: 0,74–0,78), con una exactitud del 76 %, sensibilidad del 61 % y especificidad del 79 %; el modelo RF presentó una exactitud del 75,6 %, un error out-of-bag del 25,3 % y una concordancia del 70,1 % con el GLM (1.872 casos clasificados igual) (Figuras 1 y 2).

Figura 1 (Figura 3 del artículo 1): Clasificación de los pacientes según el modelo lineal (Modelo Lineal Generalizado - GLM) y el modelo no lineal (Random Forest - RF).

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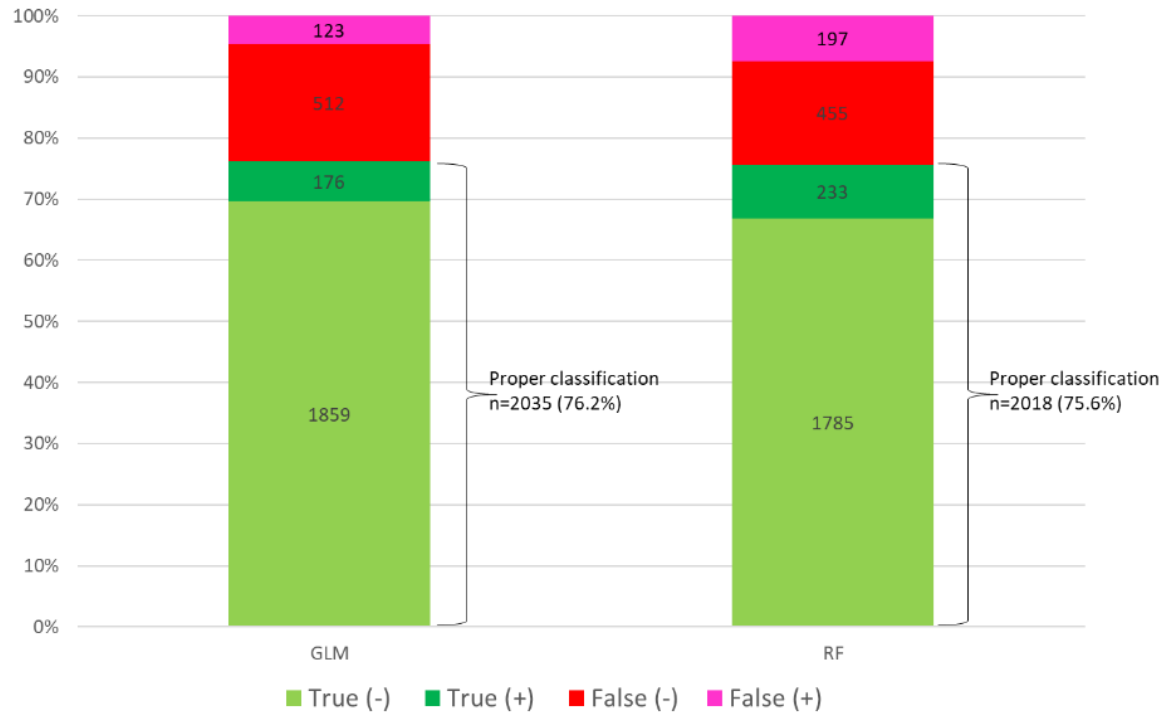
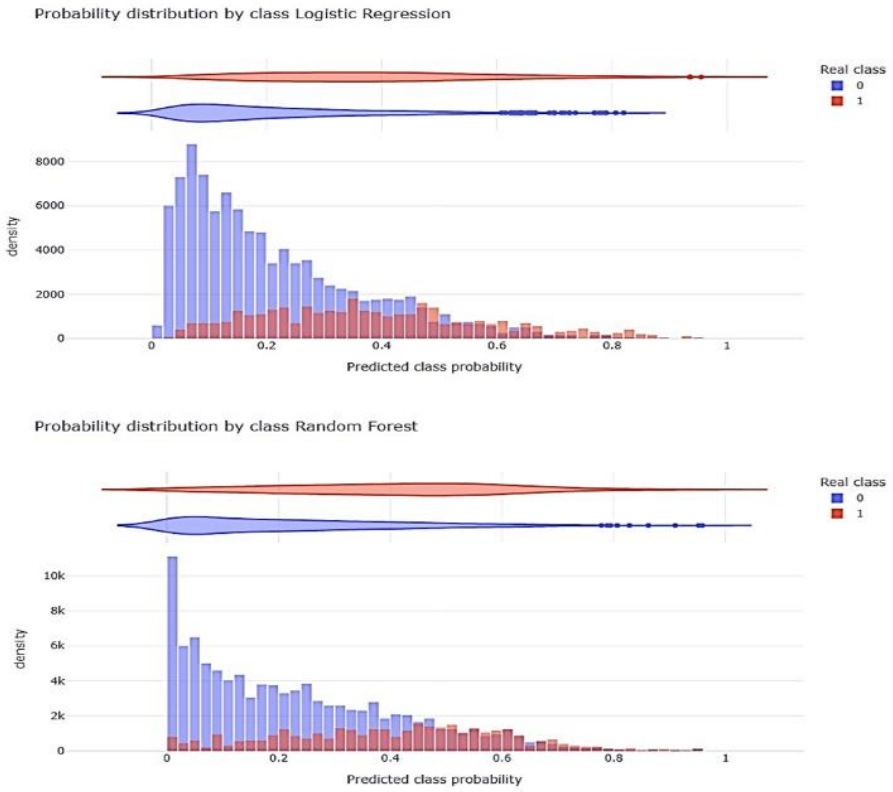


Figura 2 (Figura 4 del artículo 2): Distribución de la probabilidad generada por cada modelo (Clase) con respecto a la observada (Real). (0 = supervivientes; 1 = no supervivientes)



La regresión logística identificó 17 variables asociadas de forma independiente con la mortalidad, entre ellas infección por *Acinetobacter spp.* (OR 9,95), disfunción miocárdica (OR 3,27) y edad >58 años (OR 2,03), además de inmunosupresión, ventilación mecánica, puntuaciones elevadas de APACHE II y SOFA, y LDH elevada. El modelo RF coincidió en muchas de estas variables, pero otorgó mayor relevancia a otras no significativas en el modelo lineal, como la procalcitonina >2 ng/mL, el lactato >2 mmol/L, el dímero D >2.700 ng/mL, la CPK >200 U/L y la presencia de EPOC.

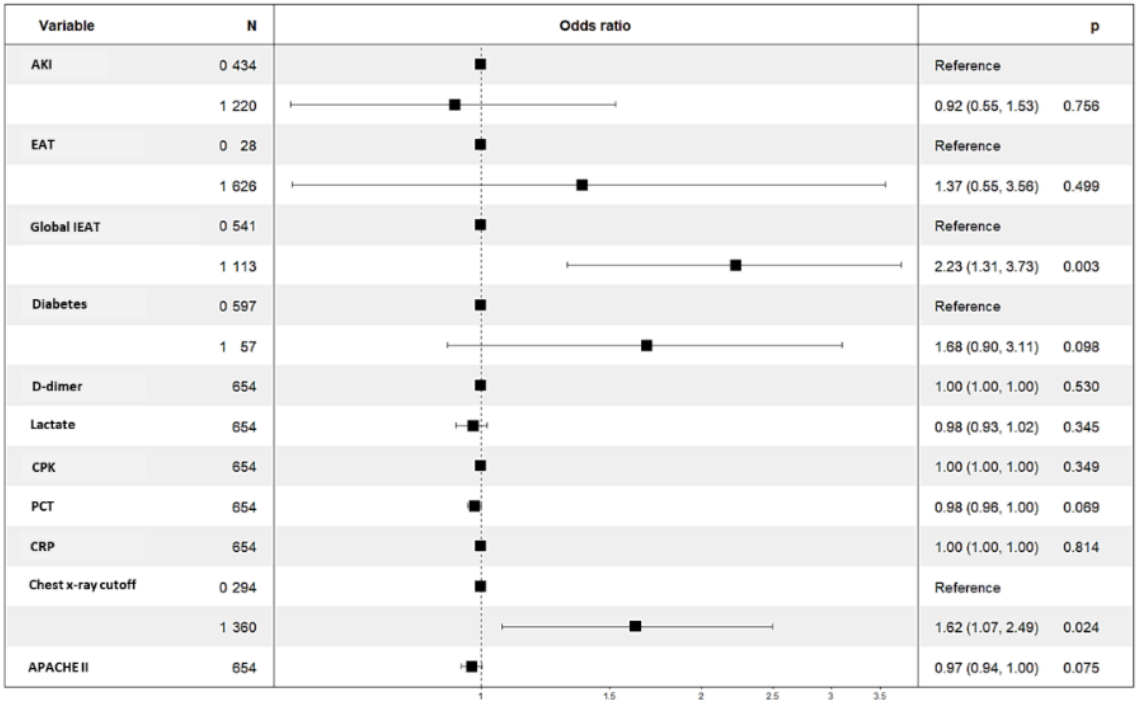
Ambos modelos coincidieron en identificar un conjunto de 13 variables clave con alto valor pronóstico, entre las que se incluyen edad, sexo masculino, gravedad clínica al ingreso (APACHE II, SOFA), presencia de shock, ventilación mecánica, inmunosupresión, diabetes, enfermedad hematológica, disfunción miocárdica, LDH y creatinina elevadas, y un patrón radiológico extenso compatible con neumonía bilateral. No obstante, se

observaron diferencias en las variables secundarias identificadas, lo que demuestra el valor complementario de aplicar ambos enfoques para enriquecer la comprensión del riesgo clínico y mejorar la estratificación pronóstica en pacientes críticos con infecciones virales graves (Tabla 2).

En el segundo estudio, también se emplearon análisis multivariados mediante regresión logística (GLM) y modelos de aprendizaje automático Random Forest (RF) donde se identificaron factores de riesgo complementarios que contribuyeron a caracterizar los desenlaces clínicos.

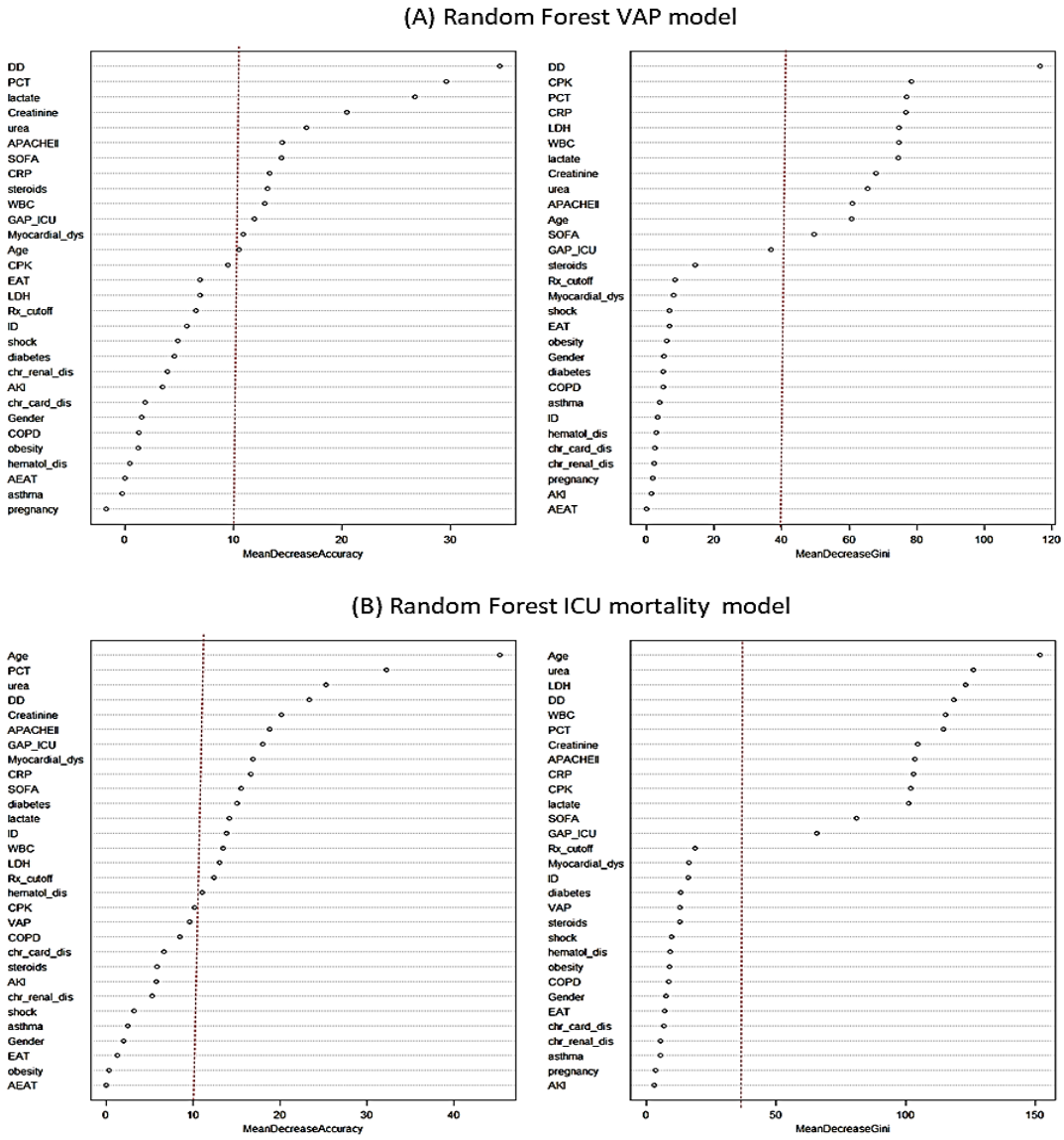
En relación con la aparición de NAVM, ambos modelos coincidieron en señalar como factores de riesgo la edad, el uso de corticoides y la elevación del lactato sérico. Además, el GLM identificó de forma específica la extensión radiológica de los infiltrados pulmonares (Figura 3), mientras que el modelo RF destacó la relevancia de biomarcadores como la procalcitonina (Figura 4A).

Figura 3 (Figura S2 del material suplementario del artículo 2): Variables asociadas al desarrollo de neumonía asociada a la ventilación mecánica (NAVM) en el modelo de regresión logística multivariable (GLM).



(CRP: proteína C reactiva; CPK: creatincinasa; PCT: procalcitonina; AKI: lesión renal aguda; Chest x-ray cutoff: más de 2 campos pulmonares ocupados por infiltrados en la radiografía de tórax; EAT: tratamiento antibiótico empírico; Global IEAT: tratamiento antibiótico empírico globalmente inapropiado, que incluye a los pacientes con IEAT más los pacientes sin EAT)

Figura 4 (Figura 6 del artículo 2). Contribución de cada variable de confusión según el modelo de Random Forest (RF) para las variables asociadas al desarrollo de neumonía asociada a la ventilación mecánica (NAVM) (A) y a la mortalidad global en UCI (B). Como puede observarse en la figura, la variable tratamiento antibiótico empírico (TAE) se sitúa por debajo de los puntos de corte considerados para determinar qué variables son importantes en el modelo (línea roja discontinua), tanto para el desarrollo de NAVM (A) como para la mortalidad en UCI (B).

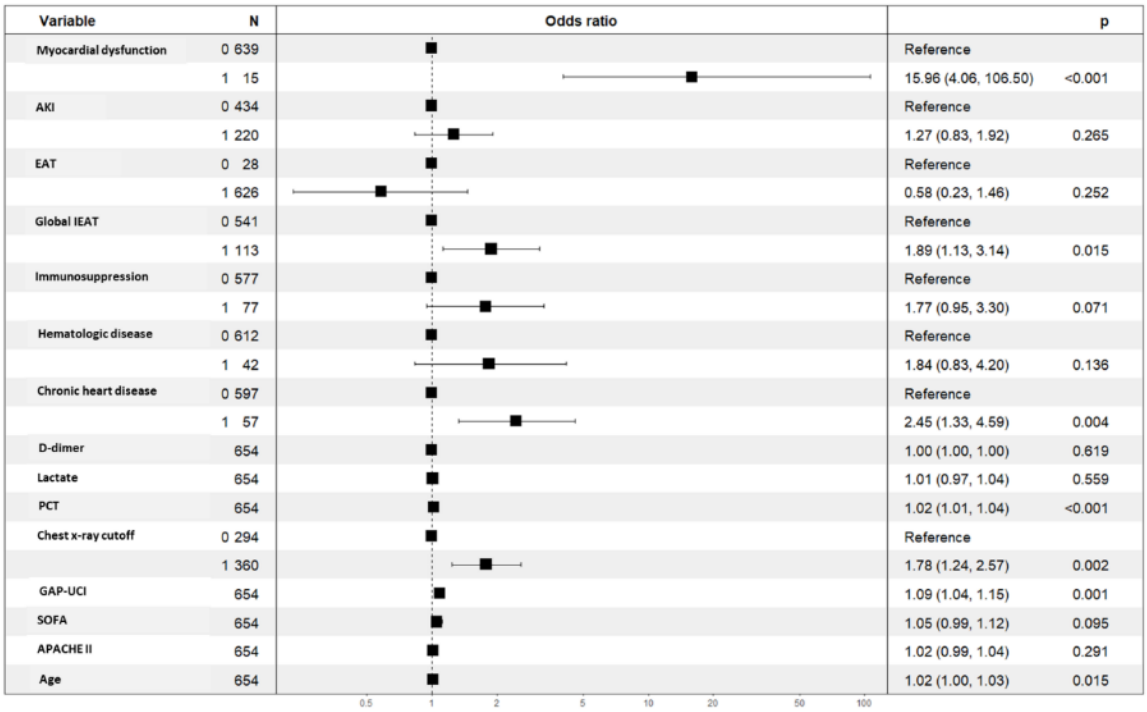


Abreviaturas: cut: punto de corte; APACHE II: Evaluación Fisiológica Aguda y de Salud Crónica II; SOFA: Evaluación Secuencial de Fallo Orgánico; EAT: Tratamiento antibiótico empírico; VAP: Neumonía asociada a la ventilación mecánica; AEAT: Tratamiento antibiótico empírico adecuado; CPK: Creatincinasa; DD: Dímero D; WBC: Recuento de leucocitos; COPD: Enfermedad pulmonar obstructiva crónica; dis: disfunción; Chr_Card_dis: Enfermedad cardíaca crónica; AKI: Lesión renal aguda; CRP: Proteína C reactiva; GAP_ICU_cut: Tiempo transcurrido entre el diagnóstico de la infección viral pandémica y el ingreso en UCI; Chr_renal_dis: Enfermedad renal crónica; ID: Inmunosupresión; Rx-cutoff: >2 campos con infiltrados en la radiografía de tórax; PCT: Procalcitonina; Hematol-dis: Enfermedad hematológica; LDH: Lactato deshidrogenasa.

En los análisis de mortalidad realizados en pacientes sin coinfección bacteriana confirmada, ni el TAE ni la NAVM se asociaron con un incremento significativo del riesgo de muerte.

En conjunto, se identificaron 12 variables pronósticas comunes a ambos modelos, entre ellas: la edad, la gravedad clínica al ingreso, la inmunosupresión, los niveles de procalcitonina y el tiempo transcurrido entre el diagnóstico de la infección viral y el ingreso en UCI. Además, se observaron variables predictivas específicas según el modelo utilizado: el sexo en el GLM (Figura 5) y la función renal y los marcadores inflamatorios (proteína C reactiva, ferritina) en el RF (Figura 4B).

Figura 5 (Figura S3 del material suplementario del artículo2): Variables asociadas con la mortalidad bruta en UCI en el modelo de regresión logística multivariable (GLM).



(AKI: lesión renal aguda; EAT: tratamiento antibiótico empírico; PCT: procalcitonina; Gap-ICU: tiempo en días desde el ingreso hospitalario hasta el ingreso en UCI; Chest x-ray cutoff: más de 2 campos pulmonares ocupados por infiltrados en la radiografía de tórax; Global IEAT: incluye a los pacientes con tratamiento antibiótico empírico inapropiado (IEAT) más los pacientes sin EAT.)

5.3 Impacto del tratamiento antibiótico empírico (EAT) sobre la aparición de neumonía asociada a ventilación mecánica (NAVM) y la mortalidad según la presencia o ausencia de coinfección bacteriana

Se diseñó un segundo estudio para evaluar el impacto clínico del TAE en pacientes con neumonía grave por virus pandémicos usando modelos de análisis lineales y no lineales.

Este estudio retrospectivo multicéntrico incluyó 4.197 pacientes críticos con neumonía viral grave (COVID-19 o gripe A H1N1) ingresados en UCIs españolas. El 88 % recibió antibiótico empírico al ingreso (EAT), eran pacientes más graves (Apache II, SOFA, Rx), más inflamados (PCR, PCT, D-Dímero), más hipoperfundidos (lactato), más disfunción orgánica (shock, AKI, ventilación mecánica invasiva). El 15,6 % (n = 654) presentaban coinfección bacteriana precoz confirmada por aislamiento microbiológico en las primeras 48 horas (Tabla 3). En este subgrupo, los pacientes que recibieron un tratamiento inadecuado (IEAT) presentaron mayor mortalidad (49,6 % frente a 38,4 %) y mayor incidencia de neumonía asociada a la ventilación (VAP) (36 % frente a 17 %) (Tabla 4).

Tabla 3 (Tabla 1 del artículo 2): Características de los 4197 pacientes con neumonía grave por virus pandémicos y ventilación mecánica invasiva (VMI) según si tenían coinfección bacteriana (COI).

Variables#	Whole population (n= 4197)			Coinfection patients (n= 654)			No Coinfection patients (n=3543)		
	Total	No EAT (n= 495)	EAT (n=3702)	Total	No EAT(n=28)	EAT (n=626)	Total	No EAT (n=467)	EAT(n=3076)
General characteristics									
Age, years	60 (49-69)	60 (46-69)	60(49-69)	59 (48-70)	62 (53-69)	59 (48-70)	60 (49-69)	60 (45-69)	60 (49-69)*
Male sex	2746 (65.4)	310 (62.6)	2436 (65.8)	433 (66.2)	19 (67.9)	414 (66.1)	2313	291 (62.3)	2022 (65.7)
APACHE II score	16 (12.21)	15(12-18)	16(12-21)***	18 (13-24)	14 (10-18)	18 (13-24)***	15 (12-20)	15 (12-18)	15 (12-21)*
SOFA score	6 (4-8)	5 (4-7)	6 (4-8)***	7 (5-10)	5 (3-7)	7(5-10)***	6 (4-8)	5 (4-7)	6 (4-8)***
Gap-ICU, days	1 (1-3)	2(1-4)	1(1-43)***	1 (0-2)	1.4 (0-4)	1.0 (0-2)	1 (1-3)	2 (1-4)	1 (1-3)***
Chest x-ray cutoff	2646 (63.0)	317 (74.9)	2329 (62.9)***	360 (55.0)	23 (82.1)	337 (53.8)***	2340 (66.0)	348 (74.5)	1992 (64.8)***
COVID	2159 (51.4)	279 (56.4)	1880 (50.8)**	191 (29.2)	20 (71.4)	171 (27.3)***	1968 (55.5)	259 (55.5)	1709 (55.6)
Influenza	2038 (48.5)	216 (43.6)	1822 (49.2)**	463 (70.8)	8 (28.6)	455 (72.7)***	1575 (44.4)	208 (44.5)	1367 (44.4)
Laboratory									
WBC x10^3	8.7 (5.6-13.0)	8.6 (6.4-11.6)	8.8 (5.4-13.1)	8.5 (4.2-13.6)	8.3 (5.3-11.7)	8.6 (4.2-13.7)	8.8 (5.8-12.8)	8.6 (6.5-11.5)	8.8 (5.7-13.0)
LDH U/L	597 (454-763)	600 (487-722)	597 (450-768)	600 (460-745)	556 (467-628)	600 (458-749)	597 (454-766)	600 (490-725)	590 (450-770)
C-RP mg/mL	22.7 (11.5-40.0)	21.1 (9.6-33.0)	23.0 (11.8-42.9)***	30.2 (16.5-80.4)	13 (6.7-29.0)	31 (17.7-82.5)***	21.3 (10.8-35.8)	21.4 (10.0-33.1)	21.4 (11.0-37.0)
PCT ng/mL	1.4 (0.30-8.90)	0.84 (0.22-3.35)	1.50 (0.32-10.1)***	5.3 (1.0-22.3)	0.73 (0.21-2.80)	5.99 (1.2-22.6)***	1.08 (0.27-3.38)	0.87 (0.22-4.48)	1.14 (0.29-7.11)***
Creatinine mg/dL	0.92 (0.70-1.32)	0.95 (0.72-1.25)	0.91 (0.70-1.34)	1.1 (0.7-1.8)	0.92 (0.65-1.41)	1.11 (0.77-1.81)	0.90 (0.70-1.26)	0.95 (0.72-1.25)	0.90 (0.70-1.27)
CPK	265 (119-485)	280 (124-487)	263 (119-485)	318 (138-589)	213 (142-358)	326 (138-602)	253 (117-473)	288 (124-497)	248 (115-469)
Lactate mmol/L	2.2 (1.5-3.6)	1.9 (1.4-2.8)	2.3 (1.5-3.7)***	3.1 (2.0-4.6)	2.0 (1.4-2.5)	3.2 (2.0-4.7)***	2.1 (1.4-3.9)	1.9 (1.4-2.8)	2.1 (1.4-3.5)**
D-dimer	4343 (1560-8170)	3316 (1360-6200)	4560 (1600-8400)***	6400 (3030-11,131)	2030 (980-6270)	6585 (3290-11,230)***	4000 (1470-7620)	3327 (1404-6200)	4111 (1480-7770)***
Comobidities									
COPD	613 (14.6)	66 (13.3)	547 (14.8)	126 (19.3)	4 (14.3)	122 (19.5)	487 (13.7)	62 (13.3)	425 (13.8)
Asthma	302 (7.2)	37 (7.4)	265 (7.1)	41 (6.3)	2 (7.1)	39 (6.2)	261 (7.3)	35 (7.5)	226 (7.3)
Chr. Heart Dis	271 (6.4)	21 (4.2)	250 (6.7)	57 (8.7)	1 (3.5)	56 (8.9)	214 (6.0)	20 (4.3)	194 (6.3)
Chr.Renal Dis.	260 (6.2)	32 (6.4)	228 (6.1)	52 (7.9)	1 (3.5)	51 (8.1)	208 (5.8)	31 (6.6)	177 (5.7)
Hematologic Dis.	215 (5.1)	27 (5.4)	188 (5.0)	42 (6.4)	2 (7.1)	40 (6.4)	173 (4.8)	25 (5.3)	148 (4.8)
Pregnancy	200 (4.8)	14 (2.8)	186 (5.0)*	53 (8.1)	0 (0.0)	53 (8.4)	147 (4.1)	14 (3.0)	133 (4.3)
Obesity	1471 (35.0)	195 (39.4)	1276 (34.5)*	183 (28.0)	9 (32.1)	174 (27.8)	1288 (36.3)	186 (39.8)	1102 (35.8)
Diabetes	493 (11.7)	83 (16.8)	410 (11.1)	57 (8.7)	5 (17.9)	52 (8.3)	436 (12.3)	78 (16.7)	358 (11.6)
Immunosuppression	349 (8.3)	33 (6.6)	316 (8.5)	77 (11.8)	1 (3.5)	76 (12.1)	272 (7.6)	32 (6.8)	240 (7.8)
Treatments and complications									
Bacterial coinfection	654 (15.6)	28 (5.6)	626 (16.9)	NA	NA	NA	NA	NA	NA
AEAT	541 (12.9)	0 (0.0)	541(86.4)	541 (82.7)	0 (0.0)	541 (86.4)	NA	NA	NA
Corticosteriods	2424 (57.8)	237 (47.9)	2187 (59.1)***	400 (61.2)	20 (32.1)	380 (60.7)	2024 (57.1)	217 (46.5)	1807 (58.7)***
VAP	743 (17.7)	88 (17.8)	655 (17.7)	135 (20.6)	10 (35.7)	125 (20.0)	608 (17.1)	78 (16.7)	530 (17.2)
AKI	821 (19.6)	63 (12.7)	758 (20.5)***	220	6 (21.4)	214 (34.2)	601 (16.9)	57 (12.2)	544 (17.7)**
Myocardial dysfunction	216 (5.1)	19 (3.8)	197(5.3)	131	1 (17.9)	130 (20.8)	201 (5.6)	18 (3.8)	183 (5.9)
Shock	2721 (64.8)	276 (55.8)	2445 (66.0)***	41	2 (7.1)	39 (6.2)	2223 (62.7)	263 (56.3)	1960 (63.7)**
Outcomes									
LOS ICU, days	16 (9-27)	16 (11 -25)	16 (9-27)	16 (9-29)	19 (12-37)	16 (8-29)	16 (10-27)	16 (11-24)	16 (9-27)
LOS Hospital, days	26 (16-40)	26 (18-35)	26 (16-40)	26 (14-44)	26 (17-47)	26 (14-44)	26 (16-39)	25 (18-35)	26 (16-40)
IMV days	12 (5-22)	8 (1-20)	12 (6.23)***	13 (7-25)	15 (7-35)	13 (7-25)	12 (5-22)	8 (1-20)	12 (6-22)***
ICU mortality	1466 (34.9)	159 (32.1)	1307 (35.3)	264 (40.4)	16 (57.1)	248 (39.6)	1202 (33.9)	143 (30.6)	1059 (34.4)

Las variables continuas se muestran como valores medianos y percentiles Q1–Q3. Las variables categóricas se presentan como número de casos (n) y porcentaje (%). (LDH: lactato deshidrogenasa; C-RP: proteína C reactiva; CPK: creatincinasa; PCT: procalcitonina; VAP: neumonía asociada a la ventilación mecánica; AKI: lesión renal aguda; LOS: duración de la estancia; ICU: unidades de cuidados intensivos; Gap-ICU: tiempo en días desde el ingreso hospitalario hasta el ingreso en UCI; Chest x-ray cutoff: más de 2 campos pulmonares ocupados por infiltrados en la radiografía de tórax; MDR: bacterias multirresistentes; EAT: tratamiento antibiótico empírico; AEAT: tratamiento antibiótico empírico adecuado.)

Tabla 4 (Tabla 2 del artículo 2): Características generales de los 626 pacientes con coinfección (COI) y tratamiento antibiótico empírico (TAE), distinguiendo entre tratamiento antibiótico empírico adecuado (AEAT) e inadecuado (IAET).

Variables#	*IEAT (n= 85)*	*AEAT (n=541)*	*p-value*
General Characteristics			
Age, years	62 (56-72)	59 (47-70)	0.009
Male sex	55 (64.7)	359 (66.4)	0.860
APACHE II score	18 (13-21)	19 (14-24)	0.170
SOFA score	7 (5-9)	7(5-10)	0.040
Gap-ICU, days	1 (1-2)	1 (0-2)	0.180
Chest x-ray cutoff	51 (60.0)	286 (52.9)	0.260
COVID	48 (56.5)	123 (22.7)	<0.001
Influenza	37 (43.5)	418 (77.3)	<0.001
Laboratory			
WBC $x10^3$	8.0 (4.9-11.6)	8.7 (3.9-13.9)	0.600
LDH U/L	630 (473-830)	600 (458-745)	0.290
C-RP mg/mL	22.4 (13.0-33.3)	33.4 (19.7-91.3)	<0.001
PCT ng/mL	1.44 (0.24-8.26)	7.86 (1.55-24.0)	<0.001
Creatinine mg/dL	0.87 (0.70-1.48)	1.14 (0.79-1.86)	0.010
CPK ng/mL	218 (119-399)	338 (151-647)	0.001
Lactate mmol/L	2.3 (1.6-3.6)	2.3 (2.2-4.8)	<0.001
D-dimer UI/L	3940 (1179-7200)	6800 (3780-11,700)	
Comorbidities			
COPD	11 (12.9)	111 (20.5)	0.130
Asthma	8 (9.4)	31 (5.7)	0.280
Chr. Heart Dis	4 (4.7)	52 (9.6)	0.200
Chr.Renal Dis.	7 (8.2)	44 (8.1)	1.00
Hematologic Dis.	4 (4.7)	36 (6.6)	0.650
Pregnancy	2 (2.3)	51 (9.4)	0.040
Obesity	34 (40.0)	140 (25.9)	0.010
Diabetes	13 (15.3)	39 (7.2)	0.020
Immunosuppression	8 (9.4)	68 (12.6)	0.510
Treatment and complications			
Corticosteroids	57 (67.1)	323 (59.7)	0.240
Presence of MDR bacteria	69 (81.2)	98 (18.1)	<0.001
VAP	31 (36.5)	94 (17.4)	<0.001
AKI	20 (23.5)	194 (35.9)	0.030
Myocardial dysfunction	4 (4.7)	10 (1.8)	0.100
Shock	61 (71.8)	424 (78.4)	0.220
Outcomes			
LOS ICU, days	22 (12-37)	16 (8-28)	0.001
LOS Hospital, days	30 (21-50)	25 (12-42)	0.008
IMV days	15 (10-30)	12 (6-24)	0.010
ICU mortality	40 (47.1)	208 (38.4)	0.160

Las variables continuas se muestran como valores medianos y percentiles Q1–Q3. Las variables categóricas se presentan como número de casos (n) y porcentaje (%). (LDH: lactato deshidrogenasa; CRP: proteína C reactiva; CPK: creatincinasa; PCT: procalcitonina; VAP: neumonía asociada a la ventilación mecánica; AKI: lesión renal aguda; LOS: duración de la estancia; ICU: unidades de cuidados intensivos; Gap-ICU: tiempo en días desde el ingreso hospitalario hasta el ingreso en UCI; Chest x-ray cutoff: más de 2 campos pulmonares ocupados por infiltrados en la radiografía de tórax; MDR: bacterias multirresistentes; * Global IEAT: incluye a los pacientes con tratamiento antibiótico empírico inadecuado (IEAT) más los pacientes sin tratamiento empírico (EAT)*).

En los 3.543 pacientes sin coinfección bacteriana documentada, el 88 % recibió antibiótico empírico. Este grupo presentaba mayor gravedad clínica basal (Tabla 3). Para reducir el sesgo por indicación, se aplicó un emparejamiento por puntuación de propensión (PSM), generando una cohorte emparejada de 3.520 pacientes con características similares. Tras este ajuste, no se observaron diferencias significativas en la incidencia acumulada de NAVM ($p = 0,8$) (Figura 6) ni en la mortalidad en UCI ($p = 0,3$) (Figura 7). Estos resultados fueron confirmados mediante modelos multivariables de regresión de Cox (HR NAVM = 1,00; HR mortalidad = 1,02), que tampoco mostraron un efecto beneficioso del EAT en estos pacientes (Figuras 8 y 9).

Figura 6 (Figura 2 del artículo 2): Curva de Kaplan-Meier para el desarrollo de neumonía asociada a la ventilación mecánica (NAVM) según si los pacientes sin coinfección bacteriana recibieron o no tratamiento antibiótico empírico (TAE). Como puede observarse, no existen diferencias significativas en la probabilidad de desarrollar NAVM entre el grupo con TAE (línea azul) y el grupo sin TAE (línea roja) (prueba de log-rank p=0,8).

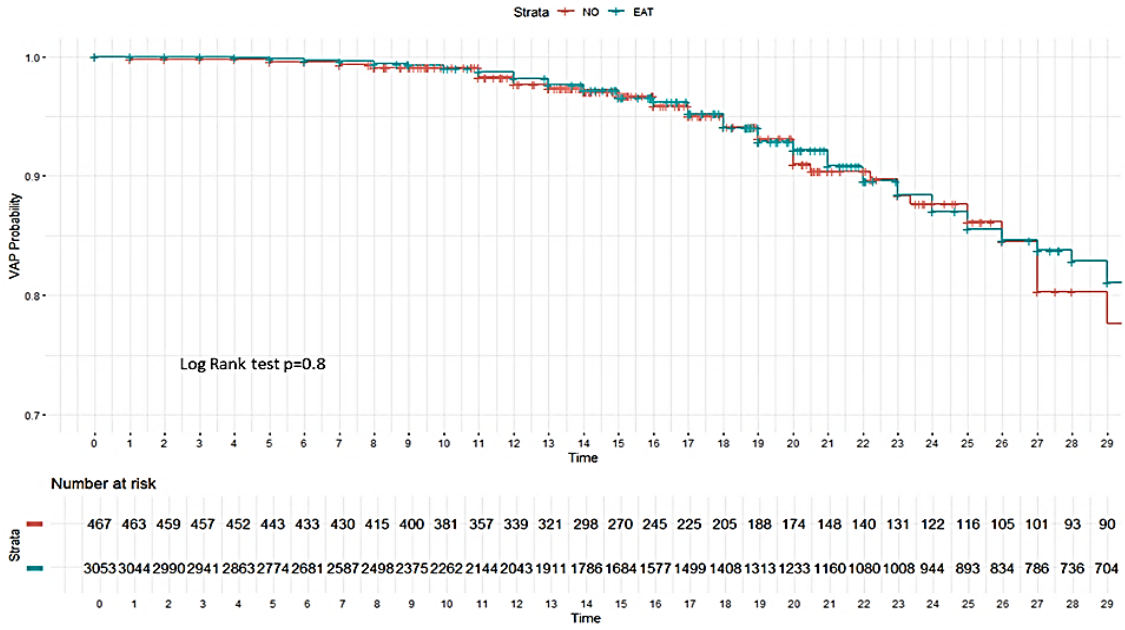


Figura 7 (Figura 3 del artículo 2): Curva de Kaplan-Meier para el desarrollo de mortalidad global en UCI según si los pacientes sin coinfección bacteriana recibieron o no tratamiento antibiótico empírico (TAE). Como puede observarse, no existen diferencias significativas en la probabilidad de supervivencia entre el grupo con TAE (línea azul) y el grupo sin TAE (línea roja) (prueba de log-rank p=0,3).

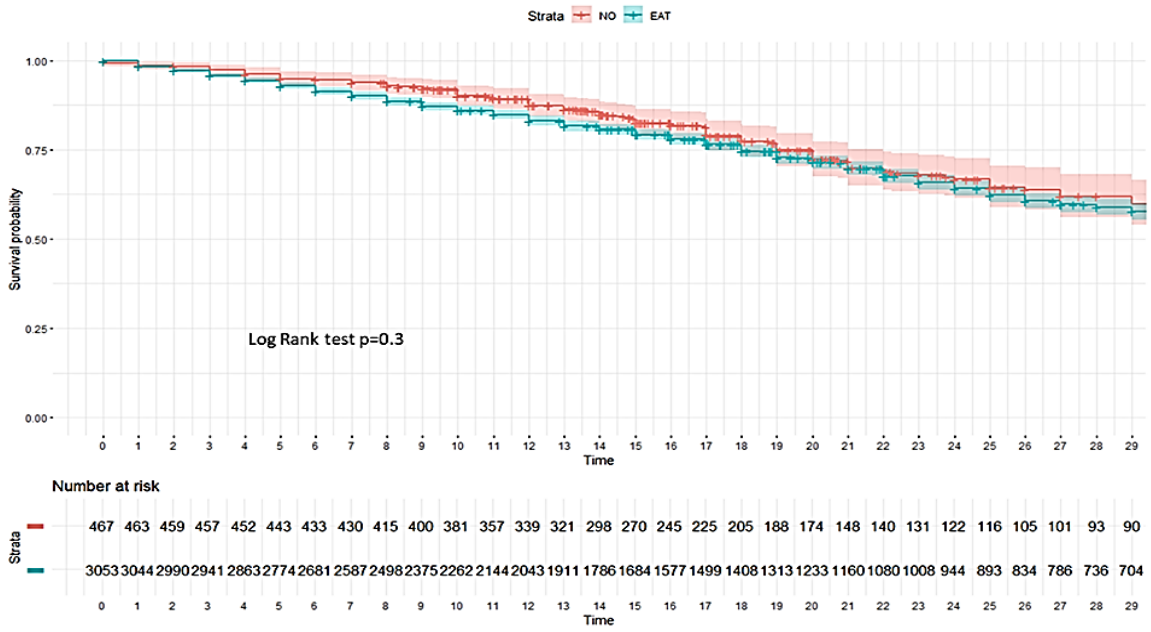


Figura 8 (Figura 4 del artículo 2): Gráfico de regresión de riesgos proporcionales de Cox para la probabilidad de desarrollar NAVM según si se recibió o no tratamiento antibiótico empírico (TAE) en la cohorte emparejada de pacientes sin coinfección. Como puede observarse, las líneas están prácticamente superpuestas, ya que no existen diferencias significativas en el riesgo diario proporcional de desarrollar NAVM entre el grupo con TAE (línea azul) y el grupo sin TAE (línea roja) (HR=1,0).

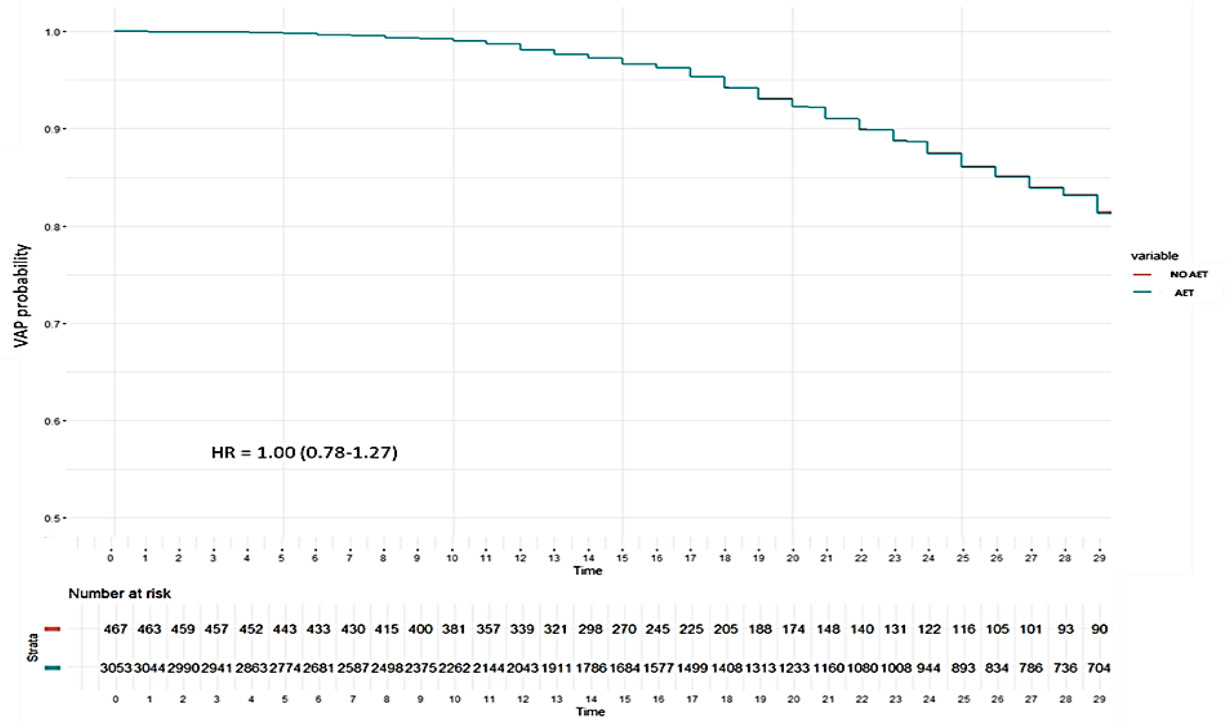
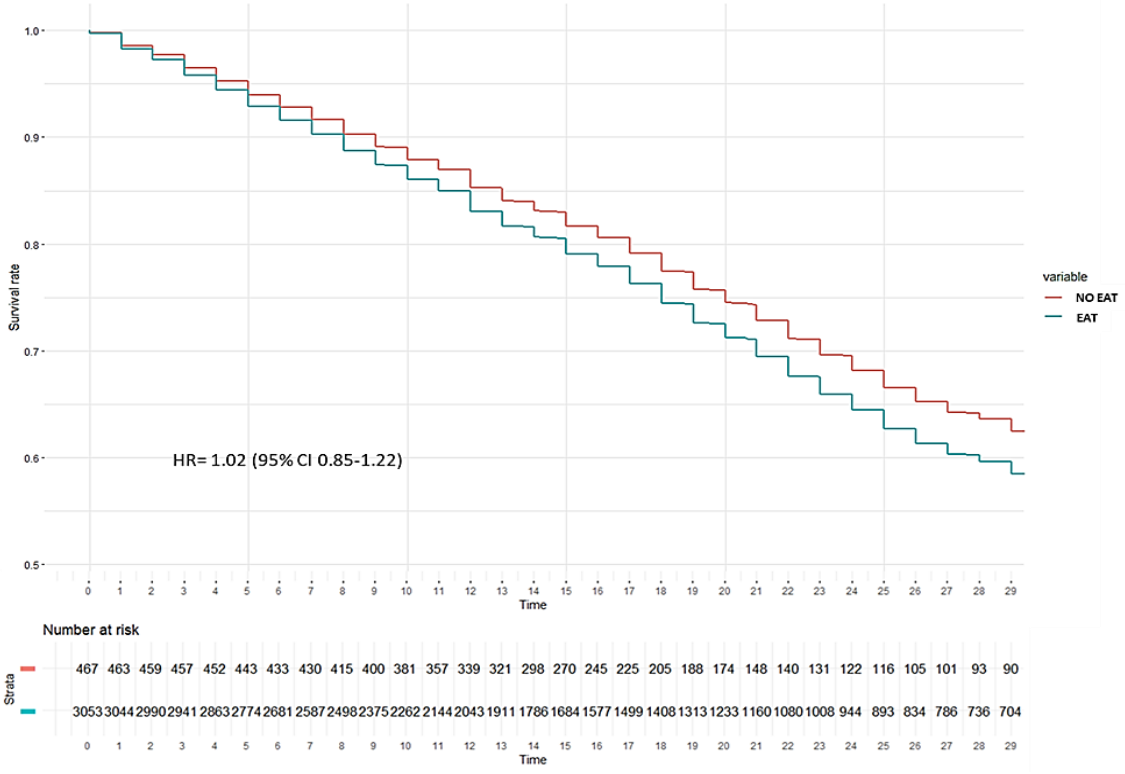


Figura 9 (Figura 5 del artículo 2): Gráfico de regresión de riesgos proporcionales de Cox para la mortalidad global en UCI según si se recibió o no tratamiento antibiótico empírico (TAE) en la cohorte emparejada de pacientes sin coinfección. Como puede observarse, no se observaron diferencias significativas en el riesgo diario proporcional de supervivencia en UCI entre el grupo con TAE (línea azul) y el grupo sin TAE (línea roja) (HR=1,02).



Neumonía asociada a ventilación mecánica (NAVM):

En los pacientes sin coinfección bacteriana, el TAE no se asoció a una menor incidencia de NAVM. En los análisis multivariados, los factores asociados al desarrollo de NAVM fueron el uso de corticoides, la inmunosupresión y la afectación radiológica extensa (Rx_cutoff). En los modelos de aprendizaje automático (Random Forest), las variables con mayor peso predictivo fueron también Rx_cutoff, uso de corticoides, inmunosupresión, edad, SOFA, procalcitonina, APACHE II, intervalo entre ingreso hospitalario y admisión en UCI (GAP-ICU), creatinina, urea, sexo femenino y dímero D. En ambos enfoques analíticos, el EAT no mostró asociación significativa ni peso predictivo relevante respecto al desarrollo de NAVM (Figuras 3 y 4A).

Mortalidad en UCI:

Tampoco se observaron diferencias significativas en la mortalidad entre los pacientes sin coinfección tratados o no con antibióticos empíricos. Tras el emparejamiento por PSM y el análisis multivariable con modelos de Cox, el EAT no se asoció a una reducción de la mortalidad (HR 1,02). En los modelos de regresión logística (GLM), los factores asociados a mayor mortalidad fueron la edad, la gravedad clínica (SOFA, APACHE II) y biomarcadores inflamatorios elevados como la procalcitonina y el dímero D (Figura 5). El modelo Random Forest identificó como variables más relevantes para la predicción de mortalidad: edad, SOFA, APACHE II, procalcitonina, lactato, dímero D, creatinina, urea, Rx_cutoff, GAP-ICU, corticoides y sexo (Figura 4B). En ninguno de los modelos el EAT tuvo un peso relevante ni se asoció de forma significativa con la mortalidad.

En conjunto, el antibiótico empírico solo fue útil en pacientes con coinfección bacteriana confirmada y tratamiento adecuado. En el resto, su uso no mejoró los resultados y puede contribuir al desarrollo de bacterias multirresistentes. Estos hallazgos respaldan la necesidad de un esfuerzo diagnóstico precoz para identificar coinfección y optimizar el uso de antibióticos, en línea con las recomendaciones de los programas PROA.

6. Resumen global de la discusión:

Esta tesis doctoral se basa en dos estudios observacionales multicéntricos realizados sobre una cohorte común de 8.902 pacientes críticos con neumonía grave por virus pandémicos (influenza A[H1N1]pdm09 y SARS-CoV-2) ingresados en más de 180 UCIs españolas. Se trata de la serie más amplia publicada hasta la fecha con estas características y el primer trabajo que aplica técnicas de machine learning a pacientes críticos con gripe A, ampliando su uso más allá de la COVID-19. Al incluir infecciones por virus emergentes y estacionales y reflejar la práctica real de las UCIs españolas, sus resultados son clínicamente relevantes y extrapolables a los picos epidémicos invernales que cada año tensionan nuestras UCIs.

6.1 Determinantes pronósticos al ingreso en pacientes con neumonía grave por virus pandémicos (influenza A H1N1 y SARS-CoV-2)

El hallazgo más importante fue que los dos enfoques analizados, la regresión logística multivariable como método estadístico lineal y el algoritmo Random Forest como técnica de aprendizaje automático no lineal, mostraron un rendimiento muy similar, con una precisión cercana al 80%. Este resultado coincide con lo descrito en otros estudios que tampoco hallaron una ventaja clara de los modelos de machine learning cuando se utilizan únicamente datos basales recogidos al ingreso (33,35,37,39).

Ambos modelos identificaron un grupo de factores que se asociaron de forma consistente con la mortalidad y que denominamos determinantes mayores: la edad avanzada, la gravedad clínica inicial, la disfunción multiorgánica y la necesidad temprana de ventilación mecánica invasiva. Estas variables fueron comunes a ambos métodos. Además, cada modelo identificó otros factores adicionales, definidos como determinantes menores. En el caso de Random Forest destacaron la procalcitonina, el dímero D y el lactato, mientras que en la regresión logística fueron relevantes la insuficiencia renal aguda y la coinfección por *Acinetobacter spp.* Este enfoque combinado demuestra que la integración de datos clínicos clásicos con biomarcadores específicos permite identificar de forma más precisa perfiles de riesgo que pueden pasar desapercibidos si se utiliza un único modelo.

Las pandemias de gripe A(H1N1) y COVID-19 han evidenciado la importancia de contar con herramientas fiables que permitan identificar de forma temprana a los pacientes con mayor riesgo de complicaciones. Este reconocimiento precoz facilita un triaje ágil, una asignación adecuada de recursos y una mejor planificación de los cuidados intensivos. Aunque estos escenarios epidémicos puedan parecer excepcionales, cada invierno los hospitales registran un incremento sostenido de ingresos por infecciones respiratorias graves, que ejerce una elevada presión asistencial, especialmente en las unidades de cuidados intensivos.

Diversos autores han empleado *machine learning* para crear modelos predictivos en pacientes con COVID-19, pero la mayoría de los estudios se basan en cohortes pequeñas y en pacientes no críticos. Por ejemplo, Huang et al. (77) describieron un AUC del 94,4% en 127 pacientes, de los cuales solo 33 eran críticos. Otros trabajos, como los de Zhu (38), Gong (50), Aloisio (51) y Liu (78), obtuvieron resultados similares con regresión logística lineal en muestras reducidas, con escasa aplicabilidad en pacientes con insuficiencia respiratoria grave. En este contexto, el presente estudio aporta evidencia más sólida al incluir casi 9.000 pacientes críticos y realizar un análisis multicéntrico en 148 UCI, lo que refuerza la validez y la generalización de los resultados. Además, la clasificación de los factores de riesgo en determinantes mayores y menores facilita su interpretación y uso en la práctica clínica.

Implicación clínica

En la práctica diaria, identificar de forma precoz los determinantes mayores permite realizar un triaje inicial más rápido y orientar la asignación prioritaria de camas y recursos en la UCI. La valoración complementaria de determinantes menores, como los biomarcadores inflamatorios y trombóticos, ayuda a anticipar intervenciones dirigidas, como la anticoagulación precoz o el inicio temprano de tratamientos antibióticos en casos seleccionados. Asimismo, reconocer la importancia de la insuficiencia renal aguda y la coinfección bacteriana subraya la necesidad de aplicar protocolos de prevención de infecciones nosocomiales y de vigilar estrechamente la función renal desde el primer día de ingreso. La combinación de estos enfoques contribuye a optimizar la gestión clínica en

situaciones de alta demanda asistencial y puede mejorar de manera significativa los resultados en pacientes con neumonía grave por virus pandémicos.

6.2 Capacidad predictiva de modelos estadísticos clásicos (regresión logística multivariable) en comparación a modelos de aprendizaje automático (Random Forest) en la predicción de mortalidad

En el primer trabajo también se exploró si la combinación de ambos enfoques analíticos podía aportar un valor añadido. En nuestro estudio, ambos modelos mostraron un rendimiento muy similar, con una precisión aproximada del 80%, lo que confirma que la regresión logística sigue siendo una herramienta eficaz y plenamente vigente, incluso frente a algoritmos más complejos. Este hallazgo coincide con estudios previos que tampoco encontraron diferencias sustanciales entre métodos estadísticos tradicionales y técnicas de machine learning cuando se utilizan exclusivamente datos recogidos al ingreso (33,37,39,79).

El análisis detallado de las variables seleccionadas reveló diferencias relevantes. Mientras que Random Forest identificó como predictores la procalcitonina, el dímero D y el lactato, la regresión logística destacó la insuficiencia renal aguda y la coinfección por *Acinetobacter spp.* Esta diferencia en los factores identificados sugiere que ambos enfoques no son redundantes, sino complementarios, ya que aportan perspectivas distintas que permiten caracterizar mejor el perfil pronóstico de cada paciente.

Otros autores han realizado comparaciones similares. Reina-Reina et al. (39) evaluaron distintas técnicas de *machine learning* en 1.200 pacientes con COVID-19 y encontraron una precisión de clasificación superior al 88% en todos los métodos. Aunque Random Forest mostró un rendimiento ligeramente mayor, se eligió finalmente la regresión logística por su mayor facilidad de interpretación clínica. No obstante, este estudio no analizó las diferencias específicas entre predictores y solo incluyó un número reducido de pacientes críticos. Pourhomayoun et al. (33), en una cohorte de más de 2,6 millones de casos, obtuvieron resultados comparables entre redes neuronales (AUC 89,98%), Random Forest

(87,93%) y regresión logística (87,91%), si bien no se compararon estadísticamente estas diferencias ni se detalló el grado de gravedad clínica de los pacientes incluidos.

Es importante señalar que muchos estudios previos utilizaron bases de datos muy desequilibradas, con un porcentaje de mortalidad bajo (41). En cambio, nuestra cohorte presentó una mortalidad del 25%, claramente superior a la de otras series publicadas (10–15%) (6,34,39,51,78), lo que aporta mayor solidez y aplicabilidad a los resultados. Este hecho también explica que el muestreo equilibrado de clases no mejorara de manera sustancial la capacidad predictiva, confirmando que el desequilibrio no comprometió la fiabilidad del modelo.

Aunque el aprendizaje automático permite identificar interacciones complejas y patrones no lineales, su aplicación clínica tiene limitaciones, como la necesidad de grandes volúmenes de datos y una menor facilidad de interpretación. Esto coincide con otros estudios que observaron un rendimiento limitado de estos modelos cuando se entrenan exclusivamente con variables clínicas basales y no incorporan datos dinámicos (37,39,40). De hecho, los modelos con mejor capacidad predictiva, como los descritos por Wang et al. (80) y Karasneh et al. (36), incluyeron información evolutiva o marcadores inmunológicos que, en la práctica, suelen no estar disponibles en las primeras horas de ingreso.

Implicación clínica

En la práctica, la combinación de la regresión logística con Random Forest permite aprovechar las fortalezas de ambos métodos: la interpretación clara de los factores clásicos y la capacidad de los algoritmos no lineales para identificar relaciones complejas entre variables. Este enfoque complementario facilita una detección más precisa y temprana de los pacientes con alto riesgo de mortalidad, mejora el triaje y la asignación de recursos críticos, y permite un seguimiento más dirigido mediante biomarcadores específicos, especialmente en periodos de alta presión asistencial o ante nuevas variantes virales. Además, conocer predictores que varían según el método empleado genera nuevas hipótesis sobre mecanismos fisiopatológicos y abre oportunidades para diseñar estrategias

terapéuticas personalizadas que puedan beneficiar de forma directa al paciente crítico con neumonía vírica grave.

6.3 Impacto del tratamiento antibiótico empírico (EAT) sobre la aparición de neumonía asociada a ventilación mecánica (NAVM) y la mortalidad según la presencia o ausencia de coinfección bacteriana

El segundo estudio mostró que el TAE administrado durante las primeras 24 horas de ingreso en UCI no se asoció con una menor mortalidad ni con menos casos de neumonía asociada a ventilación mecánica (NAVM) en los pacientes sin coinfección bacteriana confirmada. Este resultado se mantuvo tras ajustar por factores de confusión mediante *propensity score matching*, modelos multivariantes y análisis no lineales, lo que refuerza la solidez de los hallazgos y coincide con otros estudios recientes que no muestran beneficio en el uso rutinario de antibióticos sin confirmación microbiológica (31,61,81,82).

En cambio, en los pacientes con coinfección bacteriana, el uso inadecuado de antibióticos se relacionó con más NAVM, mayor mortalidad, más comorbilidad y estancias hospitalarias más largas. Estos efectos adversos son especialmente preocupantes en periodos de alta presión asistencial, cuando los recursos y las camas de UCI son limitados. Esta evidencia pone de relieve que una estrategia terapéutica inadecuada puede comprometer tanto la evolución clínica como la eficiencia del sistema sanitario (75,83).

La evidencia disponible sobre el impacto del antibiótico empírico en la neumonía viral grave sigue siendo heterogénea y limitada. Algunos trabajos, como el de Wendel-García et al. (75), describen beneficios en pacientes con COVID-19, relacionando su uso con menor sobreinfección y mortalidad. Sin embargo, otras series con ajustes metodológicos más rigurosos no encontraron diferencias significativas (81,82), y varias revisiones insisten en la baja prevalencia de coinfección bacteriana en estos pacientes (59,61,84). Estas discrepancias probablemente se deben a diferencias en las definiciones de sobreinfección, la falta de ajustes por variables de confusión o la exclusión de casos de gripe A(H1N1), lo que dificulta comparar y extrapolar resultados. En nuestra cohorte, con una definición

estricta de coinfección confirmada microbiológicamente, la prevalencia fue más alta (~15%) frente a otros registros (~4%) (61,75).

Se identificaron además factores clínicos y biológicos asociados a peor evolución, como la edad avanzada, el uso de corticoides y la afectación radiológica extensa, en línea con estudios previos (83,85). Aunque biomarcadores como la procalcitonina y la proteína C reactiva pueden ayudar a orientar el manejo inicial, su utilidad diagnóstica es limitada. El estudio de Galli et al. (31) mostró que sus niveles al ingreso no discriminan de forma fiable la coinfección, lo que resalta la importancia de valorar siempre la evolución clínica y la microbiología, y de monitorizar estos marcadores de manera secuencial.

Por otro lado, el uso indiscriminado de antibióticos de amplio espectro no mostró beneficios en la supervivencia y se asoció a más complicaciones, como un mayor riesgo de NAVM, la aparición de bacterias multirresistentes y estancias más prolongadas (56,57,64,86,87). En España, durante la pandemia, la incidencia de NAVM se duplicó (76), y más del 80% de los pacientes recibieron antibióticos empíricos pese a la baja tasa de coinfección confirmada (31,81,82,83). Este escenario refuerza la necesidad de protocolos claros y programas de optimización del uso de antimicrobianos (PROA) que promuevan la desescalada precoz, el diagnóstico rápido y la revisión constante de la indicación antibiótica.

En conjunto, estos resultados apoyan que el tratamiento empírico debe reservarse a pacientes con alta sospecha clínica o microbiológica de coinfección. La recogida precoz de muestras, el uso de técnicas de diagnóstico rápido y la interpretación cuidadosa de los biomarcadores permiten una aproximación más segura e individualizada. La implantación de programas PROA multidisciplinares, con la implicación de intensivistas, microbiólogos, farmacéuticos y especialistas en enfermedades infecciosas, resulta clave no solo para mejorar la evolución clínica, sino también para aprovechar mejor los recursos disponibles, sobre todo en situaciones de alta presión asistencial.

Implicación clínica

Los datos de este estudio apoyan un uso más racional de los antibióticos en pacientes críticos con neumonía viral grave. En la práctica, el tratamiento empírico debería reservarse a pacientes con alta sospecha de coinfección bacteriana, en especial aquellos con factores de riesgo claros como mayor gravedad clínica, edad avanzada, inmunosupresión, afectación radiológica extensa y disfunción orgánica.

En estos casos, es fundamental recoger muestras microbiológicas de calidad de forma precoz, utilizar técnicas de diagnóstico rápido y reevaluar la necesidad de continuar el tratamiento según la evolución clínica y los resultados de laboratorio.

La implantación de protocolos de actuación claros y programas de optimización de antimicrobianos (PROA), coordinados por equipos multidisciplinares, resulta clave para guiar la toma de decisiones, evitar el uso innecesario de antibióticos, reducir complicaciones como las resistencias y optimizar los recursos en contextos de alta presión asistencial.

6.1. Limitaciones

A pesar del tamaño de la cohorte y del uso de métodos estadísticos avanzados, este estudio presenta varias limitaciones que deben tenerse en cuenta al interpretar los resultados.

En primer lugar, se trata de un análisis observacional retrospectivo basado en registros asistenciales. Esto implica que algunos datos relevantes estaban incompletos o no disponibles, como determinados biomarcadores y fechas clave. Además, la información no fue monitorizada ni auditada externamente, lo que podría afectar su exactitud y consistencia.

Los criterios empleados para definir la coinfección y la adecuación del tratamiento antibiótico tampoco fueron homogéneos entre los hospitales participantes, lo que introduce variabilidad. Aunque se aplicaron técnicas como el *propensity score* y modelos de aprendizaje automático, persiste el riesgo de factores no medidos que puedan haber influido en los resultados.

No se dispuso de información detallada sobre el momento exacto del diagnóstico de la neumonía asociada a la ventilación ni sobre la duración real del tratamiento antibiótico. Dado que el análisis se centró en las primeras 24 horas de ingreso, no fue posible evaluar la evolución clínica posterior ni otros factores que podrían haber condicionado los desenlaces. Asimismo, los hospitales utilizaron protocolos diagnósticos diferentes y no se recogieron datos sobre biomarcadores inmunitarios avanzados ni sobre estrategias de desescalada antibiótica.

Otra limitación importante es que la clasificación de variables clave se realizó de forma retrospectiva. Por ejemplo, la adecuación del tratamiento se determinó según los resultados de los cultivos, lo que puede inducir errores si el aislamiento fue incompleto o incorrecto. También es posible que algunas coinfecciones pasaran desapercibidas, especialmente si no se recogieron muestras microbiológicas de calidad en las primeras 48 horas. Esta heterogeneidad en las prácticas clínicas puede haber afectado la consistencia de los datos.

Por último, todos los pacientes procedían de UCI españolas, lo que limita la aplicabilidad de los resultados a otros sistemas sanitarios o entornos asistenciales. Tampoco se recogieron variables como nivel socioeconómico, etnia o evolución clínica a lo largo de la estancia, y se observó cierto desequilibrio entre los grupos de comparación. Todos estos factores pueden influir tanto en la validez interna como en la generalización de los hallazgos.

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7. Conclusiones

Los resultados de este estudio confirman la hipótesis inicial de esta tesis: las decisiones diagnósticas y terapéuticas adoptadas durante las primeras 24 horas de ingreso en UCI influyen de forma decisiva en la evolución de los pacientes con neumonía grave por virus pandémicos. A partir de dos estudios observacionales multicéntricos y del uso combinado de modelos estadísticos y de aprendizaje automático, se obtienen las siguientes conclusiones:

1. **Factores pronósticos de mortalidad al ingreso.**
   La estratificación temprana del riesgo basada en variables clínicas accesibles permite identificar con alta consistencia un conjunto de determinantes mayores de la mortalidad: edad avanzada, gravedad clínica inicial, disfunción orgánica y necesidad de ventilación mecánica invasiva. Estos factores mantienen su relevancia independientemente del método analítico empleado, lo que subraya su utilidad en la identificación de pacientes de peor pronóstico y en la planificación del soporte intensivo.
2. **Valor complementario de los enfoques analíticos.**
   La comparación entre regresión logística multivariable (GLM) y Random Forest mostró que ambos modelos alcanzan un rendimiento predictivo similar (AUROC ≈0,76), aunque ofrecen perspectivas diferentes. La regresión logística facilita una interpretación clara del peso de cada variable, mientras que Random Forest permite identificar interacciones no lineales y patrones complejos, destacando determinantes menores como biomarcadores inflamatorios (lactato, procalcitonina, dímero D) que enriquecen la estratificación del riesgo. La combinación de ambos enfoques proporciona una visión más completa y robusta, y sienta un marco analítico replicable en futuros estudios.
3. **El tratamiento antibiótico empírico debe ser selectivo y guiado.**
   En pacientes con coinfección bacteriana confirmada, la administración precoz y adecuada de antibióticos se asoció con menor mortalidad y menos complicaciones graves. Por el contrario, en pacientes sin coinfección documentada, el uso sistemático de antibióticos empíricos no redujo la mortalidad ni la incidencia de

NAVM. Estos hallazgos apoyan una prescripción más individualizada, basada en criterios clínicos y microbiológicos objetivos, e integrando biomarcadores rápidos y métodos diagnósticos que permitan identificar precozmente la coinfección, en línea con las recomendaciones de los programas de optimización del uso de antimicrobianos (PROA).

En conjunto, estos resultados demuestran que una medicina intensiva de precisión, sustentada en modelos predictivos sólidos y en un uso racional de los antibióticos, es posible y se traduce en beneficios clínicos para los pacientes con neumonía grave por virus pandémicos. Este trabajo sienta las bases para desarrollar protocolos de decisión adaptados al riesgo individual y consolidar una práctica asistencial más sostenible, eficiente y basada en la evidencia.

8. Líneas de futuro derivadas de la tesis

1. **Ensayos clínicos sobre estrategias guiadas por biomarcadores y diagnóstico rápido.**

   Se necesitan ensayos clínicos aleatorizados que evalúen estrategias combinadas. Por un lado, el uso de paneles moleculares de diagnóstico rápido**,** especialmente en pacientes con sospecha clínica de coinfección bacteriana, permitiría confirmar precozmente la presencia de patógenos respiratorios e iniciar el tratamiento antibiótico de forma temprana y dirigida. Por otro, la procalcitonina **y** otro**s** biomarcadores deben validarse como herramienta principal para suspender de manera segura los antibióticos en pacientes sin evidencia de coinfección**.** Estas estrategias podrían reducir la prescripción innecesaria de antibióticos y su impacto sobre la mortalidad, la neumonía asociada a ventilación y la resistencia bacteriana.
2. **Seguimiento completo del ingreso en UCI y uso dinámico de modelos pronósticos.**

   La recogida de datos más allá de las primeras 24 horas, incluyendo evolución clínica, complicaciones y biomarcadores seriados, permitirá desarrollar modelos pronósticos dinámicos. Estos modelos ayudarán a evaluar cómo la selección y desescalada de antibióticos afectan los resultados clínicos. Esta aproximación debe basarse en métodos de inferencia causal y en los principios de los programas de optimización de antimicrobianos (PROA).
3. **Validación externa de los modelos predictivos.**

   Los modelos desarrollados (GLM y Random Forest) deben validarse en cohortes externas de distintos países y niveles asistenciales. Esto permitirá evaluar su aplicabilidad y ajustar su rendimiento en contextos clínicos diversos.
4. **Integración de biomarcadores inmunitarios y tecnologías ómicas.**

   La incorporación de marcadores inmunológicos y plataformas ómicas (transcriptómica, proteómica, metabolómica) permitirá caracterizar mejor la respuesta del huésped e identificar subgrupos con diferente riesgo. Estas herramientas complementarán el diagnóstico microbiológico rápido y la monitorización de biomarcadores para apoyar decisiones individualizadas sobre el inicio y la retirada de antibióticos.

5. **Desarrollo de sistemas de soporte clínico basados en inteligencia artificial.** Integrar los modelos predictivos en sistemas de soporte clínico automatizados facilitará la toma de decisiones en tiempo real. Estas herramientas podrán emitir alertas para iniciar antibióticos si los paneles moleculares confirman coinfección bacteriana en pacientes con sospecha clínica, o recomendar su suspensión si los biomarcadores indican baja probabilidad de infección.

Estas líneas de investigación contribuirán a consolidar un enfoque más seguro y eficiente en el uso de antibióticos en pacientes críticos con neumonía viral, combinando diagnóstico rápido para iniciar el tratamiento cuando sea necesario y biomarcadores fiables para suspenderlo cuando no esté indicado.

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10. Anexos

10.1 Material suplementario Artículo 1

Machine Learning-Based Identification of Risk Factors for ICU Mortality in 8,902 Critically Ill Patients with Pandemic Viral Infection

Supplementary material

Table S1: Performance of multivariate linear model (GLM) for ICU mortality.

Point estimates and 95% CIs:	
Apparent prevalence *	0.26 (0.24, 0.27)
True prevalence *	0.11 (0.10, 0.12)
Sensitivity *	0.61 (0.55, 0.66)
Specificity *	0.79 (0.77, 0.80)
Positive predictive value *	0.26 (0.23, 0.29)
Negative predictive value *	0.94 (0.93, 0.95)
Positive likelihood ratio	2.83 (2.51, 3.19)
Negative likelihood ratio	0.50 (0.43, 0.58)
False T+ proportion for true D- *	0.21 (0.20, 0.23)
False T- proportion for true D+ *	0.39 (0.34, 0.45)
False T+ proportion for T+ *	0.74 (0.71, 0.77)
False T- proportion for T- *	0.06 (0.05, 0.07)
Correctly classified proportion *	0.77 (0.75, 0.78)

* Exact CIs

Figure S1: Area under ROC curve (AUC) for multivariate lineal model for ICU mortality

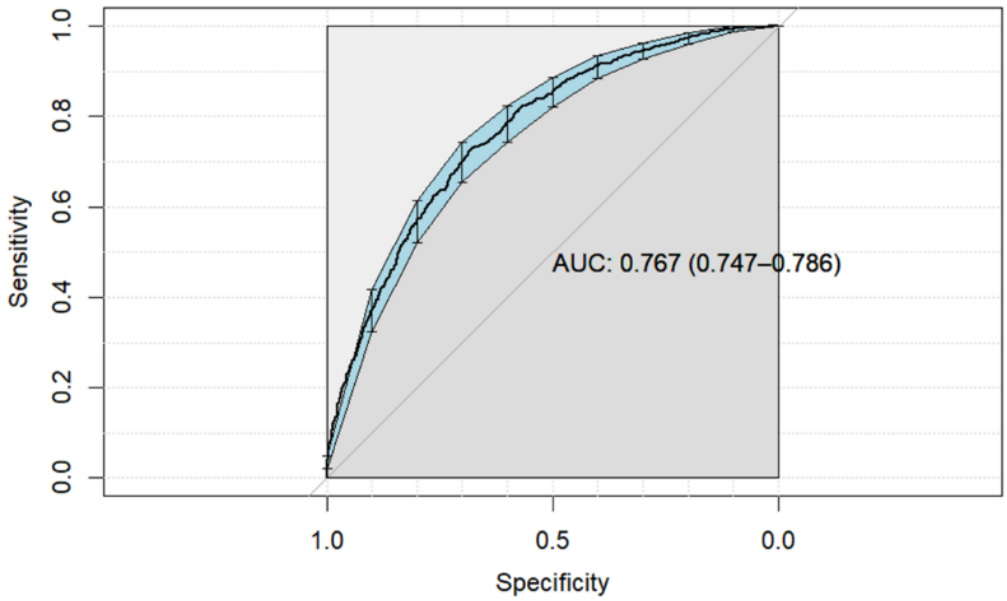


Table S2: Colinearity study by VIF (variance inflation factors) determination. For each variable the VIF number shoud be lower than 5. No colinearity was observed between teh variables included in the model.

(Cut: cut-off; AB: antibiòtics; CPK: creatine phospokinase; DD: D dímer; MR_SA: methicillin-resistant *S. Aureus*; MV: invasive mechanical ventilation; WBC: White blood cells; COPD: chronic obstructive pulmonary disease; dis: disfunction; Chr_Card_dis; chronic cardiac disease; HIV: Human immunodeficiency virus; AKI: acute kidney injury; CRP:C-reactive protein; GAP_ICU_cut: time elapsed between diagnosing pandemic viral infection and admission to ICU; Chr_renal_dis: Chronic renal disease; ID: immunosuppression ; Rx-cutoff: > 2 fields with infiltrations in chest X-ray; PCT: procalcitonin; MS_SA: Methicillin-sensitive *S. aureus*; GAP_diagnsosis_cut: Time from symptoms onset to diagnosis; hematol_dis: Hematologic disease; LDH: Lactate dehydrogenase)

Gender	Age_cut	APACHEII_cut	SOFA_cut	GAP_ICU_cut	GAP_diagnosis_cut
1.244341	1.276926	1.208923	1.226265	1.093180	1.047728
shock	asthma	COPD	chr_card_dis	chr_renal_dis	hematol_dis
1.356423	1.045245	1.145751	1.120188	1.235726	1.267477
pregnancy	obesity	diabetes	HIV	ID	steroids
1.194002	1.074920	1.166280	1.038319	1.280052	1.120085
AB_admission	MV_admission	miocardial_dis	AKI	Rx_cutoff	LDH_cut
1.057822	1.334363	1.045954	1.494582	1.094705	1.207255
CPK_cut	WBC_cut	Creatinine_cut	CRP_cut	PCT_cut	lactate_cut
1.264428	1.059907	1.390359	1.376125	1.979526	1.536026
DD_cut	klebsiella	Acinetobacter	S.pneumoniae	MS_SA	E.coli
1.633889	1.014681	1.011345	1.062170	1.025214	1.009540
MR_SA	Pseudomonas	aspergillus	antiviral_vaccine		
1.013241	1.019359	1.017844	1.072473		

Table S3: Cross-validation of multivariate linear (GLM) model.

```
Confusion Matrix and Statistics

          Reference
Prediction    0    1
         0 1866  509
         1  116  179

               Accuracy : 0.7659
                 95% CI : (0.7494, 0.7819)
    No Information Rate : 0.7423
    P-Value [Acc > NIR] : 0.00263

                  Kappa : 0.2479

 Mcnemar's Test P-Value : < 2e-16

            Sensitivity : 0.9415
            Specificity : 0.2602
         Pos Pred Value : 0.7857
         Neg Pred Value : 0.6068
             Prevalence : 0.7423
         Detection Rate : 0.6989
   Detection Prevalence : 0.8895
      Balanced Accuracy : 0.6008

       'Positive' Class : 0
```

Development of the GLM linear model for mortality with class imbalance correction

Applying the ROSE package to the training set reduced the population from 6232 patients to 3152 patients. Of these, 1606 died, giving an estimated mortality rate of 50.9%, twice the real rate (25%).

The variables included in the balanced model were the same as those used in the class imbalance model: Male, age cut-off, APACHEII cut-off, SOFA cut-off, ICU GAP cut-off, GAP diagnosis cut-off, shock, asthma, COPD, chronic heart disease, chronic kidney disease, haematological disease, pregnancy, obesity, diabetes, HIV, immunosuppression, steroids, antibiotic treatment on ICU admission, mechanical ventilation on ICU admission, Myocardial dysfunction, acute kidney injury (AKI), > 2 areas of infiltration on chest X-ray, lactate dehydrogenase cut-off, creatine phosphokinase cut-off, leukocyte cut-off, CRP cut-off, PCT cut-off, lactate cut-off, D-dimer cut-off, *Klebsiella* spp, *Acinetobacter* spp, *S. pneumoniae*, methicillin-resistant *Staphylococcus aureus*, methicillin-sensitive *Staphylococcus aureus* (MSSA), *E. coli*, methicillin-resistant *Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa, Aspergillus* spp and antiviral vaccine.

In Figure S2, the variables included in the models can be seen with their respective Odd Ratios and confidence intervals. The variables independently associated with mortality were the same as those observed in the unbalanced model.

Figure S2: Forest-Plot with the variables included in the balanced linear model with Odds Ratio.

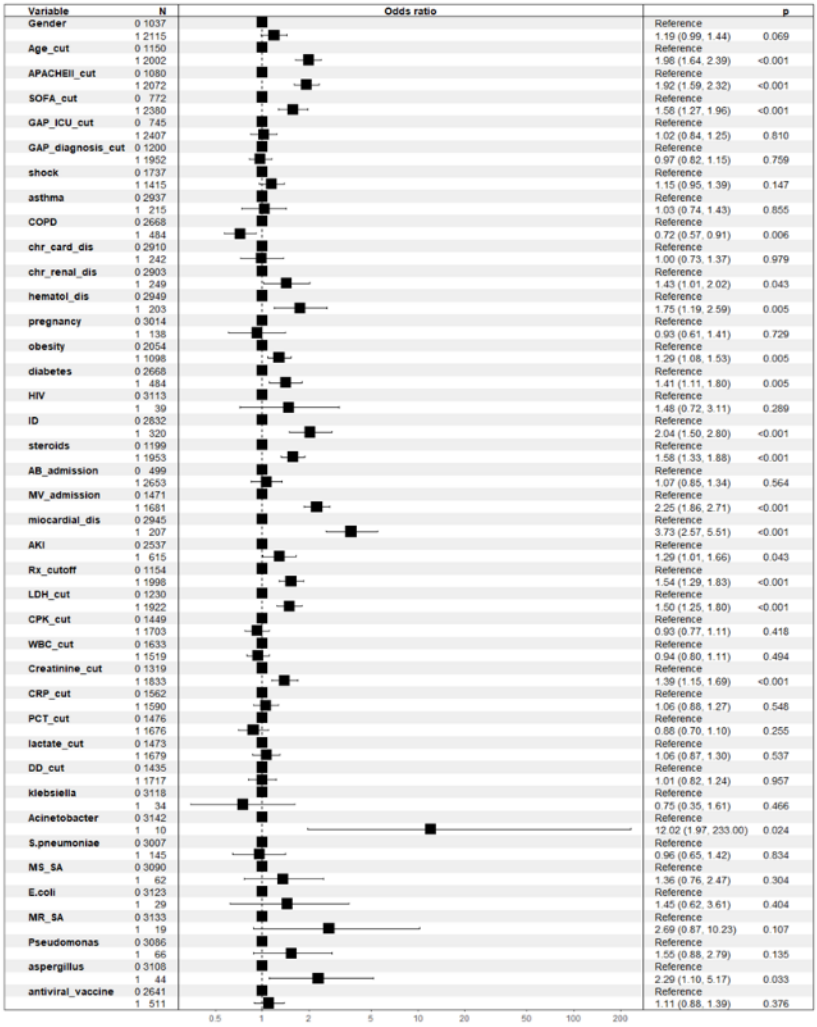


Table S4 : Performance of balanced linear model

```
Point estimates and 95% CIs:
-------------------------------------------------------------
Apparent prevalence *                  0.26 (0.24, 0.27)
True prevalence *                      0.43 (0.41, 0.45)
Sensitivity *                          0.43 (0.40, 0.46)
Specificity *                          0.87 (0.85, 0.89)
Positive predictive value *            0.72 (0.68, 0.75)
Negative predictive value *            0.67 (0.65, 0.69)
Positive likelihood ratio              3.39 (2.93, 3.93)
Negative likelihood ratio              0.65 (0.62, 0.69)
False T+ proportion for true D- *      0.13 (0.11, 0.15)
False T- proportion for true D+ *      0.57 (0.54, 0.60)
False T+ proportion for T+ *           0.28 (0.25, 0.32)
False T- proportion for T- *           0.33 (0.31, 0.35)
Correctly classified proportion *      0.68 (0.67, 0.70)
-------------------------------------------------------------
* Exact CIs
```

Figure S4: area under ROC curve of balanced mortality linear model

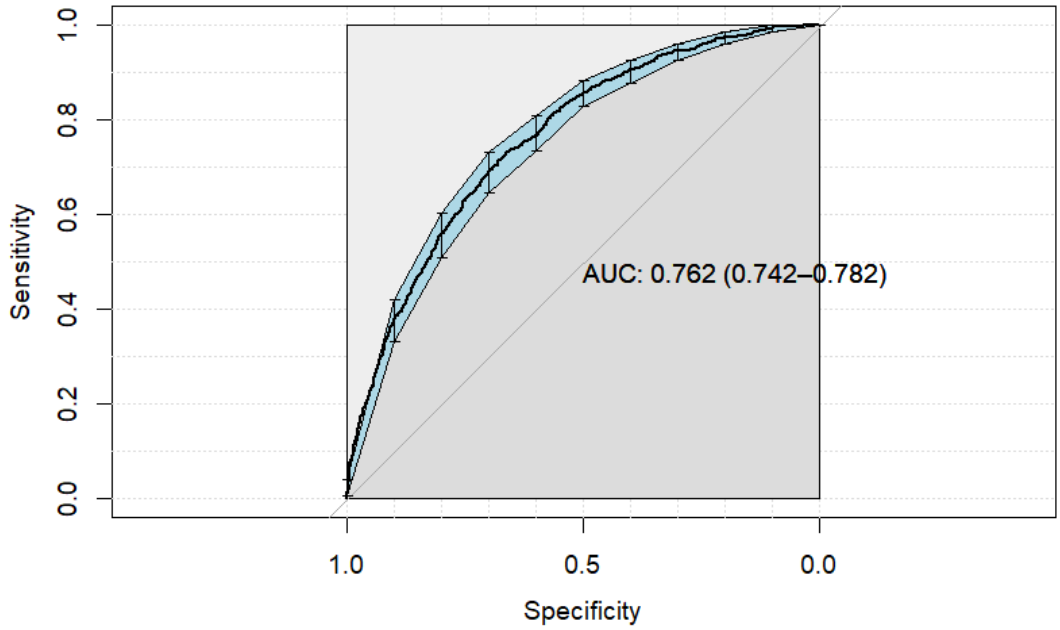
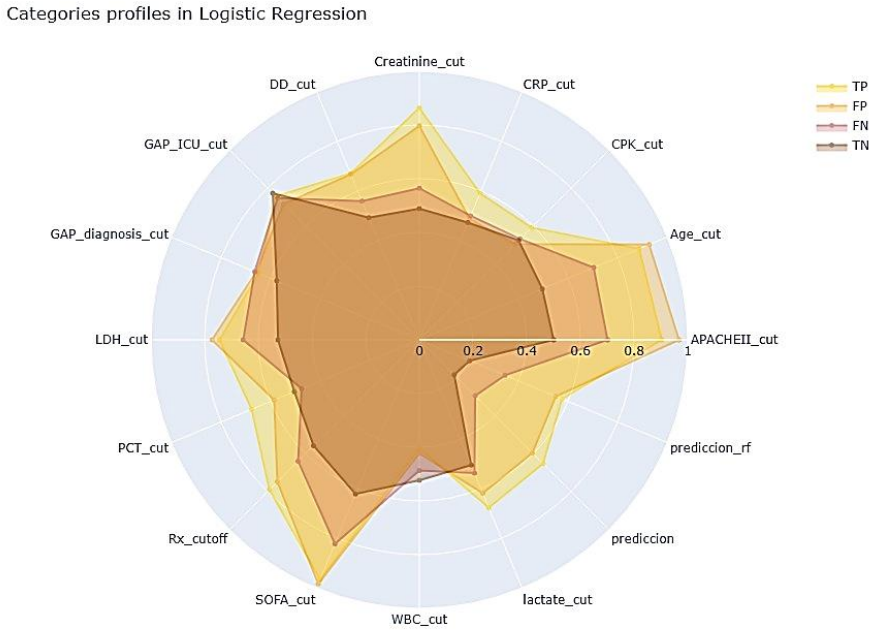
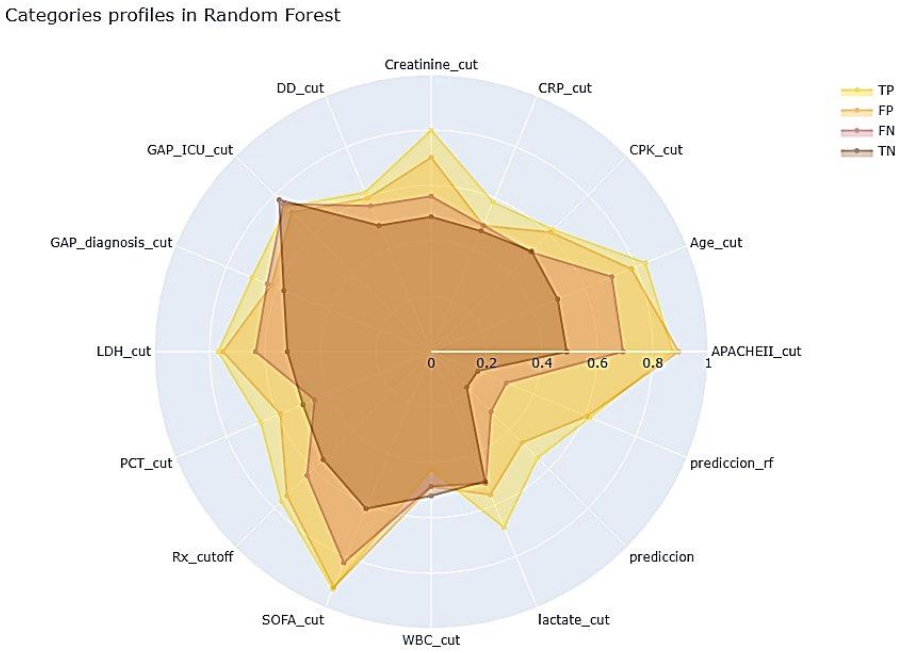


Figure S5: Categories profiles according to the model. A = linear model , B= no linear model

A



B



Abbreviations : cut: cut-off; APACHE II: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential organ failure assessment; AB: antibiòtics; CPK: creatine phospokinase; DD: D dímer; MR_SA: methicillin-resistant S. Aureus; MV: invasive mechanical ventilation; WBC: White blood cells; COPD: chronic obstructive pulmonary disease; dis: disfunction; Chr_Card_dis; chronic cardiac disease; HIV: Human immunodeficiency virus; AKI: acute kidney injury;

CRP:C-reactive protein; GAP_ICU_cut: time elapsed between diagnosing pandemic viral infection and admission to ICU; Chr_renal_dis: Chronic renal disease; ID: immunosuppression ; Rx-cutoff: > 2 fields with infiltrations in chest X-ray; PCT: procalcitonin; MS_SA: Methicillin-sensitive S. aureus; GAP_diagnsosis_cut: Time from symptoms onset to diagnosis; hematol_dis: Hematologic disease; LDH: Lactate dehydrogenase)

10.2 Material suplementario Artículo 2

Does Empirical Antibiotic Use Improve Outcomes in Ventilated Patients with Pandemic Viral Infection? A Multicentre Retrospective Study

Supplementary Material

Statistical analysis

First, we performed a descriptive analysis distinguishing between patients with and without empirical antibiotic treatment (EAT) on ICU admission. Continuous variables are presented as median and quantiles (Q1-Q3) and categorical variables as numbers (n) and percentages. Chi-square and U-Mann-Whitney tests were used to compare between groups.

Second, we performed a descriptive analysis differentiating patients with and without the presence of bacterial co-infection (COI). Within each of these subgroups, we differentiated between those with and without EAT.

Third, within the subgroup of patients with COI, we examined the impact of appropriate EAT (AEAT) on mortality, development of VAP, ICU and hospital LOS, and IMV days. For this analysis, patients with IAET were those with IEAT according to microbiological sensitivity and those without AET on ICU admission.

Fourth, within the subgroup of patients without COI, to analyse the impact of EAT on the study objectives, and to convert an observational study into a quasirandomized study, a propensity score matching analysis was performed. After matching, the effect of EAT on all cause ICU mortality and on the development of VAP was examined by Kaplan-Meier plot and differences were determined by Log Rang test.

In addition, a Cox proportional hazards (COX) and GLM model was used to determine whether EAT was a factor associated with VAP or ICU mortality in multivariate adjusted analysis. The results are expressed as hazard ratio (HR) and its 95% confidence interval (CI) for COX model and as Odds ratio (OR) and its 95% CI for GLM.

To assess whether the proportional hazard of the Cox model holds, the Schoenfeld residual test was used. The Schoenfeld test uses these residuals to test the proportional hazards hypothesis by examining whether they are correlated over time. If the test is not significant

(no correlation), the Schoenfeld residuals are considered to be uncorrelated over time, suggesting that the proportional hazards hypothesis is satisfied and that the effect of the predictor is constant.

Fifth: In addition, to evaluate the impact of EAT on patients without COI, a non-linear regression analysis (Random Forest - RF) was performed to study whether there are non-linear associations between EAT use and crude mortality or the deve-lopment of VAP that cannot be evidenced by linear analysis (GLM). Random forest models are a powerful non-linear tree-based machine learning technique. The developed model was configured to make 500 random trees, with a minimum number of 15 variables per tree. The performance of the RF model was evaluated using out-of-bag (OOB) error. This method allows the prediction error of random forests, boosted decision trees and other machine learning models to be measured using bootstrap aggre-gation. We also plotted the importance of the different variables for the model, which is related to the average loss of accuracy and the Gini index for the classification mo-del. The Gini index is a "measure of disorder", represented as "MeanDecreaseGini", which means that the higher the measure, the greater the importance in the generated models, since values close to 0 for the Gini index imply more disorder and values close to 1 imply less disorder. The higher this measure, the more variability it will contri-bute to the dependent variable. (Figure 1)

Definitions

- Respiratory co-infection (COI) was suspected if a patient presented with signs and symptoms of lower respiratory tract infection, with radiographic evidence of a pulmonary infiltrate with no other known cause (23,30,31). Coinfection had to be confirmed by laboratory testing using Centers for Disease Control and Prevention (CDC) criteria . Only respiratory infection microbiologically confirmed with a respiratory specimen or serology obtained within 2 days of ICU admission was considered community-acquired coinfection. The diagnosis of coinfection was considered "definitive" if respiratory pathogens were isolated from blood or pleural fluid and if serological tests confirmed a fourfold increase of atypical pathogens, including Chlamydia spp., Coxiella burnetti and Moraxella catarrhalis. Only patients with confirmed microbiologic diagnosis were included in the present analysis.
- Ventilator-associated pneumonia (VAP) was defined as a respiratory infection occurring in mechanically ventilated patients according to the guidelines of the European Respiratory Society (ERS), the European Society of Intensive Care Medicine (ESICM), the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), and the Asociación Latinoamericana del Tórax (ALAT). VAP was defined as pneumonia occurring more than 48 h after endotracheal intubation with fever, without other apparent causes, with new or increased sputum

production, positive endotracheal as-pirate (ETA) culture (>10^6 CFU/mL), or bronchoalveolar lavage (BAL) culture (>10^4 CFU/mL), with at least one respiratory pathogen known to cause pneumonia, and with radiographic evidence of nosocomial pneumonia.

- Empirical antibiotic treatment (EAT) were selected based on specialist clinical judgment and internal ICU protocols, which could subsequently be modified by the ASP (antimicrobial stewardship program) team, based on the clinical response in the days following VAP diagnosis or final microbiology results.
- Appropriate empiric antibiotic treatment (AEAT): Was defined as the administration of an antibiotic on admission to the ICU before the microbiological results are available and adjusted to the susceptibility of the pathogen when the microbiological results are available. AEAT was de-ermined by the attending physician in each center.
- Inappropriate empirical antibiotic treatment (IEAT): Was defined as antibiotic treatment administered on admission to the ICU that was not adapted to the susceptibility of the pathogen when microbiological results are available. In addition, the use of antibiotics at ICU admission in patients with no bacterial co-infection was also included in this definition.
- Multi-drug-resistant bacteria (MDR) are defined as those isolated strains that are not sensitive to at least one agent from three families of antimicrobials.
- Acute Kidney injury (AKI): The diagnosis of AKI was considered according to the Acute Kidney Injury Network (AKIN) described in the international KDIGO guidelines.
- GAP-UCI: was defined as the time elapsed between diagnosing pandemic viral infection and admission to ICU.
- GAP-Diagnosis: Was defined as the period of time between the onset of clinical symptoms and the microbiological diagnosis of the pandemic viral infection.
- Immunosuppression: this variable includes patients with active solid organ cancer, chemotherapy and patients on steroid therapy with a dose of prednisone > 30 mg/day or equivalent on prolonged therapy.
- Shock: was defined as any patient with noradrenaline requirements at a dose > 0.1 mcg/kg/min during the first hours of ICU admission.
- Chest x-ray cutoff: more than 2 lung fields occupied by infiltrates on chest x-ray

Figure S1: Flow Chart of included patients. (IMV: invasive mechanical ventilation; COI: coinfection; EAT: empiric antibiotic treatment; VAP: ventilator-associated pneumonia; AEAT: appropriate empiric antibiotic treatment; IEAT: inappropriate empiric antibiotic treatment; ICU: intensive care unit)

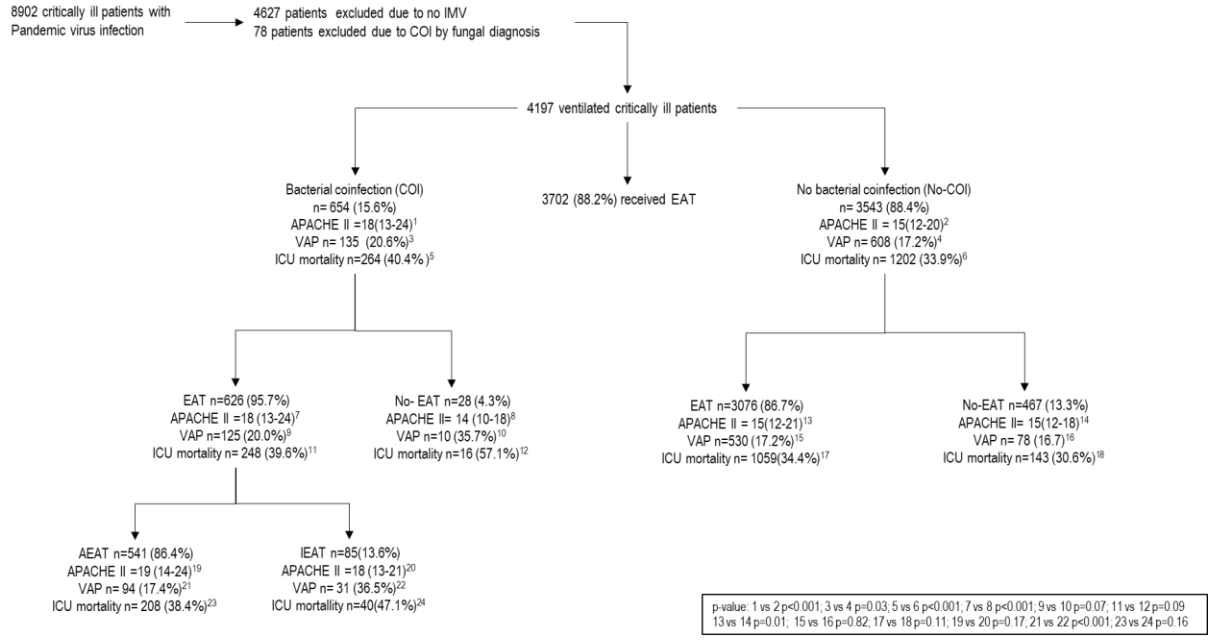
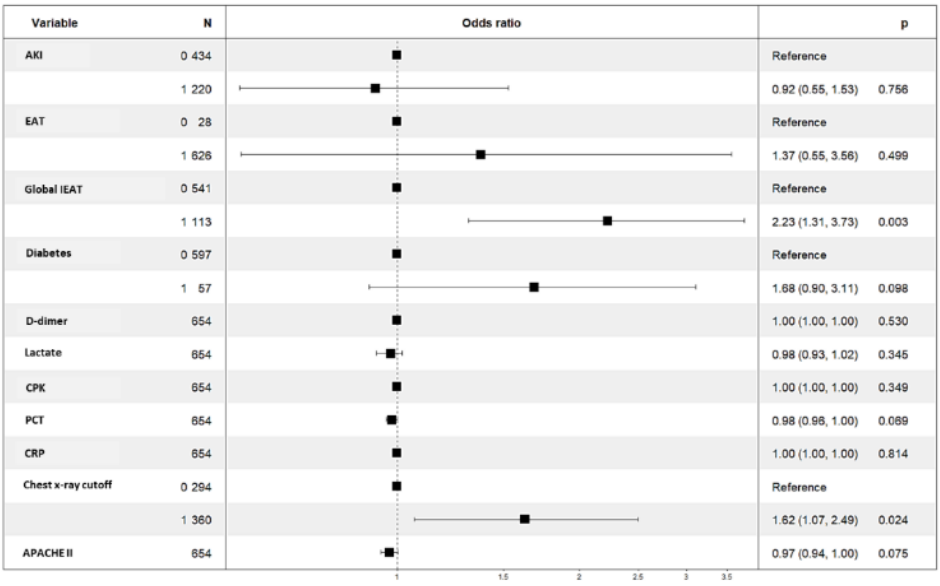


Table S1: Microorganisms isolated (in order of frequency) in 654 patients with bacterial co-infection (note that 54 patients (8.2%) had 2 microorganisms isolated and 4 (0.6%) had 3 microorganisms isolated simultaneously).

Microorganisms isolates	**n (%)***
Streptococcus pneumoniae	217 (33.2)
Methicillin-sensitive *Staphylococcus aureus*	107 (16.4)
Pseudomonas aeruginosa	88 (13.4)
Klebsiella spp.	47 (7.2)
Haemophilus influenzae	41 (6.3)
Streptococcus pyogenes	41 (6.3)
Methicillin-resistant Staphylococcus aureus	35 (5.3)
Escherichia coli	31 (4.7)
Acinetobacter baumannii	15 (2.3)
Serratia spp.	15 (2.3)
Stenotrophomonas malthophilia	13 (2.0)
Enterobacter spp.	8 (1.2)
Moraxella catarrhalis	7 (1.1)
Chlamydia pneumoniae	5 (0.8)
Legionella pneumophilia	5 (0.8)
Mycoplasma pneumoniae	5 (0.8)
Citrobacter spp.	4 (0.6)
Coxiella burnetii	3 (0.4)
Morganella morganii	3 (0.4)
Streptococcus agalactiae	3 (0.4)
Proteus spp.	3 (0.4)
Neisseria pneumoniae	3 (0.4)
Others	5 (0.8)
Total	704

* percentages are considered over the total number of patients.

Figure S2: Variables associated with the development of ventilator-associated pneumonia (VAP) in multivariate logistic regression model (GLM).



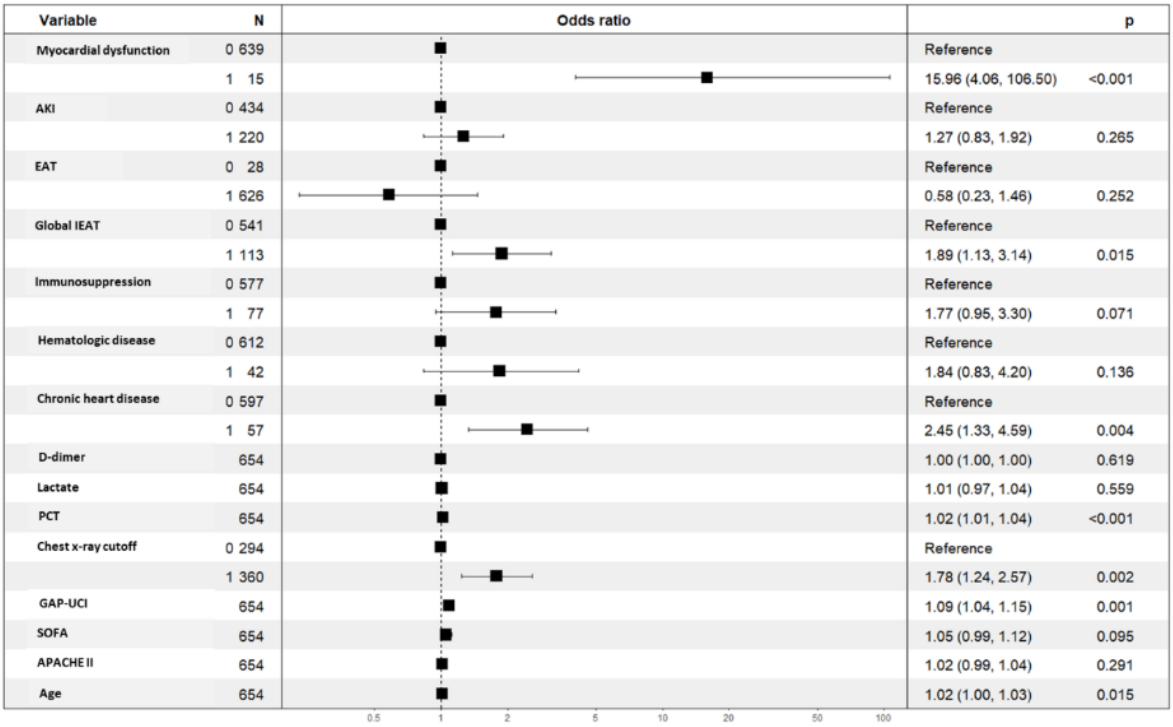
(CRP: C-reactive protein: CPK: creatine phosphokinase; PCT: procalcitonin; AKI: acute kidney injury; Chest x-ray cutoff: more than 2 lung fields occupied by infiltrates on chest x-ray; EAT: Empiric antibiotic treatment; Global IEAT: global inappropriate empiric antibiotic treatment include patients with IEAT plus patients without EAT)

Table S2: Patients with COI according to ICU outcome.

Variables	*Survivors (n=390)*	*Non-survivors (n=264)*	*p-value*
	General Characteristics		
Age, years	57 (47-68)	63 (52-74)	<0.001
Male sex	257 (65.9)	176 (66.7)	0.900
APACHE II score	18 (13-23)	20 (15-26)	<0.001
SOFA score	7 (5-9)	8 (5-10)	0.002
Gap-ICU, days	1 (0-2)	1 (0-3)	<0.001
Chest x-ray cutoff	200 (51.3)	160 (60.6)	0.020
	Laboratory		
WBC x10^3	8.5 (4.7-13.5)	8.4 (3.5-14.0)	0.510
LDH U/L	560 (456-720)	620 (670-770)	0.140
C-RP mg/mL	29.0 (16.0-76.0)	32.2 (18.1-84.5)	0.240
PCT ng/mL	4.12 (0.83-19.7)	8.26(1.32-24.4)	0.002
Creatinine mg/dL	1.0 (0.74-1.59)	1.25 (0.86-2.0)	<0.001
CPK ng/mL	320 (140-600)	315 (140-570)	0.810
Lactate mmol/L	2.9 (2.0-4.14)	3.5 (2.10-5.35)	0.010
D-dimer UI/L	5600 (2600-9540)	7340 (3760-13,560)	<0.001
	Comorbidities		
COPD	79 (20.3)	47 (17.8)	0.490
Asthma	28 (7.2)	13 (4.9)	0.310
Chr. Heart Dis	22 (5.6)	35 (13.3)	0.001
Chr.Renal Dis.	24 (6.1)	28 (10.6)	0.050
Hematologic Dis.	14 (3.6)	28 (10.6)	0.001
Pregnancy	32 (8.2)	21 (7.9)	1.000
Obesity	109 (27.9)	74 (28.0)	1.000
Diabetes	30 (7.7)	27 (10.2)	0.320
Immunosuppression	31 (7.9)	46 (17.4)	<0.001
	Treatment and complications		
Corticosteroids	223 (57.2)	177 (67.0)	0.010
EAT	378 (96.9)	248 (93.9)	0.090
AEAT	336 (86.2)	213 (80.7)	0.070
Global IEAT *	57 (14.6)	56 (21.2)	0.030
VAP	79 (20.3)	56 (21.2)	0.840
AKI	107 (27.4)	113 (42.8)	<0.001
Myocardial dysfunction	2 (0.5)	13 (4.9)	0.001
Shock	290 (74.4)	208 (78.8)	0.220
	Outcomes		
LOS ICU, days	19 (12-34)	11 (5-23)	<0.001
LOS Hospital, days	33 (22-49)	14 (6-27)	<0.001
IMV days	14 (8-27)	11 (4-22)	<0.001

#Continuous variables are shown as median values and percentiles Q1-Q3. Categorical variables are shown as number of cases (n) and percentage (%). (LDH: Lactate dehydrogenase; CRP: C-reactive protein: CPK: creatine phosphokinase; PCT: procalcitonin, VAP: ventilator associated pneumonia; AKI: acute kidney injury, LOS length of stay, ICU: intensive care units; Gap-ICU: Time in days from hospital admission to ICU admission; Chest x-ray cutoff: more than 2 lung fields occupied by infiltrates on chest x-ray; MDR: multi-drug resistant bacteria ; * Global IEAT: include patients with IEAT plus patients without EAT)

Figure S3: Variables associated with the crude ICU mortality in multivariate logistic regression model (GLM).



(AKI: acute kidney injury; EAT: empiric antibiotic treatment ; PCT: procalcitonin; Gap-ICU: Time in days from hospital admission to ICU admission; Chest x-ray cutoff: more than 2 lung fields occupied by infiltrates on chest x-ray; Global IEAT: include patients with IEAT plus patients without EAT)

Propensity Score Matching

In an attempt to address the bias of an observational study and to adjust for different covariates between groups receiving and not receiving EAT, we performed propensity score matching using the 'MatchIt' package of the 'R' statistical programme (Ho, D. E., Imai, K., King, G., Stuart, E. A. MatchIt: Nonparametric Preprocessing for Parametric Causal Inference. Journal of Statistical Software, 2011;42(8). doi:10.18637/jss.v042.i08).

MatchIt provides a simple and straightforward interface for covariate balancing in observational studies using Mahalanobis distance matching with substitution and balance assessment. We have implemented the "Full" method for optimal full matching with a caliper of 0.2, which is the width of the calipers to be used in the matching. It should be a numerical vector with each value named according to the variable to which the caliper applies. For positive values, the distance between the paired units must not be greater

than the caliper provided; for negative values, the distance between the paired units must be greater than the absolute value of the caliper provided.

After propensity score matching, there was a loss of only 23 patients who could not be matched. Finally, the matched cohort has 467 controls without EAT and 3053 cases receiving EAT. The summary of balance for all data and matched data are show in Table S5

Table S3: Summary of balance for all data (no-matched) and matched data

Table S5

Summary of Balance for All Data

	Means Treated	Means Control	Std. Mean Diff.	Var. Ratio	eCDF Mean	eCDF Max
	<chr>	<chr>	<chr>	<chr>	<chr>	<chr>
distance	0.8717	0.8453	0.5073	0.8509	0.1380	0.2233
Gender0	0.3427	0.3769	-0.0721	.	0.0342	0.0342
Gender1	0.6573	0.6231	0.0721	.	0.0342	0.0342
Age	58.5217	56.5096	0.1435	0.7814	0.0262	0.0704
GAP_ICU	2.5405	2.8617	-0.0855	1.5391	0.0955	0.2359
APACHEII	16.7395	15.8594	0.1189	1.4079	0.0454	0.1034
SOFA	6.5269	5.8387	0.2301	1.3276	0.0753	0.1369
Rx_cutoff0	0.3524	0.2548	0.2043	.	0.0976	0.0976
Rx_cutoff1	0.6476	0.7452	-0.2043	.	0.0976	0.0976
PCT	6.5431	4.6518	0.1326	1.5148	0.0595	0.1038
DD	7856.7859	6357.8477	0.0624	3.4398	0.0476	0.1167
steroids0	0.4125	0.5353	-0.2494	.	0.1228	0.1228
steroids1	0.5875	0.4647	0.2494	.	0.1228	0.1228
AKI0	0.8231	0.8779	-0.1436	.	0.0548	0.0548
AKI1	0.1769	0.1221	0.1436	.	0.0548	0.0548
shock0	0.3628	0.4368	-0.1540	.	0.0740	0.0740
shock1	0.6372	0.5632	0.1540	.	0.0740	0.0740

Summary of Balance for Matched Data

	Means Treated	Means Control	Std. Mean Diff.	Var. Ratio	eCDF Mean	eCDF Max	Std. Pair Dist.
	<chr>	<chr>	<chr>	<chr>	<chr>	<chr>	<chr>
distance	0.8720	0.8720	0.0008	1.0001	0.0018	0.0121	0.0089
Gender0	0.3416	0.3438	-0.0045	.	0.0021	0.0021	0.9214
Gender1	0.6584	0.6562	0.0045	.	0.0021	0.0021	0.9214
Age	58.5155	60.8277	-0.1649	1.0657	0.0366	0.1110	1.0384
GAP_ICU	2.4860	2.7513	-0.0706	1.5335	0.0958	0.1964	0.7784
APACHEII	16.6895	17.2528	-0.0761	1.0492	0.0501	0.0983	0.9739
SOFA	6.5106	6.2740	0.0791	1.0616	0.0259	0.0632	0.8540
Rx_cutoff0	0.3518	0.4261	-0.1556	.	0.0744	0.0744	0.7654
Rx_cutoff1	0.6482	0.5739	0.1556	.	0.0744	0.0744	0.7654
PCT	6.3828	5.7892	0.0416	1.3046	0.0468	0.0942	0.5339
DD	7840.1666	7097.0687	0.0309	2.5951	0.0348	0.0901	0.3877
steroids0	0.4107	0.4058	0.0100	.	0.0049	0.0049	0.7174
steroids1	0.5893	0.5942	-0.0100	.	0.0049	0.0049	0.7174
AKI0	0.8248	0.8012	0.0618	.	0.0236	0.0236	0.6417
AKI1	0.1752	0.1988	-0.0618	.	0.0236	0.0236	0.6417
shock0	0.3626	0.4392	-0.1594	.	0.0766	0.0766	0.8748
shock1	0.6374	0.5608	0.1594	.	0.0766	0.0766	0.8748

Figure S4: Histograms of propensity scores before and after matching**.**

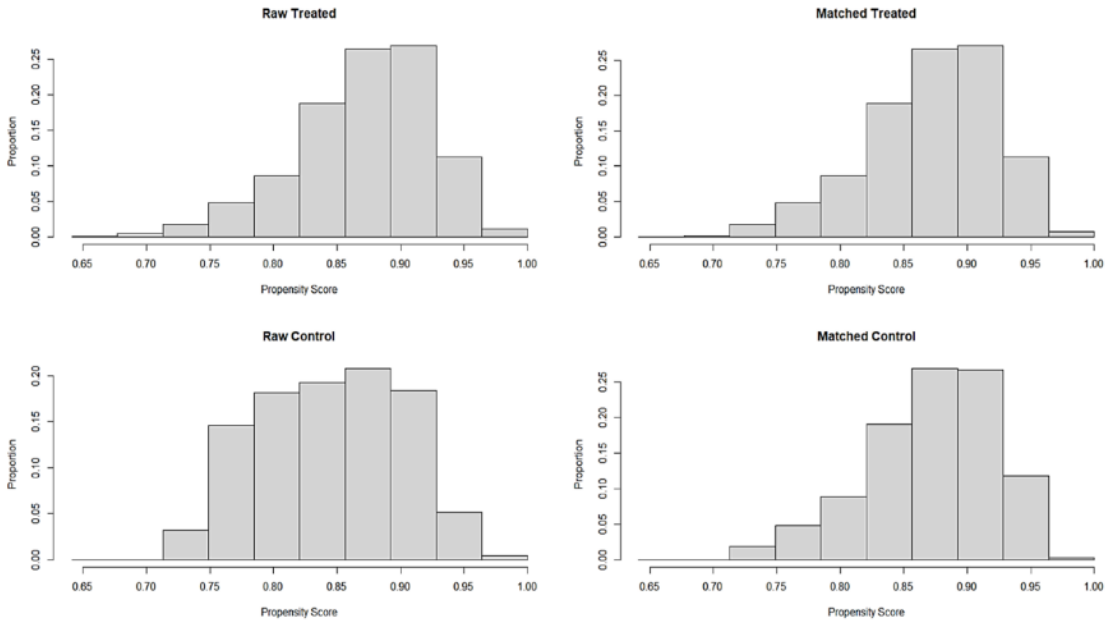


Figure S5: Plot of mean differences between unadjusted (no matched) and adjusted (matched) covariates

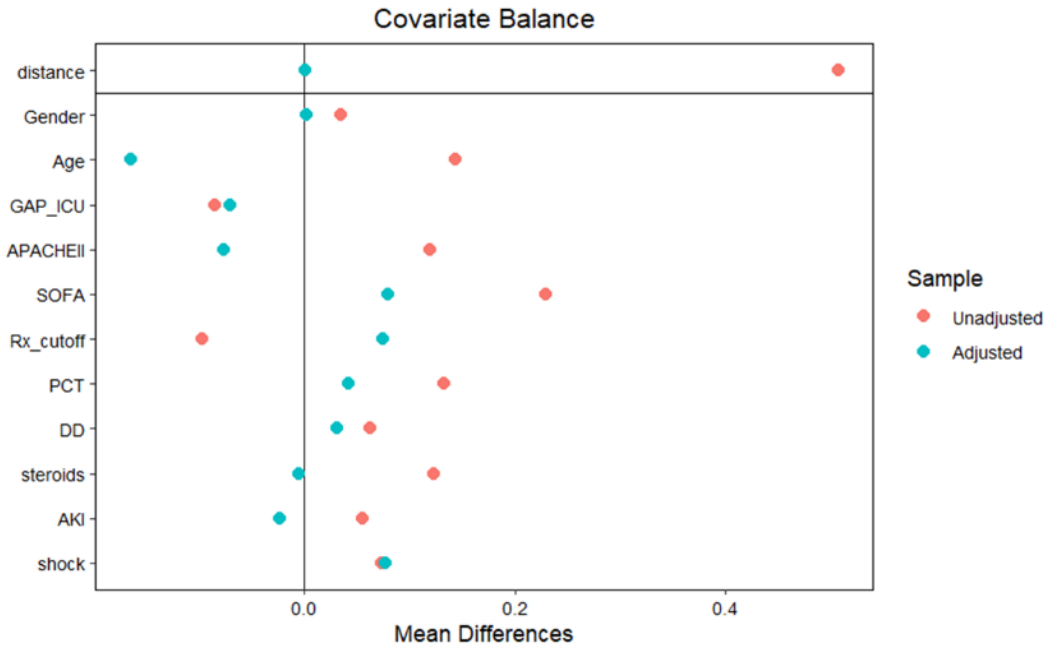


Table S4 : Characteristics of matched cohort of patients without Coinfection according to ventilator associated pneumonia.

Variables	*No VAP (n=2916)*	*VAP (n=604)*	*p-value*
	General Characteristics		
Age, years	60 (48-69)	62 (52-71)	<0.001
Male sex	1879 (64.4)	422 (69.9)	0.010
APACHE II score	15 (12-20)	15 (12-20)	0.510
SOFA score	6 (4-8)	6 (4-8)	0.320
Chest x-ray cutoff	1878 (64.4)	449 (74.3)	<0.001
	Laboratory		
WBC x10^3	8.7 (5.7-12.2)	9.0 (6.0-13.0)	0.090
LDH U/L	600 (450-770)	590 (450-740)	0.460
C-RP mg/mL	22.0 (11.2-38.5)	18.0 (9.8-29.7)	<0.001
PCT ng/mL	1.26 (0.30-7.30)	0.56 (0.20-2.05)	<0.001
Creatinine mg/dL	0.90 (0.70-1.27)	0.90 (0.70-1.22)	0.310
CPK ng/mL	260 (117-480)	230 (116-440)	0.080
Lactate mmol/L	2.2 (1.5-3.5)	2.8 (1.2-2.9)	<0.001
D-dimer UI/L	4200 (1650-7690)	2200 (750-7190)	<0.001
	Comorbidities		
COPD	401 (13.8)	81 (13.4)	0.870
Asthma	219 (7.5)	42 (6.9)	0.690
Chr. Heart Dis	184 (6.3)	29 (4.8)	0.180
Chr.Renal Dis.	171 (5.9)	34 (5.6)	0.890
Hematologic Dis.	142 (4.9)	26 (4.3)	0.620
Pregnancy	126 (4.3)	17 (2.8)	0.620
Obesity	1040 (35.7)	242 (40.1)	0.040
Diabetes	328 (11.2)	106 (17.5)	<0.001
Immunosuppression	229 (7.8)	38 (6.3)	0.210
	Treatment and complications		
Corticosteroids	1583 (54.3)	433 (71.7)	<0.001
EAT	2527 (86.7)	526 (87.1)	0.830
AKI	496 (17.0)	96 (15.9)	0.540
Myocardial dysfunction	141 (4.8)	60 (9.9)	<0.001
Shock	1856 (63.6)	353 (58.4)	0.010
	Outcomes		
LOS ICU, days	14 (9-23)	30 (20-46)	<0.001
LOS Hospital, days	24 (15-35)	40 (27-60)	<0.001
ICU mortality	953 (32.7)	239 (39.6)	0.001

#Continuous variables are shown as median values and percentiles Q1-Q3. Categorical variables are shown as number of cases (n) and percentage (%). (LDH: Lactate dehydrogenase; CRP: C-reactive protein: CPK: creatine phosphokinase; PCT: procalcitonin, VAP: ventilator associated pneumonia; AKI: acute kidney injury, LOS length of stay, ICU: intensive care units; Gap-ICU: Time in days from hospital admission to ICU admission; Chest x-ray cutoff: more than 2 lung fields occupied by infiltrates on chest x-ray; MDR: multi-drug resistant bacteria ; * Global IEAT: include patients with IEAT plus patients without EAT)

Table S5: Variables associated with VAP in the Cox Hazard regresssion analysis.

	HR	95 % CI	
EAT	1.0046	0.7898	1.2777
Age	1.0046	0.9980	1.0112
Rx_cutoff	1.2632	1.0514	1.5177*
Steroids	1.2934	1.0776	1.5524**
Diabetes	0.9475	0.7590	1.1827
Obesity	1.1317	0.9596	1.3346
Lactate	0.9646	0.9404	0.9893**

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Concordance= 0.58(se = 0.015)
Likelihood ratio test= 36.27 on 7 df,p=6e-06
Wald test = 31.51 on 7 df,p=5e-05
Score (logrank) test = 32.1 on 7 df,p=4e-05

Figure S6: Variables independently associated with VAP in logistic regression model

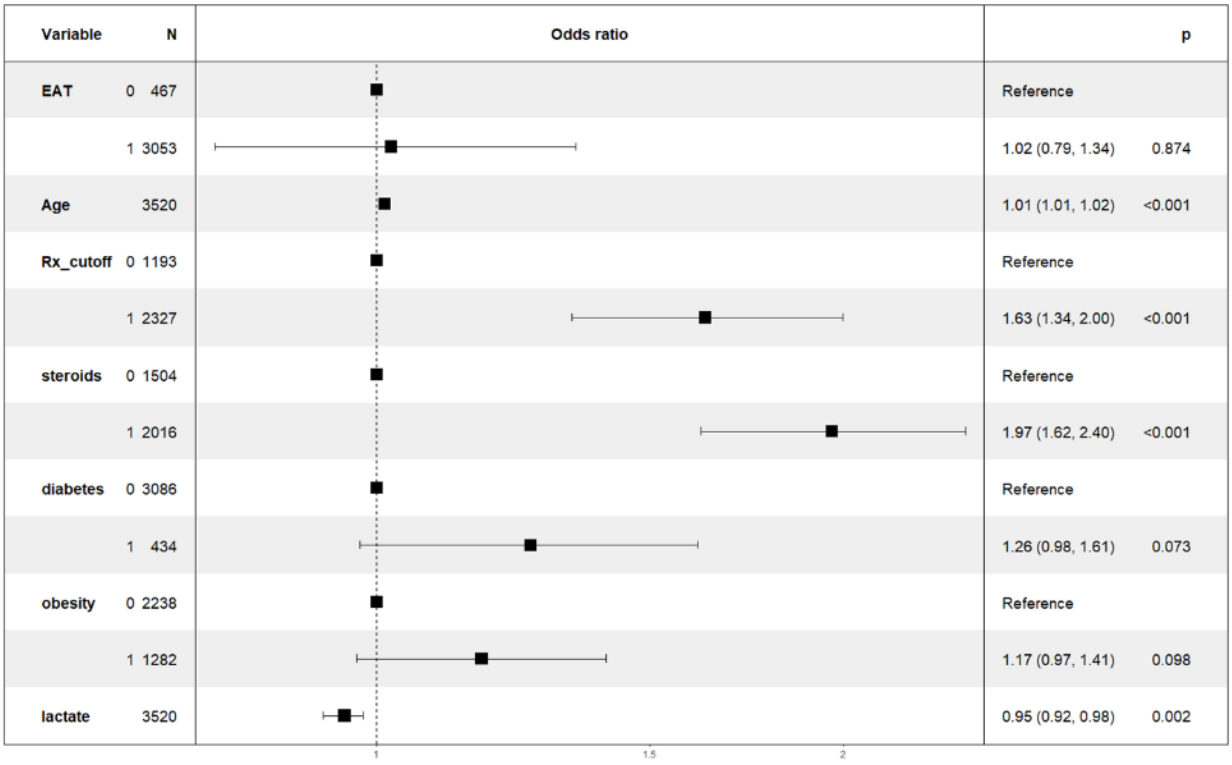


Table S6: Characteristics of matched cohort patients according to all cause ICU mortality in patients without bacterial coinfection

Variables	*Survival (n=2328)*	*Non-survival (n=1192)*	*p-value*
	General Characteristics		
Age, years	58 (46-66)	66 (55-73)	<0.001
Male sex	1466 (63)	835 (70.1)	<0.001
APACHE II score	14 (11-19)	17 (13-23)	<0.001
SOFA score	6 (4-8)	7 (5-9)	<0.001
Chest x-ray cutoff	1470 (63.1)	857 (72.0)	<0.001
GAP-UCI	1 (1-3)	2 (1-4)	0.01
	Laboratory		
WBC x10^3	8.5 (5.6-12.1)	9.5 (6.2-14.2)	<0,001
LDH U/L	586 (435-750)	620 (490-796)	<0.001
C-RP mg/mL	21.0 (10.8-36.0)	22.0 (11.0-35.4)	0.480
PCT ng/mL	1.02 (0.26-5.13)	1.25 (0.30-9.0)	<0.001
Creatinine mg/dL	0.86 (0.70-1.16)	1.01 (0.77-1.45)	<0.001
CPK ng/mL	250 (115-470)	257 (120-480)	0.870
Lactate mmol/L	2.0 (1.4-3.1)	2.3 (1.5-3.8)	<0.001
D-dimer UI/L	3700 (1300-6800)	4900 (1700-9300)	<0.001
	Comorbidities		
COPD	300 (12.9)	182 (15.3)	0.050
Asthma	185 (8.0)	76 (6.4)	0.100
Chr. Heart Dis	125 (5.4)	88 (7.4)	0.020
Chr.Renal Dis.	111 (4.8)	94 (7.9)	<0.001
Hematologic Dis.	71 (3.0)	97 (8.1)	<0.001
Pregnancy	109 (4.7)	34 (2.8)	0.010
Obesity	854 (36.7)	428 (36.0)	0.670
Diabetes	233 (10.0)	201 (17.0)	<0.001
Immunosuppression	119 (5.1)	148 (12.4)	<0.001
	Treatment and complications		
Corticosteroids	1259 (54.1)	757 (63.5)	<0.001
EAT	2004 (86.1)	1049 (88.0)	0.120
VAP	365 (15.7)	239 (20.1)	0.001
AKI	305 (13.1)	287 (24.1)	<0.001
Myocardial dysfunction	75 (3.2)	126 (10.6)	<0.001
Shock	1400 (60.1)	809 (68.0)	<0.001
	Outcomes		
LOS ICU, days	17 (11-30)	14 (7-23)	<0.001
LOS Hospital, days	30 (20-46)	18 (9-28)	<0.001

Table S7 : Variables associated with all cause ICU mortality in the Cox Hazard regresssion analysis.

	HR	95% CI	
EAT1	1.0262	0.8595	1.2252
Age	1.0210	1.0159	1.0260***
Rx_cutoff1	1.2633	1.1120	1.4352***
AKI1	1.2069	1.0319	1.4117*
Myocardial_dys1	1.6750	1.3808	2.0319***
VAP1	0.5187	0.4463	0.6027***
steroids1	1.1060	0.9785	1.2501
ID1	1.5711	1.2789	1.9301***
diabetes1	1.2156	1.0349	1.4278*
hematol_dis1	1.2721	0.9949	1.6266
chr_renal_dis1	0.8252	0.6547	1.0401
shock1	1.0595	0.9307	1.2062
DD	1.0000	1.0000	1.0000**
lactate	1.0073	0.9961	1.0186
PCT	1.0087	1.0068	1.0107***
WBC	1.0009	0.9992	1.0026
LDH	1.0003	1.0001	1.0004*
SOFA	1.0235	1.0002	1.0473***
APACHEII	1.0249	1.0156	1.0343*
GAP_ICU	1.0169	1.0031	1.0309***
Gender1	1.0359	0.9131	1.1751

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Concordance= 0.698 (se = 0.009)
Likelihood ratio test= 448.7 on 21 df, p=<2e-16
Wald test = 507.2 on 21 df, p=<2e-16
Score (logrank) test = 546.9 on 21 df, p=<2e-16

Figure S7: Variables independently associated with all cause ICU mortality in logistic regression model

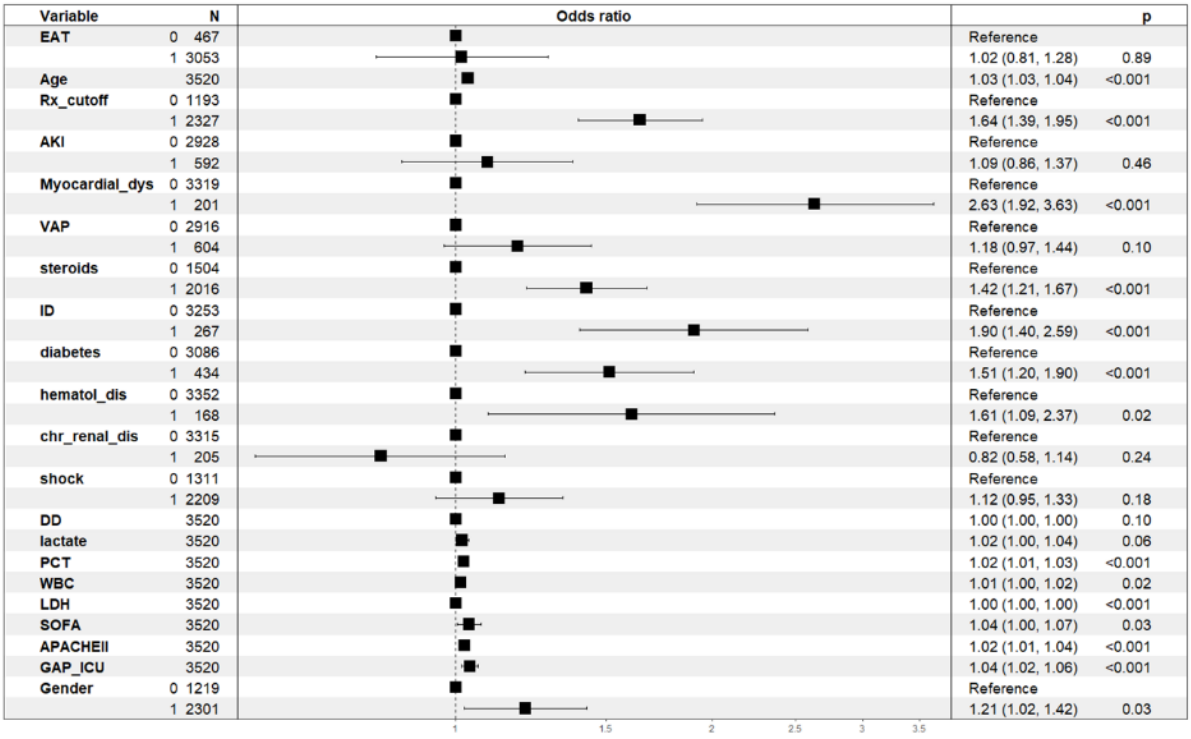


Table S10: Importance of variables for VAP according to Random Forest model

	0	1	MeanDecreaseAccuracy	MeanDecreaseGini
Gender	2.34	-1.51	1.51	5.26
Age	9.81	3.06	10.51	60.73
GAP_ICU	9.85	6.14	11.92	36.86
APACHEII	15.33	0.90	14.51	60.99
SOFA	15.43	-0.47	14.42	49.68
LDH	5.76	3.86	6.91	74.80
CPK	10.22	-0.83	9.46	78.34
WBC	12.39	2.41	12.89	74.76
Creatinine	22.44	-5.07	20.47	67.96
urea	18.13	-2.98	16.70	65.36
CRP	15.58	-7.01	13.31	76.78
PCT	29.01	-2.85	29.64	77.03
lactate	26.38	0.40	26.74	74.57
DD	28.06	18.89	34.56	116.39
shock	4.90	0.30	4.87	6.92
asthma	-0.16	-0.35	-0.28	4.04
COPD	1.07	0.61	1.28	4.88
chr_card_dis	2.15	-0.45	1.82	2.46
chr_renal_dis	4.90	-2.13	3.90	2.37
hematol_dis	1.63	-2.88	0.45	2.93
pregnancy	-1.22	-1.69	-1.73	1.89
obesity	0.11	2.09	1.20	6.04
diabetes	3.48	2.45	4.56	4.98
ID	6.06	0.44	5.71	3.24
steroids	6.33	16.23	13.15	14.36
EAT	5.62	4.39	6.92	6.79
AEAT	0.00	0.00	0.00	0.00
Myocardial_dys	8.28	6.98	10.88	8.12
AKI	4.11	-3.15	3.42	1.45
Rx_cutoff	3.89	8.12	6.55	8.37

Table S11: Importance of variables for all cause ICU mortality according to Random Forest model

	0	1	MeanDecreaseAccuracy	MeanDecreaseGini
Gender	3.04	-0.70	1.94	7.65
Age	36.89	21.67	45.31	151.75
GAP_ICU	17.46	5.93	17.99	65.83
APACHEII	13.84	12.01	18.79	103.61
SOFA	6.54	14.75	15.47	81.05
LDH	12.88	4.32	13.06	123.04
CPK	13.92	-3.19	10.11	101.83
WBC	17.98	-2.39	13.39	115.47
Creatinine	19.84	-0.66	20.12	104.58
urea	22.36	5.19	25.30	125.97
CRP	19.75	-5.74	16.65	103.08
PCT	31.81	0.20	32.22	114.59
lactate	14.41	2.37	14.12	101.06
DD	25.19	0.12	23.32	118.67
shock	-2.32	7.13	3.16	9.74
asthma	2.23	1.03	2.43	5.49
COPD	12.31	-3.94	8.46	8.65
chr_card_dis	9.45	-3.06	6.61	6.84
chr_renal_dis	9.86	-5.75	5.23	5.50
hematol_dis	8.39	6.20	11.01	9.15
pregnancy	-0.16	-0.99	-0.78	3.43
obesity	-0.05	0.59	0.29	8.80
diabetes	13.69	6.70	15.06	13.15
ID	9.27	9.92	13.84	16.18
steroids	6.13	1.68	5.85	12.83
EAT	0.74	1.03	1.29	6.93
AEAT	0.00	0.00	0.00	0.00
VAP	5.69	8.34	9.62	13.01
Myocardial_dys	13.67	10.18	16.86	16.37
AKI	6.22	-2.87	5.78	2.92
Rx_cutoff	12.49	4.64	12.41	18.85