Impacto de la disfunción muscular y de los microorganismos resistentes en las exacerbaciones de la enfermedad pulmonar obstructiva crónica.

Cristina Estirado Vera

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SUPERVISOR DE LA TESIS

Dr. Antoni Torres Marti. Departamento de Medicina, Universidad de Barcelona UB. Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS)

TUTOR DE LA TESIS

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Resumen

La Enfermedad Pulmonar Obstructiva crónica (EPOC) presenta afectación pulmonar y sistémica y periodos de exacerbación (AEPOC), que contribuyen a su progresión. En algunas ocasiones la AEPOC está causada por microorganismos resistentes a tratamiento convencional (MRCT). Comparamos las características de las AEPOC por MRCT con las producidas por otras causas. Los factores de riesgo para presentar AEPOC por MRCT fueron el tabaquismo no activo, ≥ 2 AEPOC o de ≥ 1 hospitalización por AEPOC el año previo y una baja respuesta inflamatoria al ingreso. Los pacientes con MRCT tenían estancias hospitalarias más prolongadas. La disfunción muscular es una manifestación sistémica común en la EPOC. Estudiamos la función muscular periférica y respiratoria durante la hospitalización por AEPOC. La fuerza muscular estaba disminuida, aunque en mayor grado la respiratoria. La determinación temprana de la fuerza muscular inspiratoria es un buen predictor tanto de una nueva AEPOC como de reingreso hospitalario.

Abstract

Chronic Obstructive Pulmonary Disease (COPD) is characterized by both pulmonary and systemic involvements, as well as periods of exacerbation (AECOPD), which contribute to its progression. Sometimes AECOPD is caused by microorganisms resistant to conventional treatment (MRCT). We compared the characteristics of AECOPD caused by MRCT with those produced by other causes. The risk factors for AEPOC by MRCT were non-current smoking, ≥ 2 AEPOC or ≥ 1 hospitalization for AEPOC in the previous year and a low inflammatory response at admission. Patients with MRCT had longer hospital stays. Muscle dysfunction is a common systemic manifestation in COPD. We studied the peripheric and respiratory muscle function in hospitalization for AECOPD. Muscle strength was decreased during AEPOC, although the inspiratory involvement was greater. The early determination of inspiratory muscle strength during hospitalization is a good predictor for both a new AECOPD and hospital readmission.

Prólogo

Esta tesis doctoral está basada en los siguientes estudios científicos:

1. Estirado C, Ceccato A, Guerrero M, Huerta A, Cilloniz C, Vilaró O, Gabarrús A, Gea J, Crisafulli E, Soler N, Torres A. Microorganisms resistant to conventional antimicrobials in acute exacerbations of chronic obstructive pulmonary disease. *Respir Res* 19**,** 119 (2018). https://doi.org/10.1186/s12931-018-0820-1

2. Estirado C, Dominguez-Alvarez M, Badenes-Bonet D, Martín-Ontiyuelo C, Torres A, Gea J. Muscle function during severe COPD exacerbations and risk of both a new episode and readmission. Enviado a publicación, pendiente de aceptación.

Los resultados preliminares de estas investigaciones se han presentado con anterioridad en los siguientes congresos de ámbito nacional e internacional:

Estirado C, Chalela R, Grau N, Balcells E, Dominguez M. Utilidad de la medición de la función muscular respiratoria durante la agudización hipercápnica de la enfermedad pulmonar obstructiva crónica. 49º Congreso Nacional SEPAR. *Arch Bronconeumol junio 2016; 52 suplC1:165*

Estirado C, Ceccato A, Guerrero M, Huerta A, Gabarrus A, Gea J, Soler N, Torres A. Microorganisms resistant to conventional antimicrobial treatment in acute exacerbation of COPD. European Respiratory Society Annual Congress 2017. *European Respiratory Journal 50 (suppl 61) PA4094;* ***DOI:*** *10.1183/1393003.congress-2017.PA4094.*

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Utilidad de la medición de la función muscular respiratoria durante la agudización hipercápnica de la enfermedad pulmonar obstructiva crónica. Beca SEPAR 2013. Investigadora colaboradora.

Índice

Abreviaturas

AEPOC: agudización o exacerbación de la enfermedad pulmonar obstructiva crónica
EPOC: enfermedad pulmonar obstructiva crónica
IMC: índice de masa corporal
MRCT: microorganismos resistentes a tratamiento convencional
MRSA: Sthafilococus aureus meticilin-resistente
MSCT: microorganismos sensibles a tratamiento convencional
MDR: del inglés, multidrug resistant
P.aeruginosa; Pseudomonas aeruginosa
PCR: proteína C reactiva
PI_{max}: presión inspiratoria máxima generada en boca
SNIP: presión nasal durante una inhalación máxima

1. INTRODUCCIÓN

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1.1 Exacerbación de EPOC. Generalidades

1.1. a) Impacto de la exacerbación de EPOC

Las exacerbaciones son episodios frecuentes en el curso natural de la enfermedad pulmonar obstructiva crónica (EPOC). La agudización o exacerbación de EPOC (AEPOC) se define como un episodio agudo de inestabilidad clínica que acontece en el curso natural de la enfermedad y se caracteriza por un empeoramiento mantenido de los síntomas respiratorios[1].

Desde el punto de vista fisiopatológico, las AEPOC son eventos complejos habitualmente relacionados con un incremento de la inflamación tanto local como sistémica. La respuesta inflamatoria en la vía aérea durante la exacerbación produce edema, broncoespasmo y un aumento en la producción de moco, lo que lleva a un empeoramiento de la limitación al flujo aéreo y al desarrollo de hiperinsuflación dinámica[1,2].

Estos cambios fisiopatológicos contribuyen a la aparición de síntomas, como el empeoramiento de la disnea, la tos, el incremento del volumen y/o los cambios en la coloración del esputo. La hiperinsuflación es la principal causa de disnea, el síntoma más común de la exacerbación y tiene además efectos mecánicos, cardiovasculares y de empeoramiento de intercambio gaseoso[3].

Las exacerbaciones son eventos con alto impacto en los pacientes y contribuyen de forma determinante a la progresión de la enfermedad[2]. La intensidad, duración y frecuencia de las AEPOC varía enormemente de unos pacientes a otros e incluso en el mismo paciente, por lo que resulta difícil precisar sus consecuencias para un paciente en particular[1]. Sin embargo, se ha demostrado que contribuyen de forma determinante al deterioro de la función pulmonar[4], producen un deterioro en la calidad de vida[5], y son responsables de gran parte de la morbilidad y mortalidad de los pacientes con EPOC[6].

En general, las AEPOC son más frecuentes y más severas a medida que la severidad de la enfermedad pulmonar aumenta. Sin embargo, hay grandes diferencias en la incidencia anual de exacerbaciones entre pacientes con similar severidad de EPOC. Algunos pacientes con EPOC son particularmente susceptibles a presentar agudizaciones frecuentes (definido como dos o más exacerbaciones al año) y estos pacientes han mostrado tener peor calidad de vida y morbilidad que los pacientes con menos exacerbaciones[2,5]. Los pacientes agudizadores frecuentes también presentan un mayor riesgo de ingreso hospitalario por exacerbación[7].

Además, el pronóstico a largo plazo de los pacientes con EPOC empeora tras una hospitalización por agudización, se ha descrito un ratio de mortalidad a los 5 años del 50% tras la hospitalización[8].

1.1. b) Factores predictores de AEPOC

La razón exacta de la susceptibilidad individual a la exacerbación aún no se conoce. Se han encontrado diversos factores que pueden predisponer a padecer una agudización: edad, sexo femenino, gravedad de la enfermedad. Sin embargo, el principal predictor conocido para presentar una AEPOC es el número de exacerbaciones padecida por el paciente durante el año previo[9,10]. Otros factores que se han asociado con aumento del riesgo de agudizaciones son aumento del ratio entre arteria pulmonar y aorta, mayor porcentaje de enfisema medido por TAC y la presencia de bronquitis crónica[2].

Las AEPOC parecen además eventos que se agrupan en el tiempo, se ha observado que tras una primera exacerbación, hay un período de 8 semanas de alto riesgo de recurrencia y de reingreso hospitalario (si la exacerbación precisó hospitalización) [11].

1.2 Infección bacteriana y AEPOC

Las AEPOC son eventos heterogéneos causados por interacciones complejas entre el huésped, virus respiratorios, bacterias de la vía aérea y polución ambiental, que llevan a un aumento de la carga inflamatoria tanto local como sistémica [12] .

En la mayoría de las ocasiones (50-70%) la causa de la exacerbación es la infección del árbol traqueobronquial, mientras que la contaminación ambiental puede ser la causante del 5-10% de las exacerbaciones[2,12] .

Las infecciones virales representan cerca del 30% de todas las agudizaciones de causa infecciosa, aunque algunos estudios recientes que emplean técnicas diagnósticas más precisas elevan hasta el 50% el número de exacerbaciones infecciosas causadas por virus. Los virus más frecuentemente asociados con exacerbaciones son los rinovirus, otros virus implicados incluyen coronavirus, virus respiratorio sincitial, influenza, parainfluenza y adenovirus [12].

1.2. a) Infección bacteriana

Los principales agentes de infección bacteriana identificados en las exacerbaciones de EPOC son Streptococcus pneumoniae, Haemophilus influenzae y Moraxella catarrhalis. Así, las recomendaciones vigentes de tratamiento antimicrobiano son aminopecilinas con ácido clavulánico, un macrólido o una tetraciclina [2,14].

De forma más infrecuente y sobre todo en exacerbaciones graves, pueden estar implicados otros microorganismos a menudo resistentes al tratamiento antimicrobiano habitual (MRCT), como Pseudomonas aeruginosa, Staphylococcus aureus, Enterobacterias o Stenotrophomona Maltophilia [13,15,16].

Reconocer la etiología de agudización como bacteriana, para así poder seleccionar adecuadamente los pacientes candidatos a recibir

antibioterapia, no es sencillo. Los patógenos bacterianos pueden aislarse en el esputo durante la AEPOC, pero el análisis del esputo (tinción de gram y cultivo) no se realiza de forma rutinaria en la práctica clínica habitual y puede tener como inconveniente la dificultad de obtener una muestra adecuada en algunos pacientes. Por otra parte, la realización de broncofibroscopia para obtención de muestras microbiológicas es muy dificultosa en las AEPOC.

Por tanto, en la mayor parte de los casos la aproximación diagnóstica es clínica. Anthonisen et al[17] mostraron que los pacientes que cumplían al menos dos de los tres síntomas cardinales de exacerbación (aumento de disnea, aumento del volumen del esputo y purulencia del esputo) se beneficiaban claramente de recibir tratamiento antibiótico.

Sin embargo, de los tres criterios recomendados, el que mejor predice la infección bacteriana es el cambio en la coloración del esputo (purulencia). En pacientes con EPOC grave hospitalizados por AEPOC se ha objetivado que la purulencia del esputo predice la infección en vía aérea distal (confirmada mediante cultivo de cepillado protegido obtenido mediante broncofibroscopia) con una sensibilidad del 89,5% y una especificidad del 76,2%. Por el contrario, el esputo mucoso pocas veces se asocia a infección bacteriana[18].

Por otra parte, el rol preciso de las bacterias en las AEPOC es difícil de establecer , dado que la colonización bacteriana en vía aérea en el paciente con EPOC estable se asocia con los mismos microorganismos que los aislados en las exacerbaciones y representa además un estímulo añadido para la inflamación de la vía aérea [19]. Se estima que al menos el 30% de los pacientes con EPOC están colonizados por potenciales patógenos cuando se encuentran en fase estable de su enfermedad, fundamentalmente por Haemophilus Influenzae, Streptococcus Pneumoniae y Moraxella catarrhalis [20,21].

Las AEPOC se asocian con un sobrecrecimiento en la vía aérea de estos gérmenes potencialmente patógenos (Haemophilus Influenzae, Streptococcus Pneumoniae, Moraxella catarrhalis) y también con la aparición de otros nuevos como Pseudomonas aeruginosa [20].

1.2. b) Microorganismos resistentes.

La exacerbación de EPOC está infrecuentemente causada por microorganismos que habitualmente son resistentes al tratamiento antibiótico recomendado por las guías (aminopenicilinas con ácido clavulánico, un macrólido o una tetraciclina)[2,14] como Pseudomonas aeruginosa (P. aeruginosa), Staphylococcus aureus meticilin-resistente (MRSA), Stenotrophomonas maltophilia o enterobacterias (Klebsiella pneumoniae, Escherichia coli, Serratia marcescens, Morganella morganii, Proteus mirabilis, Enterobacter cloacae)[13,15,16].

Los pacientes con AEPOC producida por estas bacterias habitualmente tienen una limitación al flujo más severa; en concreto se ha encontrado una correlación entre el deterioro de función pulmonar y la agudización secundaria a infección por Pseudomonas Aeruginosa [16,22].

Existe asimismo una relación entre la gravedad de la AEPOC y la infección por patógenos no habituales. Así, en los pacientes hospitalizados por AEPOC se ha objetivado una alta prevalencia de infección por estos microorganismos, destacando los aislamientos de P. Aeruginosa que en pacientes hospitalizados se sitúan entre el 15-25% en los diversos estudios[23,24,25].

Además, la infección bacteriana por gérmenes no habituales es mayor en el grupo de pacientes con EPOC que requieren frecuentes hospitalizaciones por exacerbación (más de dos anuales), por lo que podría ser un factor fundamental en el riesgo de reingreso hospitalario por agudización. En este subgrupo de pacientes se han aislado un 71,1% de patógenos no habituales, sobre todo P. Aeruginosa, Stenotrophomona maltophilia, Enterobacterias y MRSA[23].

Los estudios realizados sugieren además que los pacientes con AEPOC por P. Aeruginosa tienden a presentar un peor pronóstico, con mayor mortalidad y hospitalizaciones más frecuentes, aunque hay algunos resultados contradictorios[23-27].

Sólo el 0,5% de los pacientes con EPOC estable están colonizados por enterobacterias, P. Aeruginosa o Stenotrophomonas maltophilia[20]. En un reciente estudio en más de 2000 pacientes con EPOC estable, se ha demostrado que la colonización por P. Aeruginosa predice un marcado aumento del riesgo de hospitalización por exacerbación y de mortalidad[28].

Los factores que predicen el riesgo de infección por gérmenes no habituales en la AEPOC aún no están totalmente aclarados. Se han descrito la severidad de la limitación al flujo aéreo, el número de ingresos hospitalarios por agudización en el año previo, el uso de tratamiento esteroideo sistémico y de antibioterapia previa y en el caso de P. Aeruginosa, el aislamiento previo de dicho germen[16,22,23,24].

Conocer los factores de riesgo para la infección por estos microorganismos resistentes a tratamiento convencional (MRCT) en las AEPOC podría llevar a mejorar el tratamiento de estos pacientes.

1.2. c) Antibioterapia

El papel del tratamiento antimicrobiano en las AEPOC es controvertido. Con excepción de los pacientes que precisan ventilación mecánica e ingreso en una unidad de cuidados intensivos, los antibióticos no han demostrado tener un efecto significativo en la mortalidad ni en el tiempo de estancia hospitalario en pacientes hospitalizados[29-32].

Debido a estos efectos inconsistentes del tratamiento antimicrobiano se han tratado de encontrar signos clínicos y biomarcadores que puedan ayudar a identificar los pacientes que se benefician de la antibioterapia para así evitar los inconvenientes de dicho tratamiento; incluyendo efectos secundarios, costes y riesgo de desarrollo de multirresistencias.

Así, se ha encontrado evidencia para respaldar el uso de tratamiento antibiótico en los pacientes con AEPOC que presentan esputo purulento[33,34].

Existe además una gran actividad de investigación sobre biomarcadores de infección bacteriana en las agudizaciones. La proteína C reactiva (PCR) ha sido uno de los más estudiados, con resultados iniciales contradictorios. Estudios más recientes han mostrado una marcada reducción de antibioterapia sin repercusiones clínicas ni aumento de fracaso terapéutico al utilizarlos únicamente cuando la PCR es baja[35,36].

Otro marcador investigado ha sido la procalcitonina. En un metaanálisis reciente se sugiere que la procalcitonina podría ser de utilidad para disminuir la prescripción de antibióticos, sin que afecte a la tasa de fracasos terapéuticos, la duración de hospitalización, la recurrencia o la mortalidad[37].

No existe sin embargo aún la suficiente evidencia para utilizar biomarcadores en la práctica clínica habitual, por lo que la recomendación es utilizar antibioterapia en aquellas exacerbaciones que presentan los tres síntomas cardinales de Anthonisen (aumento de disnea, aumento de volumen del esputo y purulencia del esputo), en las que presentan sólo dos síntomas cardinales si uno de ellos es la purulencia del esputo y en las agudizaciones graves que requieren asistencia ventilatoria [1,2].

1.3. Fuerza muscular y AEPOC

La EPOC es una entidad de presentación heterogénea en la que, además de la limitación al flujo aéreo que caracteriza la enfermedad, hay una afectación sistémica. Así, los pacientes presentan con frecuencia pérdida de peso y disfunción de sus músculos, tanto respiratorios como de las extremidades, lo que contribuye a su morbilidad y mortalidad[38-41].

La etiología de la disfunción muscular en la EPOC es multifactorial y dentro de los factores predisponentes pueden destacarse el tabaquismo, las alteraciones nutricionales, la hipoxia crónica y la hipercapnia, el uso de esteroides y otros fármacos lesivos, y en el caso de los músculos de las extremidades, el desuso por reducción en la actividad física[38,39,42].

La disfunción muscular representa una comorbilidad muy importante en la EPOC y se asocia con peor calidad de vida de los pacientes, con una disminución de la supervivencia y con un aumento de la frecuencia de las exacerbaciones [43,44] .

1.3. a) Impacto de la disfunción muscular en AEPOC

Aunque la mayor parte de estudios sobre la disfunción muscular se han realizado en pacientes con EPOC en fase estable, se ha visto que esta alteración empeora durante la exacerbación. El empeoramiento de la fuerza muscular ocurre tanto en la musculatura periférica como respiratoria [45,46].

Los mecanismos que se han implicado en el empeoramiento de la fuerza muscular periférica son la mayor inflamación sistémica y estrés oxidativo que ocurren durante la agudización, así como el mayor grado de hipoxia e hipercapnia, el tratamiento administrado durante la exacerbación (corticoides sistémicos) y la inactividad física[46-48].

Los músculos respiratorios están indudablemente sobrecargados durante las exacerbaciones. Además de estar expuestos a los mismos mecanismos que los músculos periféricos (excepto la inactividad física), se enfrentan a una desventaja mecánica específica causada por los cambios en el volumen pulmonar durante la exacerbación. La longitud del diafragma, principal músculo inspiratorio, se acorta al aumentar los volúmenes pulmonares, alejándose de su longitud óptima de contracción y de su capacidad de generar fuerza. Además la musculatura intercostal también se ve afectada por modificación de la orientación de las costillas [39,49,50] .

Existen diferentes métodos no invasivos para medir la fuerza de la musculatura inspiratoria en la AEPOC. El más utilizado es la determinación de la presión máxima generada en boca (PI_{max}). Se realiza mediante una maniobra estática (sin flujo aéreo) y refleja la fuerza realizada por todos los músculos inspiratorios. Al ser una maniobra voluntaria, es esencial la coordinación con el técnico. Otro método es la medición de la presión nasal durante una inhalación máxima (SNIP), que es una maniobra dinámica y no requiere coordinación ni aprendizaje[59]

En pacientes hospitalizados por AEPOC se ha observado una elevada tasa de disfunción muscular tanto inspiratoria como periférica[51-55]. La disfunción muscular en la exacerbación se instaura rápidamente aunque la duración del deterioro no está clara: algunos estudios han mostrado una recuperación durante la propia hospitalización[53,54] , mientras que otros han observado un deterioro progresivo durante el episodio agudo [56-58] aunque la función muscular tendía a normalizarse un mes después del alta hospitalaria[56].

La disfunción muscular durante la exacerbación tiene consecuencias funcionales, contribuyendo a la reducción de la actividad física y disminuyendo la capacidad de los pacientes de realizar las actividades de la vida diaria [45,53].

Aunque las consecuencias clínicas de la disfunción muscular en el contexto de una hospitalización por agudización de EPOC no están del todo aclaradas, varios estudios han puesto de relieve la relación entre el deterioro de la fuerza muscular y la evolución clínica

adversa, incluyendo la hospitalización prolongada, el reingreso hospitalario y la mortalidad [51,53,58].

2. HIPÓTESIS

2. HIPÓTESIS

Las AEPOC son eventos con alto impacto en los pacientes y contribuyen de forma determinante a la progresión de la enfermedad y a su mortalidad.

En algunas ocasiones, las AEPOC están causadas por microorganismos resistentes (MRCT) pero la relación de la AEPOC con los datos microbiológicos no está aún aclarada. Nuestra hipótesis fue que los pacientes con AEPOC por microorganismos resistentes (MRCT) tienen características y evolución clínica diferente de aquellos con AEPOC secundaria a otras causas; y que existen factores de riesgo específicos para presentar una AEPOC por MRCT. Conocer dichos factores de riesgo podría llevar a mejorar el tratamiento de estos pacientes.

Por otra parte, la disfunción muscular representa una comorbilidad muy importante en la EPOC y se asocia con peor pronóstico. Nuestra hipótesis es que la disfunción muscular tanto respiratoria como periférica está disminuida durante la hospitalización por AEPOC y que la disfunción muscular inspiratoria podría predecir el riesgo de padecer una nueva AEPOC con o sin reingreso hospitalario.

3. OBJETIVOS

3. OBJETIVOS

1. Comparar tanto las características clínicas como la evolución de los pacientes hospitalizados por AEPOC secundaria a MRCT con las de los pacientes con AEPOC secundaria a otras causas.

2. Identificar los factores de riesgo asociados a padecer una infección por MRCT

3. Valorar simultáneamente la evolución de la función muscular tanto respiratoria como periférica durante la hospitalización por AEPOC .

4. Evaluar si la presencia de disfunción muscular en la AEPOC puede predecir una nueva AEPOC o un reingreso hospitalario.

4. METODOLOGÍA

4. METODOLOGIA

Para el primer y segundo objetivo se realizó un estudio de cohortes observacional entre enero de 2009 y diciembre de 2015, en el que se reclutó a todos los pacientes hospitalizados con diagnóstico de AEPOC en el departamento de Neumología de un hospital universitario. A todos ellos se les realizó un estudio microbiológico del esputo previo al inicio de antibioterapia. Para el análisis los pacientes fueron clasificados en tres grupos: el primero de pacientes con aislamiento de microorganismos resistentes (MRCT), el segundo pacientes con aislamiento de microorganismos sensibles (MSCT) y el tercero de pacientes con microbiología negativa y que no habían recibido tratamiento antimicrobiano en los 7 días previos. Se compararon las características clínicas y la evolución de los pacientes con MRCT respecto a los grupos controles y se investigaron los factores de riesgo para padecer AEPOC por MRCT.

Para el tercer y cuarto objetivo se diseñó un estudio prospectivo y observacional entre enero 2014 y diciembre 2019 , que incluyó de forma aleatoria pacientes hospitalizados por AEPOC en el departamento de Neumología de un hospital universitario. Se realizó medición de fuerza muscular periférica mediante hand-grip y de fuerza muscular inspiratoria mediante maniobras estáticas y dinámicas (PI_{max} y SNIP) en el momento de la inclusión, a las 24 horas del ingreso hospitalario y al alta hospitalaria. Se investigó si la medición de fuerza muscular inspiratoria podía predecir el riesgo de padecer una nueva AEPOC o un reingreso hospitalario.

El conjunto de mediciones realizadas, su metodología detallada y los métodos estadísticos se describen en el siguiente capítulo en la descripción de cada uno de los trabajos científicos.

5. RESULTADOS

5. RESULTADOS

5.1 Resultados estudio 1

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Respiratory Research

RESEARCH Open Access

Microorganisms resistant to conventional antimicrobials in acute exacerbations of chronic obstructive pulmonary disease

Cristina Estirado[1†], Adrian Ceccato[2†], Monica Guerrero[2], Arturo Huerta[2], Catia Cilloniz[2], Olivia Vilaró[2], Albert Gabarrús[2], Joaquim Gea[1], Ernesto Crisafulli[3], Nestor Soler[2] and Antoni Torres[2,4*]

Abstract

Background: Antimicrobial treatment for acute exacerbations of chronic obstructive pulmonary disease (AECOPD) remains controversial. In some cases AECOPD are caused by microorganisms that are resistant to treatments recommended by guidelines. Our aims were: 1) identify the risk factors associated with infection by microorganisms resistant to conventional treatment (MRCT), 2) Compare the clinical characteristics and outcomes of patients with AECOPD resulting from MRCT against those with AECOPD from other causes.

Methods: We prospective analysed a cohort of patients admitted with severe AECOPD (2009 to 2015) who were assigned to three groups: patients with MRCT (those patients with germs resistant to antibiotics recommended in guidelines), patients with microorganisms sensitive to conventional antimicrobial treatment (MSCT), and patients with negative microbiology results who had not previously received antibiotics. Multinomial logistic regression analyses were used to examine the associations between microbial aetiology groups and risk factors. The association between LOS and risk factors was also tested in simple and multiple analyses, and similar inclusion criteria were applied for the linear regression analysis.

Results: Of the 451 patients admitted, 195 patients (43%) were included. Respiratory cultures were positive in 86(44%) and negative in 109(56%). MRCT were isolated in 34 cases (40%) and MSCT in 52 (60%). Patients with MRCT had more AECOPD in the previous year, received more antibiotic treatment in the previous three months, had more severe disease, higher dyspnoea and a positive respiratory culture in the previous year (mainly for *Pseudomonas aeruginosa*). The following conditions were independent factors for MRCT isolation: non-current smoker (odds ratio [OR] 4.19 [95% confidence interval [CI] 1.29–13.67], $p = 0.017$), ≥ 2 AECOPD or ≥ 1 admission for AECOPD in the previous year (OR 4.13 [95% CI 1.52–11.17], $p = 0.005$), C-reactive protein < 5 mg/dL; (OR 3.58 [95% CI 1.41–9.07], $p = 0.007$). Mortality rates were comparable at 30-days, one year and 3 years; however, patients in the MRCT group had longer hospital stays.

Conclusion: In conclusion, there are risk factors for resistant germs in AECOPD; however, the presence of these germs does not increase mortality. Patients with isolation of MRCT had longer length of stay.

Keywords: COPD, Exacerbation, Resistance to antimicrobials

* Correspondence: atorres@clinic.cat
†Cristina Estirado and Adrian Ceccato contributed equally to this work.
[2]Pneumology Department, Respiratory Institute (ICR), Hospital Clinic of Barcelona - Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona (UB), SGR 911- Ciber de Enfermedades Respiratorias (CIBERES), ICREA Academia, Barcelona, Spain
[4]Department of Pneumology, Hospital Clinic of Barcelona, Villarroel 140, 08036 Barcelona, Spain
Full list of author information is available at the end of the article

Background

Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) negatively affect hospitalisation, readmission, disease progression and mortality rates in patients with COPD [1]. Severe AECOPD are mainly triggered by bacterial infection, viral infection or environmental agents, with the most common causes of bacterial infection being *Streptococcus pneumoniae, Haemophilus influenzae* and *Moraxella catarrhalis* [2–4]. Thus, current recommendations for antimicrobial treatment are aminopenicillin with or without clavulanic acid, a macrolide or a tetracycline [5, 6]. AECOPD are infrequently caused by microorganisms—such as *Pseudomonas aeruginosa*, methicillin-resistant *Staphylococcus aureus* (MRSA), *Stenotrophomonas maltophilia* or enterobacteria—that are resistant to these treatments. Guidelines and previous studies of severe AECOPD suggest that these patients have increased frequencies of exacerbations, previous antibiotic use, previous hospital admissions and more severe airflow limitations [2, 5, 7, 8].

At least 30% of COPD patients are colonised by a potential pathogen when in a stable phase of their disease; however only 0.5% are colonised by *Enterobacteriaceae*, *P. aeruginosa* or *S. maltophilia* [9]. Also, AECOPD are associated with the overgrowth of potential pathogens and with the occurrence of *P. aeruginosa* in the lower airway [10]. Knowing the risk factors to microorganisms resistant to conventional antibiotic treatment (MRCT) in AECOPD could lead to improved prophylaxis and empirical antimicrobial treatment.

We hypothesised that specific factors predict the presence of MRCT. Our primary aim was to identify the risk factors associated with infection by MRCT. Our secondary aim was to compare the clinical characteristics and outcomes of patients with AECOPD resulting from MRCT against those with AECOPD from other causes.

Methods

Study design and patients selection

This observational cohort study was performed between January 2009 and December 2015, and included all patients admitted with a diagnosis of AECOPD to the Respiratory Department of the Hospital Clinic, Barcelona, Spain. COPD was defined according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines [5], with spirometry performed in a stable disease phase and at least six months prior to hospital admission. Patients with a smoking history of 10 pack-years were considered positive smokers. A worsening of respiratory symptoms compared with the preceding days, and which required a change in home care medication, was used as a clinical definition for AECOPD [5, 11]. Exacerbation severity was based on the respiratory symptoms/signs and the presence of potential indications for hospitalisation [5]. The exclusion criteria were: 1) documented history of asthma or bronchiectasis as the predominant illness and 2) clinical pneumonia or acute heart failure identified at admission.

Ethics approval and consent to participate

The study protocol was approved by the Hospital Research and Ethics Committee (CEIC 2008/4106) and the study was conducted in accordance with good clinical practice guidelines and the declaration of Helsinki. Written informed consent was obtained from all enrolled patients.

Microbiological evaluation

Sputum samples were obtained at admission for bacterial culture, before starting antibiotic therapy. Routine antimicrobial susceptibility testing included the disc diffusion method or E-test for *P. aeruginosa*. The results of susceptibility testing were interpreted according to the European Committee on Antimicrobial Susceptibility Testing guidelines [12]. Multidrug-resistant (MDR), extensively drug resistant (XDR) and pan-drug resistant bacteria were categorised according to criteria set out by Magiorakos et al. [13]. The quality of sputum samples was assessed using the Murray and Washington scoring system. Patients with poor quality sputum samples (> 10 epithelial cells or < 25 leucocytes) were excluded from analysis [14]. Patients with mycobacterial, fungal isolation (e.g., Aspergillus or Candida) or *Nocardia spp.* were also excluded.

Patients were classified into 3 groups: 1) patients with the isolation of microorganism sensitive to conventional treatment (MSCT) according to GOLD guidelines (i.e., aminopenicillin with clavulanic acid, a macrolide or a tetracycline); 2) patients with MRCT isolation, (i.e., *P. aeruginosa,* MRSA, *S. maltophilia, Enterobacteriaceae* producer of extended spectrum of beta lactamase and *Acinetobacter baumannii*); and 3) patients with negative microbiology results who did not receive antibiotics in the 7 days previous at admission.

Previous antibiotic treatment was not considered as inclusion/exclusion criteria in MRCT or MSCT groups. Nobody patient used macrolide as chronic treatment, thus it was not considered as variable.

Clinical measurements and outcomes

Demographic variables, body mass index (BMI), smoking history (former smoker was considered as those patients who quit smoke more than 12 months), presence of co-morbidities measured by Charlson index [15], baseline dyspnoea grade based in modified medical research council (mMRC), COPD severity score measured by a questionnaire (COPDSS) [16] and BODEx index (i.e., BMI, airflow obstruction, dyspnoea and exacerbations) [17], use of long-term oxygen therapy (LTOT) and

use of domiciliary medications (i.e., inhaled bronchodilators, such as short-acting β_2 agonist [SABA], long-acting β_2 agonist [LABA], anticholinergics or inhaled corticosteroids) were recorded at hospital admission. Characteristics of any exacerbations during the previous year, any previous antibiotic treatment (3 months before admission) and any microorganism isolated in the previous year were also recorded. Vital signs (body temperature, respiratory rate, heart rate and blood pressure) were assessed at admission. Arterial blood gases and laboratory parameters (i.e., leukocytes, haematocrit, haemoglobin, C-reactive protein, glucose and creatinine) were recorded at admission and at day 3.

Variables relating to clinical progression included length of hospital stay (LOS), use of non-invasive mechanical ventilation (NIMV), use of invasive mechanical ventilation (IMV) and intensive care unit (ICU) admission during the initial hospitalisation. Data on prognosis (cumulative number of deaths for all-causes and time to death) were recorded at 30 days, 1 year and 3 years.

Statistical analysis

We report the number and percentage of patients for categorical variables and the median and interquartile range (IQR) for continuous variables. Categorical variables were compared using the chi-square test, and continuous variables were compared by one-way analysis of variance or the nonparametric Kruskal–Wallis test. Post-hoc pairwise comparisons were carried out via the Bonferroni method to control for the experiment-wise error rate. Survival curves were obtained using the Kaplan–Meier method and compared using the Gehan-Breslow-Wilcoxon test. Patients lost to follow-up were censored in the survival analysis.

Multinomial logistic regression analyses were used to examine the associations between microbial aetiology groups (i.e., MRCT or MSCT relative to unknown aetiology) and risk factors (i.e., baseline characteristics and clinical presentation). Variables were included in the multivariate model when univariate comparisons yielded a level of significance of $p < 0.05$ due the limited number of patients in the MRCT and MSCT groups and in order to exclude bias related to overestimation or underestimation of regression coefficient variance. The final multivariate model was calculated in a stepwise forward selection procedure ($p_{in} = 0.05$, $p_{out} = 0.10$). To identify the problem of collinearity, we calculated the r coefficient of 2 variables; that is, if 2 independent variables were highly correlated ($r > |\pm 0.30|$), the variable with the largest variance was excluded from the multivariate analysis [18]. The association between LOS and risk factors was also tested in simple and multiple analyses, and similar inclusion criteria were applied for the linear regression analysis ($p < 0.05$). The odds ratios (ORs) or beta coefficients (βs) and their 95% confidence intervals (CIs) were estimated. The Cox and Snell R^2 and the Nagelkerke R^2 were calculated to assess the overall fit of the multinomial logistic regression model and the R^2 for the linear regression model. The area under the receiver operating characteristic (ROC) curve of the multivariate model to predict MRCT was calculated. Internal validation of the prediction models was conducted using ordinary nonparametric bootstrapping with 1000 bootstrap samples and bias-corrected, accelerated, 95% CIs [19]. The same logistic regression analyses for microbial aetiology groups were also performed but using a multinomial logistic regression model for MRCT with only P. aeruginosa or MSCT relative to negative microbiology.

We investigated the missing data patterns for covariates, assumed missing at random [20], and used multiple imputation [21] to generate 5 datasets to evaluate the prediction performance for the microbial aetiology group. The model for multiple imputation included all covariates of the risk models as well as the microbial aetiology group. For simplicity, in the evaluation of the performance we filled in missing values with the first set of imputed values from the multiple imputation.

The level of significance was set at 0.05 (two-tailed). All analyses were performed with IBM SPSS Statistics 23.0 (Armonk, New York).

Results

Patient characteristics

Of the 451 patients admitted with an AECOPD during the observation period, 256 (57%) were excluded. The study population therefore comprised 195 patients (43%), of which 86 (44%) had positive respiratory cultures and 109 (56%) had negative microbiology and no history of previous antibiotic therapy (Fig. 1). AECOPD was associated with MRCT isolation in 34 cases (40%), and other pathogens were isolated in the remaining 52 cases (60%).

Compared with the other groups, patients with MRCT tended to be non-current smokers, have more AECOPD episodes in the previous year, have more hospital admissions in the previous year, receive more antibiotic treatments in the previous 3 months and have more severe disease (higher mMRC dyspnoea grades, higher BODEx indexes and higher COPDSS values) (Table 1). No differences were observed at baseline in purulent sputum, Anthonisen AECOPD classification or pulmonary gas exchange. A higher percentage of patients with MRCT had a positive respiratory culture in the previous year, mainly for *P. aeruginosa.*

Microbiological findings

In the group of patients with MRCT, the most frequent pathogen was *P. aeruginosa* (25 patients [74%]). Two

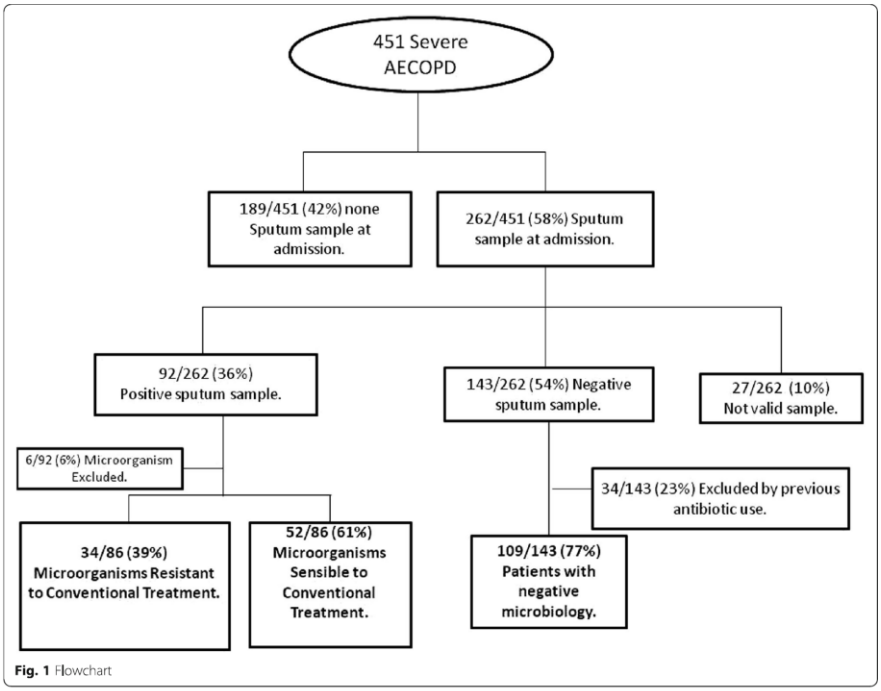

Fig. 1 Flowchart

patients had methicillin-resistant *S. aureus*, one patient *S. maltophilia*, another had *A. baumannii* and 5 had polymicrobial aetiology (Fig. 2 and Additional file 1: Table S1). In total, 9 patients (50%) with previous *P. aeruginosa* isolation had received effective treatment. Among the patients with MSCT, *S. pneumoniae* and *H. influenzae* were the most common pathogens (35 and 31%, respectively), but 2 patients had *Enterobacteriaceae* (*Klebsiella spp.* and *Serratia spp.*) that were sensitive to aminopenicillins (Fig. 2). *P. aeruginosa* isolates were categorised as MDR in 10 cases (40%) and XDR in 3 cases (12%).

Antibiotic treatment

Data on antibiotic treatment were available for 163 patients (88%). The most frequent regimen was fluoroquinolone monotherapy ($n = 82$; 50%), penicillin monotherapy ($n = 27$; 17%) and antibiotic combination therapy ($n = 44$; 27%). The group with MRCT received more combination therapy ($p = 0.003$) and less fluoroquinolone monotherapy ($p = 0.012$) compared with the other 2 groups. The most frequent used combinations were β-lactam plus macrolide in the MSCT group and fluoroquinolones based combinations in the MRCT group. Empirical antimicrobial treatment was inadequate in 20 cases with positive microbiology (24%), of which 15 (44%) and 5 (10%) were among patients with MRCT and MSCT, respectively ($p < 0.001$).

Risk factors for MRCT and MSCT

The following risk factors showed significant associations with the microbial aetiology groups in individual multinomial logistic regression, and were thus used for the initial multivariate model: smoker status, ≥2 AECOPD episode or ≥ 1 AECOPD admission in the previous year, bronchiectasis, LTOT, BODEx index and C-reactive protein (data not shown). The results of the multivariate model are displayed in Table 2. The model shows that the OR for MRCT isolation was significantly increased if the patients was a non-current smoker, had ≥2 AECOPD episodes or ≥ 1 AECOPD admission in the previous year and had a low systemic inflammatory

Table 1 Patient characteristics

Variable	Patients with microorganisms resistant to conventional treatment ($n = 34$)	Patients with microorganisms sensitive to conventional treatment ($n = 52$)	Patients with negative microbiology ($n = 109$)	*P* value
Age, mean (SD), years	73 (10)	71 (10)	71 (11)	0.546
Male sex, n (%)	29 (85)	43 (83)	91 (83)	0.950
BMI, mean (SD), Kg/m^2	28 (5)	27 (5)	27 (5)	0.756
Current smoker, n (%)	4 (12)[b,c]	21 (40)[a]	43 (39)[a]	***0.008***
Packs/year, median (IQR)	33 (30; 90)	50 (40; 60)	60 (50; 95)	***0.043***
AECOPD in the previous year, n (%)	25 (74)[c]	25 (48)	41 (38)[a]	***0.001***
≥2 AECOPD in the previous year, n (%)	16 (47)[c]	16 (31)	19 (18)[a]	***0.003***
Admissions by AECOPD in the previous year, n (%)	20 (59)[c]	17 (33)	28 (26)[a]	***0.002***
≥ 2 AECOPD or ≥ 1 admission for AECOPD in the previous year, n (%)	24 (71)[b,c]	21 (40)	32 (30)[b]	***< 0.001***
Prior antibiotic treatment (last 3 months), n (%)	26 (79)[b,c]	22 (43)[a,c]	22 (21)[a,b]	***< 0.001***
Prior antibiotic treatment, n (%)	9 (27)	14 (27)	0 (0)	***< 0.001***
Inhaled corticosteroids use, n (%)	17 (50)	19 (41)	35 (38)	0.480
Bronchiectasis, n (%)	13 (48)	10 (28)	29 (38)	0.251
Long-term oxygen therapy, n (%)	18 (53)[c]	15 (29)	31 (28)[a]	***0.023***
Charlson index, median (IQR)	2 (1; 3)	2 (1; 3)	2 (1; 3)	0.459
BODEx index, median (IQR)	3 (0; 6)[c]	0 (0; 4.5)	0 (0; 0)[a]	***0.001***
mMRC Dyspnoea, median (IQR)	3 (2; 3)[b,c]	2 (1; 3)[a]	2 (1; 3)[a]	***< 0.001***
COPDSS, median (IQR)	19 (14; 21)[b,c]	15 (9; 19)[a]	13 (8; 18)[a]	***< 0.001***
FEV_1, median (IQR), % ref	33 (27; 41)	45 (31; 55)	39 (28; 57)	0.073
$FEV_1 < 35\%$ ref., n (%)	17 (55)	13 (28)	39 (41)	0.064
Positive sputum cultures in the previous year, n (%)	18 (53)[b,c]	12 (23)[a]	11 (10)[a]	***< 0.001***
Pseudomonas aeruginosa in the previous year, n (%)[d]	8 (44)	1 (8)	1 (9)	***0.048***
Respiratory rate, mean (SD)	22 (20; 26)	22 (20; 28)	24 (20; 26)	0.423
Anthonisen classification, n (%)				0.793
Type I	17 (52)	20 (40)	42 (40)	
Type II	9 (27)	19 (38)	38 (36)	
Type III	7 (21)	11 (22)	25 (24)	
Purulent sputum, n (%)	18 (55)	18 (36)	41 (39)	0.203
Haemoglobin, median (IQR), gr/L	134 (120; 146)	142 (127; 151)	139 (124; 153)	0.159
pH, median (IQR)	7.40 (7.36; 7.45)	7.39 (7.34; 7.43)	7.39 (7.35; 7.43)	0.907
$PaCO_2$, median (IQR), mmHg	49 (42; 61)	44 (38; 58)	45 (38; 58)	0.340
PaO_2/FiO_2, median (IQR), mmHg	257 (230; 321)	248 (207; 293)	267 (232; 311)	0.490
C-reactive protein, median (IQR), mg/dL	2.5 (1.5; 5.4)	5.4 (1.5; 17.4)	4.9 (1.6; 12.8)	0.113

Abbreviations: *AECOPD* acute exacerbation of chronic obstructive pulmonary disease, *BMI* body mass index, *BODEx* body mass index, airflow obstruction, dyspnoea and exacerbations, *COPDSS* chronic obstructive pulmonary disease severity score, FEV_1 forced expiratory volume in the 1st second, *IQR* interquartile range, *mMRC* modified medical research council, *SD* standard deviation

Data are shown as number and percentage of patients, mean (SD), or median (1st quartile; 3rd quartile)

Percentages are calculated on non-missing data

[a] $P < 0.05$ vs. Patients with microorganisms resistant to conventional treatment

[b] $p < 0.05$ vs. Patients with microorganisms sensitive to conventional treatment

[c] $p < 0.05$ vs. Patients with negative microbiology

[d] Percentages calculated for patients with positive sputum cultures in the previous year

Bold Italic entries indicate statistical significance

response. The OR for MSCT isolation, however, was strongly decreased with a high BODEx index (4th quartile) (Table 3). The AUC was 0.80 (95% CI, 0.72–0.87) for the model predictive of MRCT isolation (Fig. 3). The data for internal validation of the logistic regression model (using bootstrapping with 1000 samples) are

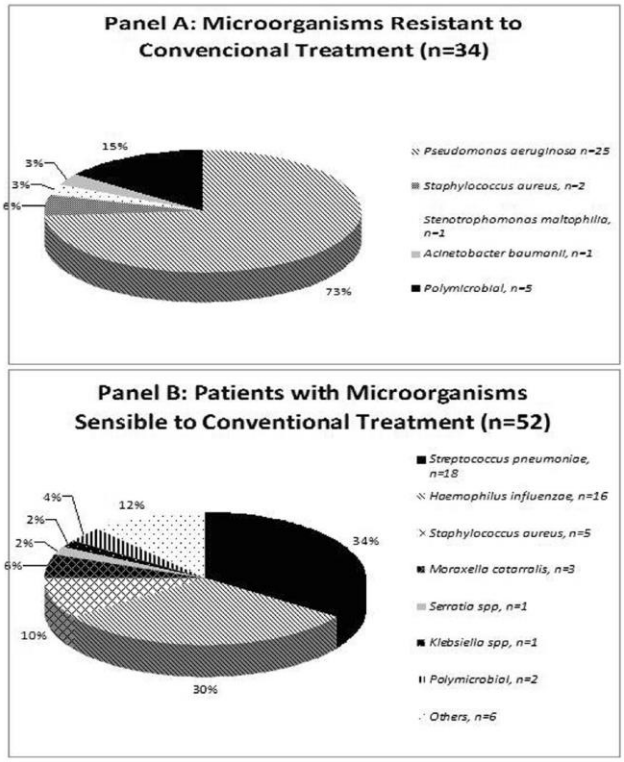

Fig. 2 Microbial aetiology. Panel **a** Microorganisms Resistant to Conventional Treatment ($n = 34$). Panel **b** Patients with Microorganisms Sensitive to Conventional Treatment ($n = 52$). Polymicrobial Isolation includes: *3 Pseudomonas aeruginosa, 2 Stenotrophomonas maltophilia, 1 Staphylococcus aureus, 3 Streptococcus pneumoniae, 1 other.* Others isolation include: 3 Corynebacterium spp., 2 Pasteurella spp., 1 Capnocytophaga spp.

presented in Additional file 1: Table S2. The variables included in the model demonstrated robust results, with small 95% CIs around the original coefficients. When differentiating MRCT with and without *P. aeruginosa,* previous isolation of *P. aeruginosa* was the most important predictor of *P. aeruginosa* isolation (Additional file 1: Table S3, Table S4 and Figure S1).

Outcomes

Patients with MRCT had longer median hospital stays than the other 2 groups (9 days [7–14] vs. 8 days [6–10] in both cases, respectively; $p = 0.026$) (Table 3). No differences were observed in ICU admission, IMV or NIMV rates among the groups. Mortality rates were comparable at 30-days, one year and 3 years, and the number of AECOPD after discharge did not differ among the groups. The Kaplan-Meier survival curves depicting the 3-year mortality rates as a function of the 3 microbial aetiology groups are shown in Fig. 4. No differences were observed when comparing patients with adequate and inadequate empiric antibiotic treatment in each group (MRCT and MSCT) or in overall population (Additional file 1: Table S5).

The simple linear regression analysis revealed several variables significantly associated with length of hospital stay (Table 4). BODeX index, CRP levels, requirement of mechanical ventilation (invasive or non-invasive) and isolation of MRCT were those independently

Table 2 Multinomial logistic regression model for microorganisms resistant to conventional treatment or microorganisms sensitive to conventional treatment relative to negative microbiology

Variable	Patients with microorganisms resistant to conventional treatment			Patients with microorganisms sensitive to conventional treatment		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Non-current smoker	4.19	1.29 to 13.67	**0.017**	0.78	0.38 to 1.59	0.49
≥ 2 AECOPD or 1 admission by AECOPD in the previous year	4.13	1.52 to 11.17	**0.005**	1.75	0.76 to 3.99	0.19
BODEx index						
1st quartile: 0–2	1	–	–	1	–	–
2nd quartile: 3–4	2.32	0.67 to 7.98	0.18	0.62	0.21 to 1.88	0.40
3rd quartile: 5–6	1.85	0.58 to 5.90	0.30	1.12	0.44 to 2.88	0.82
4th quartile: 7–9	0.48	0.10 to 2.33	0.37	0.14	0.03 to 0.70	**0.016**
C-reactive protein < 5 mg/dL at admission	3.58	1.41 to 9.07	**0.007**	1.14	0.57 to 2.27	0.72

Abbreviations: AECOPD indicates acute exacerbation of chronic obstructive pulmonary disease exacerbation, *BODEx* body mass index, airflow obstruction, dyspnoea and exacerbations, *CI* confidence interval, *OR* odds ratio
Data are shown as estimated ORs (95% CIs) of the explanatory variables observed at admission of patients in the microorganisms resistant to conventional treatment (MRCT) and microorganisms sensitive to conventional treatment (MSCT) groups. The OR is defined as the probability of membership of the groups MRCT or MSCT divided by the probability of membership of the negative microbiology group
The P value is based on the null hypothesis that all ORs relating to an explanatory variable equal unity
Model characteristics: likelihood ratio X^2 test, $p = 0.48$; R^2 coefficients = 0.21 (Cox and Snell), 0.24 (Nagelkerke)

associated with length of hospital stay in the multiple analyses. The data for internal validation of the linear regression model (using bootstrapping with 1000 samples) are presented in Additional file 1: Table S8. The variables included in the model demonstrated robust results, with small 95% CIs around the original coefficients.

Patients with *P. aeruginosa* isolation in the MRCT group had higher hospital stays than patients without *P. aeruginosa* in the same group. Patients with isolation of MDR or XDR *P. aeruginosa* had the longest stays, but there was no difference in mortality (Additional file 1: Table S3, Table S4, Figure S1). The 3-year mortality among patients with < 2 AECOPD episodes and no admissions for AECOPD in the previous year differed significantly between groups in the Kaplan-Meier analysis ($p = 0.019$; Additional file 1: Figure S2).

Discussion

In our study, we analysed 3 well-characterised groups, comparing patients with MRCTs against controls groups of patients with MSCTs and patients with negative

Table 3 Clinical outcomes

	Patients with microorganisms resistant to conventional treatment ($n = 34$)	Patients with microorganisms sensitive to conventional treatment ($n = 52$)	Patients with negative microbiology ($n = 109$)	*P* value
AECOPD after 30 days of discharge, n (%)	24 (73)	21 (47)	57 (56)	0.070
Number of AECOPD after 30 days of discharge, median (IQR)	1 (0; 3)	0 (0; 2)	1 (0; 1)	0.075
Time to the next AECOPD, median (IQR), days	39 (19; 170)	52 (27; 166)	86 (26; 182)	0.577
Length of stay, median (IQR), days	9 (7; 14)[c]	8 (6; 10.5)	8 (6; 10)[a]	**0.026**
ICU admission, n (%)	4 (12)	6 (12)	12 (11)	0.981
IMV, n (%)	2 (6)	1 (2)	3 (2)	0.564
NIMV, n (%)	6 (18)	10 (19)	16 (15)	0.780
30-day mortality, n (%)	1 (3)	1 (2)	4 (4)	0.834
1-year mortality, n (%)	11 (32)	12 (23)	19 (17)	0.173
3-years mortality, n (%)	16 (59)	19 (56)	40 (43)	0.211

Abbreviations: *AECOPD* indicates acute exacerbation of chronic obstructive pulmonary disease exacerbation, *ICU* intensive care unit, *IMV* invasive mechanical ventilation, *IQR* interquartile range, *NIMV* non-invasive mechanical ventilation. Data are shown as number of patients (%), or median (1st quartile; 3rd quartile). Percentages are calculated on non-missing data. [a]$P < 0.05$ vs. patients with microorganisms resistant to conventional treatment. [b]$p < 0.05$ vs. patients with microorganisms sensitive to conventional treatment. [c]$p < 0.05$ vs. patients with negative microbiology

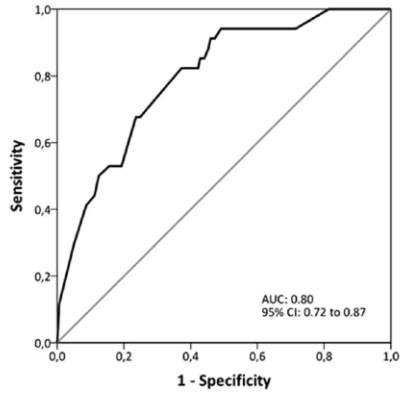

Fig. 3 Receiver operating characteristic curve for multinomial logistic regression model to predict MRCT isolation. *Abbreviations*: AUC indicates area under the curve; CI, confidence interval

microbiology and no previous antibiotic use. Our analyses revealed that not currently smoking, ≥ 2 AECOPD episodes or ≥ 1 admission for AECOPD in the last year, and a low systemic inflammatory response at admission were independent risk factors for AECOPD caused by an MRCT. However, although patients with MRCT had longer hospital stays, they did not have higher mortality or more severe AECOPD than the control groups. At baseline, patients with MRCT had more severe disease, as measured by the dyspnoea scale, COPDSS scale, BODEx index and history of previous AECOPD. There were no differences in symptoms or pulmonary gas exchange features at admission.

AECOPD are events that mark disease progression, and as taken into account by the GOLD guidelines [5], are as important as airflow limitation. Indeed, it is evident that there are patients who are susceptible to frequent exacerbations, and in these, the most important predictor of future episodes is the history of AECOPD [22]; however, the association with microbiologic data has been poorly analysed to date.

A low systemic inflammatory response was a risk factor for MRCT isolation in this study, which could be due to lower virulence or reduced ability to produce acute phase reactants in the presence of these microorganisms. Similar results were observed in patients with community

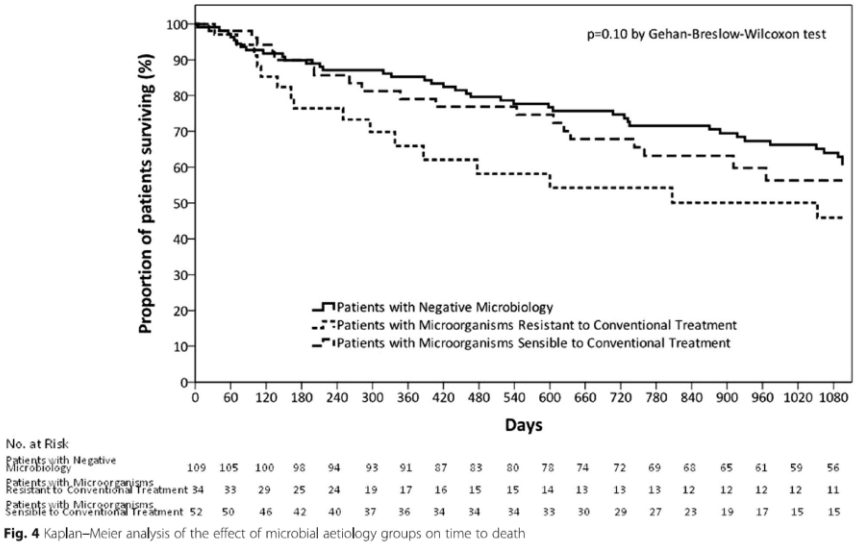

Fig. 4 Kaplan–Meier analysis of the effect of microbial aetiology groups on time to death

Table 4 Significant simple and multiple linear regression analyses of associations of risk of length of hospital stay

Variable	Simple			Multiple[a]		
	β	95% CI	*P* value	*β*	95% CI	*P* value
≥ 2 AECOPD or 1 admission by AECOPD in the previous year	1.89	0.05 a 3.72	0.044	–	–	–
Bronchiectasis	1.70	−0.19 a 3.61	0.079	–	–	–
Long-term oxygen therapy	1.73	−0.19 a 3.66	0.077	–	–	–
BODEx index	0.89	0.08 a 1.70	0.032	0.81	0.04 a 1.59	0.039
C-reactive protein (mg/dL)	−1.56	−3.37 a 0.26	0.092	–	–	–
$PaCO_2$	2.14	0.34 a 3.94	0.020	–	–	–
Previous positive sputum culture for *Pseudomonas aeruginosa*	5.88	1.83 a 9.92	0.005	–	–	–
Adequate Empiric Treatment	−1.54	−2.86 a −0.22	0.023	–	–	–
Invasive mechanical ventilation	8.06	2.91 a 13.21	0.002	5.92	0.82 a 11.02	0.023
Non-invasive mechanical ventilation	3.82	1.45 a 6.19	0.002	3.18	0.84 a 5.53	0.008
MRCT Isolation	3.53	1.19 a 5.88	0.003	3.11	0.84 a 5.37	0.007

Abbreviations: β unstandardized beta coefficient, *AECOPD* indicates acute exacerbation of chronic obstructive pulmonary disease exacerbation, *BODEx* body mass index, airflow obstruction, dyspnoea and exacerbations, *CI* confidence interval
[a]Adjusted R^2 coefficient of determination = 11.8%

acquired pneumonia or ventilator associated pneumonia in whom *P. aeruginosa* was isolated [23, 24].

There was also an association between smoking status and MRCT isolation, specifically in favour of non-current smoking status. It is known that smoke increases upper respiratory tract colonisation of *S. pneumoniae, H. influenzae, M. catarrhalis* and *Streptococcus pyogenes* [25], and that smoking facilitates colonisation of the lung with these bacteria [9]. This is probably related to the decreased phagocytic ability of alveolar macrophages and the decreased cytokine response associated with smoking [26, 27]. The association between smoking status and MRCT isolation in this study should not, therefore, weaken the recommendation for smoking cessation for all patients. Other explanations to this point maybe those individuals who develop respiratory symptoms due to more severe disease being more likely to quit smoking.

Previous studies have produced controversial data about the presence of *P. aeruginosa* in isolates, though they have tended to show that sensitive *P. aeruginosa* had higher mortality [28–31]. We found no differences in mortality between patients with *P. aeruginosa*, including those with MDR strains. In other respiratory diseases, such as cystic fibrosis or non-cystic fibrosis bronchiectasis, microbiologic isolation of *P. aeruginosa* and MRSA has been shown to have an important role in disease progression [32–36]. Although there is evidence that eradication with antibiotic treatment would be beneficial in these diseases, there is no such evidence that similar benefits would exist for patients with COPD.

The role of antimicrobial treatment remains controversial in AECOPD. With the exception of patients who require mechanical ventilation and ICU admission, the benefits of antibiotic treatment are limited, and are mainly observed in patients with purulent sputum or in those with AECOPD graded as type I by the Anthonisen classification [37–41]. The effect of inadequate antibiotic treatment is poorly understood in patients with AECOPD. In this study, we did not observe any differences in outcomes between patients with inadequate and adequate empiric antibiotic treatment.

The predictive factors identified in this study represent the first step in the development of a prediction model. To move forward, the potential model will need to undergo external validation with larger patient cohorts from multiple centres. We could also apply the results of internal validation techniques to understand how likely this model will be replicable to future studies and to studies at other centres. Bootstrapping techniques were applied to our data, and the results indicated that the coefficients obtained from the prediction model were quite robust. Notably, previous *P. aeruginosa* isolation was the one factor that the bootstrap analysis indicated might have limited repeatability in future work. Thus, we opted to remove previous *P. aeruginosa* isolation from the overall model and include it in a specific multivariate analysis for *P. aeruginosa*. In the real-world clinical setting where this prediction model could be used, previous *P. aeruginosa* isolation remains an important clinical characteristic that can play a substantial role in decision making.

We did not observe differences in the majority of outcomes when comparing MRCT vs non-MRCT exacerbations. However; length of stay was longer in the MRCT group. This is an important outcome to be taken into account to make efforts in predicting and treating these microorganisms in AECOPD.

Our study has some limitations that should be acknowledged. First, the study was carried out at only one centre in Spain. Second, the small sample limited the analysis of specific factors per bacterium. There is limited information about MRCT isolation in patients with AECOPD, and where there is, it is mainly for bacteria other than *P. aeruginosa*. A confirmation of our results in a large and well balanced, international cohort of AECOPD is therefore desirable. Finally, other limitation of this study was the use of sputum cultures and the potential difficulty to distinguish between colonization and infection. However, we only accepted samples of good quality and we did not culture those of low quality. In addition this is the usual way to diagnose lower airway infection in AECOPD in the majority of studies, given that performing bronchoscopy in these patients is extremely difficult. Moreover we validated sputum cultures some years ago in comparison with bronchoscopic samples [42].

Conclusions

In conclusion, non-current smoking status, ≥2 AECOPD episodes or ≥ 1 admissions for AECOPD in the previous year, and low systemic inflammatory response are independent risk factors to have an AECOPD caused by a MRCT. Length of stay was significantly longer in AECOPD caused by MRCT microorganisms.

Additional file

Additional file 1: Table S1. Microbiological Isolations. **Table S2.** Internal Validation of the Multivariate Logistic Regression Model using Bootstrap Method. **Table S3.** Multinomial Logistic Regression Model for Microorganisms Resistant to Conventional Treatment (with *Pseudomonas aeruginosa*) or Microorganisms Sensitive to Conventional Treatment Relative to Negative Microbiology. **Table S4.** Internal Validation of the Multinomial Logistic Regression Model for Microorganisms Resistant to Conventional Treatment (with *Pseudomonas aeruginosa*) or Microorganisms Sensitive to Conventional Treatment using Bootstrap Method. **Table S5.** Outcomes according to Appropriateness of Empiric Treatment. **Table S6**. Comparison of Outcomes between Patients with *Pseudomonas Aeruginosa* and Patients without *Pseudomonas Aeruginosa* in Microorganisms Resistant to Conventional Treatment Group. **Table S7.** Comparison between *Pseudomonas Aeruginosa* MDR/XDR Isolation with other Microorganism Isolated in Microorganisms Resistant to Conventional Treatment Group. **Table S8.** Internal Validation of Risk of Length of Hospital Stay Using Bootstrap Technique. **Figure S1.** Receiver Operating Characteristic Curve for Multinomial Logistic Regression Model to *Pseudomonas aeruginosa*. **Figure S2.** Kaplan–Meier Analysis of the Effect of Microbial Aetiology Groups on Time to Death. **Figure S3.** Kaplan–Meier Analysis of the Effect of Microbial Aetiology Groups on Time to Death. A) Patients with < 2 AECOPD and none admission by AECOPD in the previous year; B) Patients with ≥ 2 AECOPD or 1 admission by AECOPD in the previous year. (DOC 265 kb)

Abbreviations

AECOPD: Acute exacerbations of chronic obstructive pulmonary disease; BMI: Body mass index; CI: Confidence intervals; COPD: Chronic obstructive pulmonary disease; COPDSS: COPD severity score; GOLD: Global Initiative for Chronic Obstructive Lung Disease; LTOT: Long-term oxygen therapy; MDR: Multidrug-resistant; mMRC: Modified medical research council; MRCT: Microorganism resistant to conventional treatment; MRSA: Methicillin-resistant *Staphylococcus aureus*; MSCT: Microorganisms sensitive to conventional antimicrobial treatment; OR: Odds ratios; ROC: Receiver operating characteristic; XDR: Extensively drug resistant

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Availability of data and materials

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

Authors' contributions

Study concept and design: AT, CE, AC; data collection: CE, AC, MG, CC, AH, OV, EC, NS; statistical analysis: AG, analysis and interpretation of data: CE, AC, MG, AH, EC, JG, NS, AT.; drafting of the manuscript: AC, CE; critical revision of the manuscript for important intellectual content: JG, EC, NS, AT; and study supervision: AT. AT 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 read and approved the final manuscript.

Ethics approval and consent to participate

The study protocol was approved by the Hospital Research and Ethics Committee (CEIC 2008/4106) and the study was conducted in accordance with good clinical practice guidelines and the declaration of Helsinki. Written informed consent was obtained from all enrolled patients.

Competing interests

The authors declare that they have no competing interests.

Publisher's Note

Author details

[1]Pulmonology Department, Hospital del Mar-IMIM. CEXS, Universitat Pompeu Fabra, CIBERES, ISCIii, Barcelona, Spain. [2]Pneumology Department, Respiratory Institute (ICR), Hospital Clinic of Barcelona - Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona (UB), SGR 911- Ciber de Enfermedades Respiratorias (CIBERES), ICREA Academia, Barcelona, Spain. [3]Respiratory and Lung Function Unit, Department of Medicine and Surgery, University of Parma, Parma, Italy. [4]Department of Pneumology, Hospital Clinic of Barcelona, Villarroel 140, 08036 Barcelona, Spain.

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Additional file

Microorganisms Resistant to Conventional Antimicrobials in Acute Exacerbations of Chronic Obstructive Pulmonary Disease

Cristina Estirado, MD[1*]; Adrian Ceccato, MD[2*]; Monica Guerrero, MD, PhD[2]; Arturo Huerta, MD, PhD[2]; Catia Cilloniz, PhD[2]; Olivia Vilaró, RN[2]; Albert Gabarrús, MSc[2]; Joaquim Gea, MD, PhD[1]; Ernesto Crisafulli, MD, PhD[3]; Nestor Soler, MD, PhD[2]; Antoni Torres, MD, PhD[2]

Table S1. Microbiological Isolations

	Patients with Microorganisms Resistant to Conventional Treatment (n = 34)	Patients with Microorganisms Sensitive to Conventional Treatment (n = 52)
Pseudomonas aeruginosa, n (%)	25 (74)	0
Streptococcus pneumoniae, n (%)	0	18 (35)
Haemophilus influenzae, n (%)	0	16 (31)
Staphylococcus aureus, n (%)	2 (6)	5 (10)
Moraxella catarrhalis, n (%)	0	3 (6)
Stenotrophomonas maltophilia, n (%)	1 (3)	0
Serratia spp., n (%)	0	1 (2)
Klebsiella spp., n (%)	0	1 (2)
Acinetobacter baumannii, n (%)	1 (3)	0
Polymicrobial, n (%)[a]	5 (15)	2 (4)
Others, n (%)	0	6 (12)

[a] Polymicrobial Isolation includes: *3 Pseudomonas aeruginosa, 2 Stenotrophomonas maltophilia, 1 Staphylococcus aureus, 3 Streptococcus pneumoniae, 1 others.*

Table S2. Internal Validation of the Multivariate Logistic Regression Model using Bootstrap Method

Group	Variable	Original	Bias	Standard Error	*P* value	95% Confidence Interval	
						Lower	Upper
Patients with Microorganisms Resistant to Conventional Treatment	Intercept	-3.982	-0.681	2.669	0.021	-7.271	-2.876
	Non-current smoker	1.433	0.515	2.589	0.016	0.360	3.676
	⩾2 AECOPD or 1 admission by AECOPD in the previous year	1.417	0.086	0.503	0.001	0.550	2.493
	BODEx index 4th quartile: 7-9	-0.727	-0.966	4.288	0.363	-20.469	0.801
	BODEx index 3rd quartile: 5-6	0.613	0.058	0.632	0.282	-0.537	1.983
	BODEx index 2nd quartile: 3-4	0.840	0.018	0.724	0.182	-0.504	2.253
	C-reactive protein <5 mg/dL at admission	1.274	0.094	0.508	0.002	0.447	2.501
Patients with Microorganisms Sensitive to Conventional Treatment	Intercept	-0.631	-0.012	0.424	0.102	-1.534	0.191
	Non-current smoker	-0.250	-0.002	0.401	0.512	-0.981	0.513
	⩾2 AECOPD or 1 admission by AECOPD in the previous year	0.558	0.023	0.490	0.234	-0.370	1.530
	BODEx index 4th quartile: 7-9	-1.935	-2.655	6.655	0.006	-22.123	-0.723
	BODEx index 3rd quartile: 5-6	0.112	0.001	0.543	0.819	-1.039	1.170
	BODEx index 2nd quartile: 3-4	-0.473	-0.136	0.981	0.419	-2.262	0.683
	C-reactive protein <5 mg/dL at admission	0.129	0.002	0.378	0.738	-0.639	0.857

Abbreviations: AECOPD indicates acute exacerbation of chronic obstructive pulmonary disease exacerbation; BODEx, body mass index, airflow obstruction, dyspnoea and exacerbations.

Table S3. Multinomial Logistic Regression Model for Microorganisms Resistant to Conventional Treatment (with *Pseudomonas aeruginosa*) or Microorganisms Sensitive to Conventional Treatment Relative to Negative Microbiology

Variable	Patients with Microorganisms Resistant to Conventional Treatment (with *Pseudomonas aeruginosa*)			Patients with Microorganisms Sensitive to Conventional Treatment		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Non-current smoker	2.38	0.69 to 8.16	0.17	0.77	0.38 to 1.58	0.47
⩾2 AECOPD or 1 admission by AECOPD in the previous year	3.08	0.98 to 9.64	**0.054**	1.75	0.76 to 4.02	0.19
BODEx index						
1st quartile: 0-2	1	-	-	1	-	-
2nd quartile: 3-4	2.64	0.61 to 11.54	0.20	0.62	0.21 to 1.89	0.41
3rd quartile: 5-6	2.52	0.65 to 9.68	0.18	1.10	0.42 to 2.84	0.85
4th quartile: 7-9	0.69	0.12 to 3.91	0.67	0.14	0.03 to 0.69	**0.016**
C-reactive protein <5 mg/dL at admission	4.18	1.36 to 12.87	**0.013**	1.17	0.59 to 2.34	0.65
Previous positive sputum culture for *Pseudomonas aeruginosa*	38.61	3.59 to 415.66	**0.003**	2.33	0.13 to 40.55	0.54

Abbreviations: AECOPD indicates acute exacerbation of chronic obstructive pulmonary disease exacerbation; BODEx, body mass index, airflow obstruction, dyspnoea and exacerbations; CI, confidence interval; OR: odds ratio. Data are shown as estimated ORs (95% CIs) of the explanatory variables observed at admission of patients in the microorganisms resistant to conventional treatment (with *Pseudomonas aeruginosa*) (MRCT with *Pseudomonas aeruginosa*) and microorganisms sensitive to conventional treatment (MSCT) groups. The OR is defined as the probability of membership of the groups MRCT with *Pseudomonas aeruginosa* or MSCT divided by the probability of membership of the negative microbiology group. The P value is based on the null hypothesis that all ORs relating to an explanatory variable equal unity. Model characteristics: likelihood ratio X^2 test, p = 0.88; R^2 coefficients = 0.31 (Cox and Snell), 0.36 (Nagelkerke).

Table S4. Internal Validation of the Multinomial Logistic Regression Model for Microorganisms Resistant to Conventional Treatment (with *Pseudomonas aeruginosa*) or Microorganisms Sensitive to Conventional Treatment using Bootstrap Method

Group	Variable	Original	Bias	Standard Error	*P* value	95% Confidence Interval	
						Lower	Upper
Patients with Microorganisms Resistant to Conventional Treatment (with *Pseudomonas aeruginosa*)	Intercept	-4.114	-0.854	2.702	0.001	-17.152	-2.871
	Non-current smoker	0.868	0.540	2.444	0.154	-0.315	12.321
	⩾2 AECOPD or 1 admission by AECOPD in the previous year	1.123	0.126	0.587	0.025	0.180	2.505
	BODEx index 4th quartile: 7-9	-0.376	-1.047	3.679	0.608	-15.481	1.228
	BODEx index 3rd quartile: 5-6	0.923	0.009	0.724	0.134	-0.526	2.559
	BODEx index 2nd quartile: 3-4	0.972	-0.043	1.539	0.235	-1.040	2.851
	C-reactive protein <5 mg/dL at admission	1.430	0.206	1.009	0.008	0.378	3.141
	Previous positive sputum culture for *Pseudomonas aeruginosa*	3.653	6.448	9.673	0.016	1.183	23.902
Patients with Microorganisms Sensitive to Conventional Treatment	Intercept	-0.644	-0.023	0.412	0.101	-1.504	0.123
	Non-current smoker	-0.263	0.013	0.400	0.500	-1.017	0.511
	⩾2 AECOPD or 1 admission by AECOPD in the previous year	0.559	0.012	0.489	0.222	-0.459	1.489
	BODEx index 4th quartile: 7-9	-1.955	-2.172	5.349	0.006	-18.195	-0.729
	BODEx index 3rd quartile: 5-6	0.091	0.008	0.538	0.872	-1.021	1.108
	BODEx index 2nd quartile: 3-4	-0.470	-0.125	0.998	0.427	-1.961	0.674
	C-reactive protein <5 mg/dL at admission	0.159	-0.012	0.377	0.652	-0.586	0.902
	Previous positive sputum culture for *Pseudomonas aeruginosa*	0.848	-0.308	12.735	0.167	-18.482	19.531

Abbreviations: AECOPD indicates acute exacerbation of chronic obstructive pulmonary disease exacerbation; BODEx, body mass index, airflow obstruction

Table S5. Outcomes according to Appropriateness of Empiric Treatment

Variable	Inadequate Empiric Treatment				Adequate Empiric Treatment						
	Patients with Microorganisms Resistant to Conventional Treatment (n = 15)	Patients with Microorganisms Sensible to Conventional Treatment (n = 5)	Total (n = 20)	*P* value	Patients with Microorganisms Resistant to Conventional Treatment (n = 19)	Patients with Microorganisms Sensible to Conventional Treatment (n = 47)	Total (n = 66)	*P* value	*P* value[a]	*P* value[b]	*P* value[c]
AECOPD after 30 days of discharge, n (%)	10 (72)	1 (25)	11 (61)	0.25	14 (74)	19 (50)	33 (58)	0.088	>0.99	0.61	0.81
Number of AECOPD after 30 days of discharge, median (IQR)	1 (0; 3)	0 (0; 0.5)	1 (0; 2)	0.076	1 (0; 3)	0.5 (0; 2)	1 (0; 2)	0.22	0.94	0.23	0.94
Time to the next AECOPD, median (IQR), days	35 (25; 170)	126 (126; 126)	55 (30; 167)	0.66	40 (19; 144)	51 (27; 166)	48 (19; 166)	0.75	0.98	0.69	0.99
Length of stay, median (IQR), days	9 (8; 14)	10 (7; 17)	9.5 (7.5; 15)	0.90	9 (7; 19)	8 (6; 10.5)	8 (6; 12)	0.11	0.99	0.39	0.19
ICU admission, n (%)	1(7)	0 (0)	1 (5)	>0.99	3 (16)	6(15)	9(15)	>0.99	0.61	>0.99	0.44
IMV, n (%)	1(7)	0 (0)	1 (5)	>0.99	1(5)	1(3)	2 (3)	0.52	>0.99	>0.99	0.57
NIMV, n (%)	3 (20)	0 (0)	3 (15)	0.54	3 (16)	10 (23)	13 (21)	0.74	>0.99	0.57	0.75
30-day mortality, n (%)	1(7)	0 (0)	1 (5)	>0.99	0 (0)	1(3)	1 (2)	>0.99	0.44	>0.99	0.43
1-year mortality, n (%)	6 (40)	1 (20)	7 (35%)	0.61	5 (26)	11 (25)	16 (25)	>0.99	0.48	>0.99	0.40
3-years mortality, n (%)	9 (69)	1 (50)	10 (67)	>0.99	7 (50)	18 (62)	25 (58)	0.52	0.31	>0.99	0.56

Abbreviations: AECOPD indicates acute exacerbation of chronic obstructive pulmonary disease exacerbation; ICU, intensive care unit; IMV, invasive mechanical ventilation; IQR, interquartile range; NIMV, non-invasive mechanical ventilation. Data are shown as number of patients (%), or median (1st quartile; 3rd quartile). Percentages are calculated on non-missing data. [a] P values are for the comparison of inadequate empiric treatment/MRCT with adequate empiric treatment/MRCT. [b] P values are for the comparison of inadequate empiric treatment/MSCT with adequate empiric treatment/MSCT. [c] P values are for the comparison of inadequate empiric treatment/total with adequate empiric treatment/total.

Table S6. Comparison of Outcomes between Patients with *Pseudomonas Aeruginosa* and Patients without *Pseudomonas Aeruginosa* in Microorganisms Resistant to Conventional Treatment Group

Variable	Patients with *Pseudomonas aeruginosa* (n = 28)	Patients without *Pseudomonas aeruginosa* in patients with MRCT (n = 6)	*P* value
AECOPD after 30 days of discharge, n (%)	18 (67)	6 (100)	0.16
Number of AECOPD after 30 days of discharge, median (IQR)	1 (0; 2)	2.5 (1; 3)	0.092
Time to the next AECOPD, median (IQR), days	35 (19; 170)	58 (35; 79)	0.88
Length of stay, median (IQR), days	11 (8; 17.5)	5 (4; 7)	0.002
ICU admission, n (%)	4 (14)	0 (0)	>0.99
IMV, n (%)	2 (7)	0 (0)	>0.99
NIMV, n (%)	6 (21)	0 (0)	0.56
30-day mortality, n (%)	1 (4)	0 (0)	>0.99
1-year mortality, n (%)	9 (32)	2 (33)	>0.99
3-years mortality, n (%)	14 (56)	2 (100)	>0.99

Abbreviations: AECOPD indicates acute exacerbation of chronic obstructive pulmonary disease exacerbation; ICU, intensive care unit; IMV, invasive mechanical ventilation; IQR, interquartile range; NIMV, non-invasive mechanical ventilation. Data are shown as number of patients (%), or median (1st quartile; 3rd quartile). Percentages are calculated on non-missing data.

Table S7. Comparison between *Pseudomonas Aeruginosa* MDR/XDR Isolation with other Microorganism Isolated in Microorganisms Resistant to Conventional Treatment Group

Variable	Patients with *Pseudomonas aeruginosa* MDR and XDR (n = 13)	Patients without *Pseudomonas aeruginosa* MDR and XDR (n = 21)	*P* value
AECOPD after 30 days of discharge, n (%)	9 (75)	15 (71)	>0.999
Number of AECOPD after 30 days of discharge, median (IQR)	1 (0.5; 3)	1 (0; 2)	0.892
Time to the next AECOPD, median (IQR), days	37 (19; 173)	40 (25; 115)	0.900
Length of stay, median (IQR), days	14 (10; 21)	8 (7; 10)	**0.002**
ICU admission, n (%)	3 (23)	1 (5)	0.274
IMV, n (%)	1 (8)	1 (5)	>0.999
NIMV, n (%)	4 (31)	2 (10)	0.173
30-day mortality, n (%)	1 (8)	0	0.382
1-year mortality, n (%)	5 (39)	6 (29)	0.709
3-years mortality, n (%)	6 (55)	10 (63)	0.710

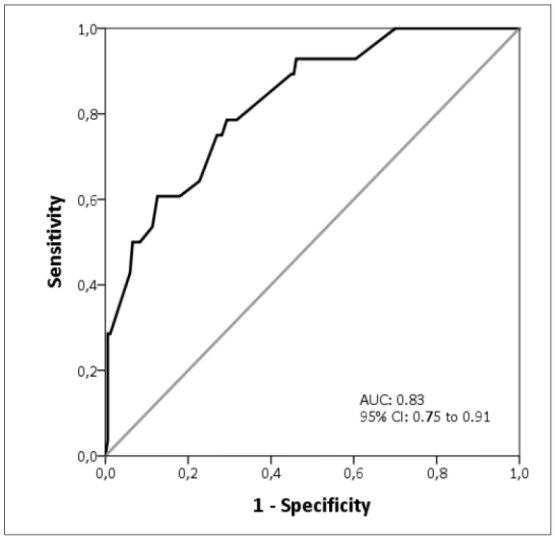
Abbreviations: AECOPD indicates acute exacerbation of chronic obstructive pulmonary disease exacerbation; ICU, intensive care unit; IMV, invasive mechanical ventilation; IQR, interquartile range; MDR, multi-drug resistant; NIMV, non-invasive mechanical ventilation; XDR extensive-drug resistant.

Table S8. Internal Validation of Risk of Length of Hospital Stay Using Bootstrap Technique

	Original	Bias	SE	*p*-value	95% BCTo CI	
Constant	6,628	,004	,667	,001	5,252	7,989
BODEx index	,814	-,009	,335	,027	,223	1,463
Invasive mechanical ventilation	5,919	,564	8,050	,492	-5,496	25,300
Non-invasive mechanical ventilation	3,183	,073	1,725	,061	-,049	6,774
MRCT Isolation	3,107	-,001	1,466	,039	,304	5,857

BCa indicates adjusted bootstrap; CI, confidence interval; SE, standard error

Figure S1. Receiver Operating Characteristic Curve for Multinomial Logistic Regression Model to *Pseudomonas aeruginosa*



Abbreviations: AUC indicates area under the curve; CI, confidence interval.

Figure S2. Kaplan–Meier Analysis of the Effect of Microbial Aetiology Groups on Time to Death

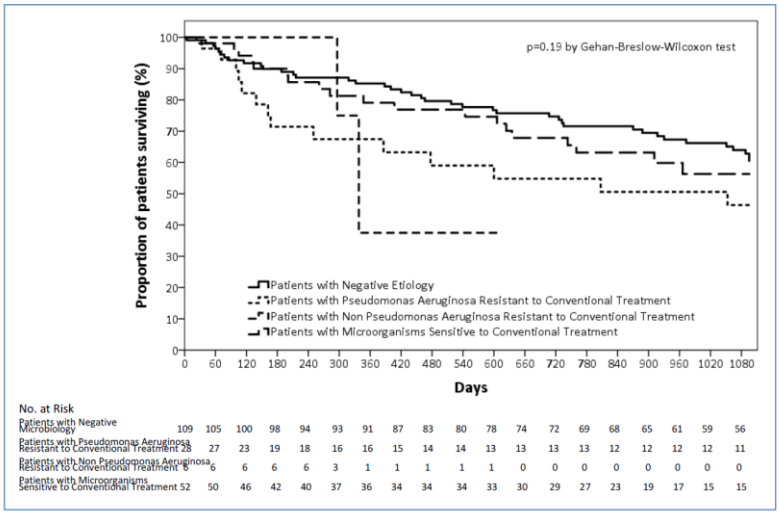
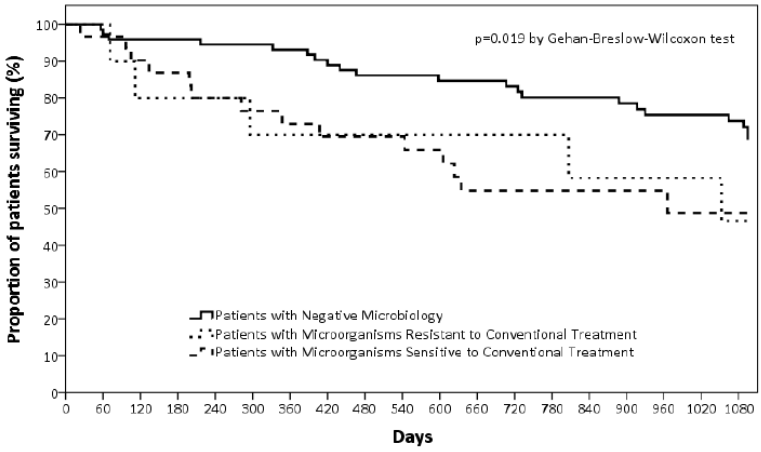
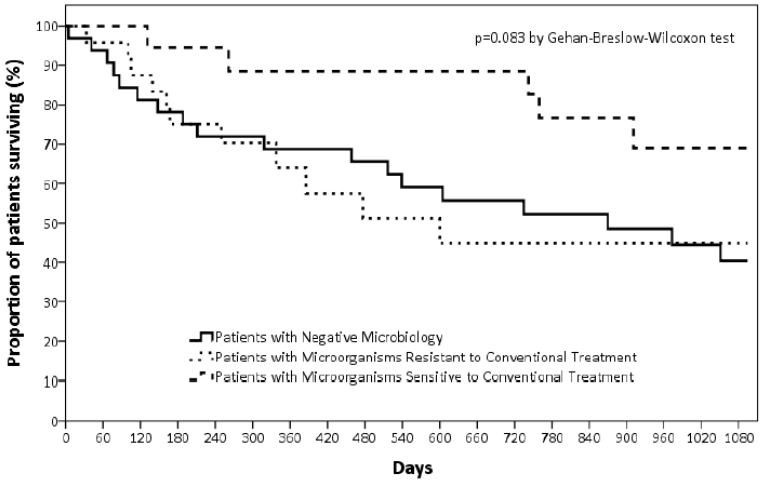


Figure S3. Kaplan–Meier Analysis of the Effect of Microbial Aetiology Groups on Time to Death. A) Patients with <2 AECOPD and none admission by AECOPD in the previous year; B) Patients with ⩾2 AECOPD or 1 admission by AECOPD in the previous year.

A



B



Abbreviations: AECOPD indicates acute exacerbation of chronic obstructive pulmonary disease exacerbation.

5.2 Resultados estudio 2

MUSCLE FUNCTION DURING SEVERE COPD EXACERBATIONS AND RISK OF BOTH A NEW EPISODE AND READMISSION

Cristina Estirado[1,2], Marisol Domínguez-Alvarez[1,2], Diana Badenes-Bonet[1,2], Clara Martín-Ontiyuelo[1,4], Antoni Torres[4-6], Joaquim Gea[1,2,6]

1. Department of Respiratory Medicine, *Hospital del Mar* - IMIM. PSMAR, Barcelona, Spain.

2. CEXS Department. *Universitat Pompeu Fabra*. Barcelona, Spain.

4. Department of Respiratory Medicine, *Institut Clínic del Torax* (ICT). *Hospital Clinic*, Barcelona. Spain

5. Department of Medicine. *Universitat de Barcelona* (UB), Barcelona, Spain

6. *Centro de Investigación en Red de Enfermedades Respiratorias* (CIBERES), Groups CB06/06/0043 & CB06/06/0028. *Instituto de Salud Carlos III* (ISCIII). Barcelona, Spain.

Corresponding Author: Dr. Joaquim Gea
Servei de Pneumologia
Hospital del Mar
Pg. Marítim 27
E-08003
Barcelona, Spain
E-mail:
jgea@psmar.cat

ABSTRACT (196 words)

Chronic Obstructive Pulmonary Disease (COPD) is characterized by both pulmonary and systemic involvements, as well as periods of exacerbation (AECOPD). One of the most common systemic manifestations is respiratory and/or limb muscle dysfunction, which appears to further increase in AECOPD. Our objective was to assess the evolution of muscle function during these acute episodes and its ability to predict both future exacerbations and hospital readmissions (at 90 days). Fifty patients admitted for AECOPD were consecutively included and we assessed the strength of their respiratory (mouth and nasal maximum pressures; PI_{max} and SNIP, respectively) and upper limb (hand grip, HG) muscles at admission, 24 h and discharge. The strength was globally diminished from the beginning but recovered progressively during hospitalization. The initial and 24 h PI_{max} values were associated with both a new AECOPD episode and readmission for this reason in the univariate and multivariate analyses. Furthermore, with cut-off points of 53.5 and 52%, respectively, the PI_{max} at 24 h acceptably predicted the chances of a new acute episode (79% sensitivity and 68% specificity) and readmission (77% sensitivity and 65% specificity). An early determination of PI_{max} during hospitalization for AECOPD is a good predictor of future episodes.

Keywords

Exacerbation - COPD - Respiratory Muscles - Limb Muscles – Readmission

Highlights

- Early assessment of inspiratory pressure during exacerbation predicts new episodes
- Prediction of new exacerbations is better with static inspiratory maneuvers
- Dysfunction is predominant in respiratory muscles during exacerbations

INTRODUCCION

Chronic obstructive pulmonary disease (COPD) is an entity with a very heterogeneous presentation, which includes pulmonary and systemic involvement, as well as periods of exacerbation of symptoms[1,2]. Thus, in addition to the characteristic airflow limitation, patients frequently show weight loss and muscle dysfunction, factors that contribute to their morbidity and mortality[1-6]. The etiology of muscle dysfunction in COPD is multifactorial, and incudes tobacco smoking, nutritional abnormalities, muscle activity, chronic hypoxia and hypercapnia, and treatments with steroids and other harmful drugs, among others[3,4,7]. All of them are common to respiratory and peripheral muscles except the level of activity that is different for each muscle groups. While increased in the former, if compared to healthy subjects, it is generally decreased in the latter[3, 4, 7]. COPD exacerbations (AECOPD) in turn are frequent in the natural course of the disease and also have a high impact on patients' health, contributing decisively to disease progression and a worse quality of life[1, 2]. Some different factors may predispose to suffering an AECOPD (age, presence of emphysema, severity of the disease, etc.), but the main predictor appears to be the occurrence of AECOPD in the preceding year[2, 8, 9].

Although most studies on muscle dysfunction in COPD have been conducted on patients in a stable phase, it has also been observed that this abnormality worsens during AECOPD. This is probably due to greater systemic inflammation and oxidative stress, degree of hypoxia and hypercapnia, deleterious changes in lung mechanics

with increases in the work of breathing, and physical inactivity[3, 10-15]. Although various studies have assessed the evolution of either peripheral or respiratory muscle function during AECOPD as prognostic factors for new episodes, fewer have simultaneously assessed the function of both muscle groups[13, 14, 16, 17]. Some of these studies reported that patients with AECOPD show a more severe degree of respiratory and limb muscle dysfunction than those in a stable situation[13, 14, 16]. In addition, members of our group have showed that this muscle dysfunction is associated with a higher risk of suffering a new and severe AECOPD[13]. However, in the latter, and in other studies, muscle function assessment was unique, without homogenizing the specific moment of its realization. This point is important since there is some controversy about the evolution of muscle functional impairment through AECOPD. Some authors have shown a recovery, at least partial, during the exacerbation episode itself[15, 18], whereas others have observed a progressive deterioration[16, 19], tending to return to normal only one or more months after discharge in some of the studies[14, 17]. All of this highlights the importance to determine the appropriate time to assess muscle function during AECOPD in order to allow prediction of future episodes. Therefore, the objective of the present study was to assess the evolution of respiratory and peripheral muscle function simultaneously and repeatedly during hospitalization for AECOPD, and determine when it best predicts the appearance of a new episode of exacerbation as well as a subsequent hospital readmission.

MATERIAL & METHODS

Design and Population

This is a prospective and observational study, where patients hospitalized in our center for AECOPD[2] were consecutively recruited. Inclusion criteria were: a COPD (clinical history and FEV_1/FVC <0.7 after bronchodilator) and AECOPD diagnoses[2] requiring hospital admission (defined as a stay of more than 24 hours). Those patients associating other chronic or acute respiratory diseases, neuromuscular disorders or other relevant chronic diseases (severe liver disease, chronic renal failure, heart disease or active neoplastic process) were excluded. We also excluded patients who required orotracheal intubation and were admitted to the ICU.

The present study was approved by the Ethics Committee at our institution and all patients gave their written inform consent. During the study implementation, the national and international ethical guidelines (our own institutional ethics code, declaration of Helsinki[20]), as well as legal regulations on data confidentiality (Organic Law 15/1999 of December 13, Protection of Personal Data [LOPD]) were followed.

Measurements

Anthropometric and demographic data of the patients were collected at the time of inclusion, as well as the most relevant clinical variables, including symptoms, respiratory function, treatments, presence of previous germs in the sputum and comorbidities. Dyspnea on stability was assessed using both Medical Research Council (MRC) and Borg scales. The specific

characteristics of the AECOPD episode in turn were collected at the time of inclusion, and included semiology, blood gases and muscle function, as well as APACHE II and Glasgow scales. All patients received the treatment considered most appropriate for their AECOPD according to the criteria of the responsible physician (independent of the research team). This treatment included inhaled bronchodilators, systemic and/or inhaled steroids, antibiotic therapy, and oxygen therapy; as well as occasionally, non-invasive respiratory support. All these procedures followed the recommendations of the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR)[1].

Assessment of both respiratory and peripheral muscle strength, as well as arterial blood gases and dyspnea (Borg scale in this case) were performed in all patients in 3 different situations: the first 4 hours following their arrival at the emergency room, 24 hours after admission, and at the time of hospital discharge. Respiratory muscle strength was determined through both the maximum inspiratory pressure (PI_{max}) measured at the mouth using a static maneuver, and the maximum nasal inspiratory pressure (SNIP) measured with the sniff dynamic maneuver. For these determinations, a portable manometer (MicroRPM, CareFusion, San Diego, CA, USA) was used, following the recommendations of both SEPAR and the European Respiratory Society (ERS)[4, 21]. In the measurement of PI_{max}, an occludable mouthpiece with a small hole to prevent the closure of the glottis and the use of the buccinator muscles was employed. The patient was verbally stimulated until 3 acceptable maneuvers with a variability of less than 20% were achieved, and

the best of them was taken. In turn, SNIP measurement was performed by occluding one of the nostrils and performing a minimum of 10 maneuvers, selecting the highest value. Reference values for Caucasian populations were used for both PI_{max} and SNIP[22, 23]. The strength of peripheral muscles was evaluated through hand dynamometry (flexors function in a grip maneuver, JAMAR, Nottinghamshire, UK) in both dominant and non-dominant hands. The maximum value of 3 valid and reproducible maneuvers was chosen for the analysis, being expressed both in absolute (Kg) and percentage of predicted values[24].

Complications occurring during hospitalization and the length of stay were also recorded at discharge, and patients were followed up for three more months, collecting the new episodes of AECOPD, hospital readmissions during this period and eventual deaths.

Statistical analysis

The sample calculation was carried out based on a previous study of our group[13]. This indicated that at least 40 COPD patients were needed for the establishment of valid predictions. Quantitative variables are expressed as mean and standard deviation vs. median and interquartile range (IQR), depending on their normality, whereas the qualitative ones are expressed as frequencies (number and percentage). Categorical variables were compared by Chi-square or Fisher exact test, as appropriate, and quantitative variables by the Student t-test. The correlations between quantitative variables were analyzed using Spearman or Pearson coefficients.

Mulitivariate logistic regression was performed to check factors associated to two main outcomes, new AECOPD episodes and hospital readmissions (90 days after discharge). Variables in the multivariate analysis were introduced on the basis of clinical criteria taking into account those that appeared significant or nearly significant ($p<0.1$) in the bivariate analysis. In all cases, $p<0.05$ was taken as significant. In addition, empirical cutoff points were calculated for inspiratory muscle strength (PI_{max}) based on Youden criteria: the sample point that maximizes the Youden index (sensitivity + specificity - 1). Accuracy diagnose measures and ROC curve were also displayed. STATA version 15.1 (StataCorp, College Station, TX, USA) was used for all the statistical analysis.

RESULTS

Fifty patients hospitalized for AECOPD were successively included. Their general characteristics are summarized in Table 1. Most of them were male, smokers or ex-smokers, in the seventh-eighth decade of life, and with moderate to high number of comorbidities. All had severe or very severe COPD according to lung function, with moderate to severe dyspnea during their periods of stabilization. Three-quarters of the patients presented an AECOPD during the previous year, with just over half requiring hospital admission for this. Functionally, and in addition to airway obstruction, they showed air trapping and a marked decrease in their DLco. Regarding the nutritional status, it was globally conserved since only 16% showed low weight. All the patients were taking inhaled bronchodilator treatment and up to a third were also receiving inhaled steroids. A relatively small group required home oxygen therapy for chronic respiratory failure. Regarding microorganisms present in their respiratory secretions, *Pseudomonas aeruginosa* was found in 14%, with MRSA being very rare.

Table 2 shows the AECOPD characteristics: the Apache scale showed a moderate affectation (corresponding to a predicted mortality of 15%), with a PaO_2/F_IO_2 that indicated a mild-moderate degree of oxygenation impairment, although up to 64% associated hypercapnia. As expected, the degree of dyspnea was much higher than at baseline. A small group needed short periods of non-invasive respiratory support. The patients remained hospitalized for a median of 6 days, without relevant complications.

Muscle function during hospitalization

Table 3 shows the evolution of respiratory and peripheral muscle function, arterial blood gases and dyspnea through hospitalization. The initial PI_{max} was already reduced by a half at the time of admission, with progressive improvement until a moderate impairment at discharge. The SNIP, in turn, showed a very similar evolution, although its values were somewhat lower. On the other hand, the grip strength of both hands was very slightly decreased at the time of admission, but it also showed a progressive improvement until discharge. The initial PI_{max} was inversely correlated with the degree of air trapping expressed by the RV/TLC ratio (Rho=-0.41, p=0.02).

Muscle Strength and Prognosis

Almost half of the patients presented a new AECOPD within the 3 months following hospital discharge, with up to a third requiring a new admission for this. In contrast, mortality in this short period was only 2% (Table 4). The relative values of PI_{max} at the beginning and 24 hours after admission were inversely associated with both subsequent exacerbations of the disease and hospital readmissions (tables 5a and 5b). The multivariate model showed that the inspiratory strength value 24 hours after admission was a good predictor for the probability of both to present a new AECOPD episode and require a new hospital readmission for this (tables 6a and 6b). Moreover, inspiratory strength was the only factor, along with a history of AECOPD in the previous year, that reached statistical significance in the prediction. In addition, an optimal cut-off point could be established for PI_{max} at 24 hours (53.5% pred.) to detect the probability of a new AECOPD in the 3 months following discharge, with a sensitivity of 79% and a specificity of 68% (figure 1). Similar values were obtained for the prediction of a new admission, with a cut-off of 52 in this case, and a sensitivity of 77% and specificity of 65%.

DISCUSSION

The most novel finding of the present study is that the early determination of the inspiratory muscle function (at the time of admission and especially at 24 h later), is associated with a risk of presenting both a new episode of AECOPD and a readmission for this. It also confirms that patients hospitalized for AECOPD present muscle dysfunction, especially of their inspiratory muscles, which is proportional to the degree of air trapping, and is somewhat less marked in the peripheral muscles. Both muscle groups progressively improve their function throughout hospitalization.

Several studies have previously reported a high rate of inspiratory muscle dysfunction in patients admitted for AECOPD[4, 13, 25]. Furthermore, our own group observed in a larger series that COPD patients with exacerbation present a higher degree of respiratory and limb muscle dysfunction than those in a stable situation, which is also a factor predicting future hospitalizations for AECOPD[13]. However, the precise moment for measuring muscle function in this and many other studies has been widely heterogeneous and there are clear discrepancies regarding the evolution of this function throughout an acute episode. For some authors, it progressively worsens[14, 16, 17, 19], whereas for others, as in the present study, it improves throughout hospitalization[15, 18], although for some this improvement would last for weeks or even months after discharge[14, 17, 18]. Therefore, it is relevant to have defined here that the early assessment of inspiratory strength (at the beginning of the hospitalization or even better, at 24 h.) best associates with the

prediction of either new AECOPD episodes or readmissions for this reason. Moreover, it is worth noting that in our study the significance of these predictions was only reached by PI_{max} and the factor classically considered as the gold standard for them: to have suffered an acute episode in the previous year[2]. Furthermore, a specific threshold for PImax that allows an acceptable prediction of either new episodes of AECOPD or readmission has been obtained for the first time. This prediction is very relevant, given the enormous impact that AECOPD has on the health system (utilization and costs) and patients' health, quality of life and prognosis[1, 2, 26]. In fact, some patients are particularly susceptible to developing frequent AECOPD, which is associated with higher morbidity and mortality[2], and entails differentiated recommendations for clinical management and treatment[2]. Thus, the presence of a sustained or occasional inspiratory muscle dysfunction during AECOPD is being repeatedly confirmed as a relevant risk factor for suffering exacerbations. This factor, however, has not yet been sufficiently studied from a pathophysiological point of view or considered in the guidelines. This is somewhat surprising since various studies have shown that respiratory muscle dysfunction in AECOPD, even evaluated through clinical variables such as the simple observation of the use of accessory respiratory muscles, has prognostic value for both a new AECOPD episode and even mortality[27-31]. In our study, mortality was very low, and this has not allowed us to establish a prediction model based on muscle dysfunction.

Another novel aspect of the present study was that the classical determination of the inspiratory force by means of a static maneuver was complemented with the dynamic sniff maneuver, which is considered much easier for patients to understand and execute since it requires no learning and, being less affected by the action of buccinator muscles[32], does not need coordination with the technician. This led us to anticipate that it could be more efficient for predictions. However, both determinations showed a very similar evolution throughout hospitalization, and surprisingly the best predictive value was obtained with the static maneuver.

Regarding the relationship of maximum inspiratory pressure with lung volumes during AECOPD, it has also been observed by other authors such as Mesquita et al.[18], and most probably expresses the loss of the diaphragm contractile force as it shortens due to an increase in lung volumes[4, 33]. Moreover, this factor has probably played a determining role in the greater dysfunction observed inspiratory muscles compared to peripheral ones, where only systemic factors and light deconditioning would have acted[4, 10, 34].

Peripheral muscle function indeed, determined here through handgrip strength, was only slightly diminished during the AECOPD, and progressively improved throughout hospitalization. This confirms previous observations, where a variable strength loss in either upper and/or lower limbs has also been evidenced during AECOPD[14, 16, 19, 35], showing improvement during hospital stay in some of these studies[14]. The causes that have been proposed for limb muscle dysfunction mainly include disuse, systemic

inflammation, nutritional alterations and treatments with deleterious effects on the muscles[10, 36, 37], all of them are factors that may be even more relevant during AECOPD[3, 10, 11, 38-40]. We could speculate that in those studies where the short-term recovery was not observed or patients even showed a progressive loss of strength[16, 17, 19], may be due to an associated loss of weight or lean mass, or longer hospital stays with a greater level of deconditioning[16]. Although some authors have studied the predictive capacity of peripheral muscle function, and mainly handgrip strength, with respect to new AECOPD, hospitalizations and/or mortality, the results have generally been inconclusive[41-43] and only some of them have found associations with the risk of future AECOPD[13, 44, 45].

Another interesting consideration regarding the present study is that, as in some previous authors[16], the strength of both hands was determined. It is usually considered that the non-dominant limb is probably more representative of the systemic status of peripheral muscle strength than the dominant one since the latter would logically be subject to a higher activity on a day-to-day basis. In this same way, different authors have found functional differences between both hands for the same subject[46, 47]. However, this was not the case in our study.

The loss of muscle mass did not seem to have been a relevant factor in our series given the mean BMI values and the low percentage of patients with underweight. This is different from other similar studies, in which nutritional alterations and/or even clear sarcopenia were much more prevalent, were frequently

associated with more severe muscle dysfunction and/or had a good predictive capacity regarding readmissions or mortality[14, 27, 35, 48]. These differences would explain why, like us, some other authors have not found this type of associations in the prediction of outcomes related to AECOPD[28]. This should not be surprising because discrepancies in the prevalence and impact of nutritional alterations in COPD patients are frequent and have been attributed both to differences in regional lifestyles and to different recruitment environments (general COPD populations, institutionalized patients, rehabilitation clinics, etc.)[49].

An important clinical aspect to be considered is the role that respiratory rehabilitation, and more specifically muscle training or even electrical or magnetic stimulation, during and after hospitalization, can play in the prevention or limitation of muscle dysfunction. Based on our own results and those from other authors, we suggest that this intervention could help in preventing or delaying new episodes of AECOPD[50-53].

Potential limitations

A potential limitation of the present study is the absence of determinations of muscle function prior to the acute episode in the same patients. So, it cannot be said with certainty that the values observed at the beginning of AECOPD were entirely the result of it. However, the improvement observed at the time of discharge suggests that this was actually the case, at least in part.

The strength of lower limb muscles was not determined in the present study, and some authors have demonstrated that, although

muscle dysfunction is currently present in the upper and lower extremities during AECOPD, there are some quantitative differences and only the latter would show progressive deterioration[14,18]. Therefore, the lack of lower limb muscle assessment can be considered a potential limitation. Nevertheless, it may also be a potential source of information. Lower limb strength appears to be more dependent on the level of daily physical activity and potential deconditioning[37]. We speculate that the mild dysfunction detected in the present study for the upper limbs probably better reflects the impact of other factors such as systemic inflammation or oxidative stress[3, 37, 54], with a more general/systemic impact.

CONCLUSIONS

In conclusion, and as a newer finding, the early determination of inspiratory muscle strength during hospitalization is a good predictor for both a new AECOPD and hospital readmission. We also confirm that both respiratory and peripheral muscle strengths are decreased in AECOPD, progressively improving as it resolves. Inspiratory muscle involvement is greater than that of peripheral muscles, probably due to the relative weight of local factors such as air trapping.

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Table 1. Clinical Characteristics of patients (n=50)

Age (years), mean±SD	67.6±8.6
Male, No (%)	38 (76)
Tobacco, current smoker, No (%)	22 (44)
Tobacco (packs/year), mean±SD	66±33
BMI (Kg/m^2), mean±SD	25.6±5.0
BMI <20 Kg/m^2, No (%)	8 (16)
Charlson index, median (IQR)	2 (1:3.4)
AECOPD exacerbations in the previous year, n (%)	37 (74)
AECOPD in the previous year, median (IQR)	2 (0:3)
Admissions for AECOPD in the previous year, n (%)	27 (54)
Admissions for AECOPD in the previous year, median (IQR)	1 (0:2)
Dyspnea MRC scale, median (IQR)	2 (2:3)
Dyspnea Borg scale, median (IQR)	3 (2:4)
FEV_1 (% pred.), mean±SD	36±14
TLC (% pred.), mean±SD	107±18
RV/TLC (%), mean±SD	65±7
DLCO (% pred.), mean±SD	37±15
Inhaled corticosteroid, No. (%)	35 (70)
Home oxygen therapy, No (%)	17 (34)
Pseudomonas Aeruginosa, No (%)	7 (14)
MRSA, No (%)	2 (4)

Abbreviations: SD, standard deviation; BMI, body mass index; IQR, interquartile range; FEV_1, forced expiratory volume in the first second; TLC, total lung capacity; RV, residual volume; DLco, transfer factor for CO; MRSA, methicillin-resistant Staphylococcus aureus

Table 2. Clinical Characteristics of the AECOPD

Apache II, mean±SD	11.5±3
Dyspnea Borg, median (IQR)	8 (6:9)
C reactive protein (mg/dL), mean±SD	5.2±6.7
pH, mean±SD	7.38±0.06
$PaCO_2$, mmHg, median (IQR)	50 (39:61)
PaO_2, mmHg, median (IQR)	70 (62:84)
PaO_2 /FIO_2 mmHg, median (IQR)	265 (229-317)
Non-invasive ventilatory support, No (%)	6 (12)

Abbreviations: *SD, standard deviation; pH, inverse logarithm of the concentration of hydrogen ions; PaO_2, oxygen partial pressure in arterial blood; $PaCO_2$, CO_2 partial pressure in arterial blood; FIO_2, inspiratory oxygen fraction*

Table 3. PI_{max}, SNIP and HGS throughout the hospitalization period

	Admission	24 h	Discharge	p*	p#
PI_{max} (cm H_2O), mean±SD	52.0±25.4	58.7±28.7	62.6±28.3	0.04	<0.001
$PI_{max,}$ (%pred.), mean±SD	51.2±21.4	57.8±24.8	61.3±24.9	<0.001	<0.001
SNIP (cm H_2O), mean±SD	40.2±19.5	45.5±20.7	51.4±22.8	0.01	<0.001
SNIP (% pred.), mean±SD	39.7±18.9	45.5±20.3	51.6±20.7	0,08	<0.001
Dominant HGS (Kg), mean±SD	27.7±8.7	29.7±8.8	29.8±8.8	<0.001	<0.001
Dominant HGS (% pred.), mean±SD	77.4±19.4	81.2±18.8	83.6±17.4	0.05	<0.001
Non dominant HGS (Kg), mean±SD	25.5±8.1	27.2±8.1	28.4±8.8	0.04	<0.001
Non dominant HGS (% pred.), mean±SD	77.1±20.8	82.4±20.4	85.1±20.1	0.07	<0.001
PaO_2/F_IO_2 , median (IQR)	265 (229-317)	279 (251:320)	314 (280-357)	0.2	0.003
$PaCO_2$ (mmHg), median (IQR)	50 (39:61)	47 (38:58)	44 (38:55)	0.02	0.01
Dyspnea (Borg), median (IQR)	8 (6:9)	5 (3:7)	2 (1:3)	<0.001	<0.001

Abbreviations: PI_{max}, maximal inspiratory pressure measured at the mouth; SNIP sniff nasal inspiratory pressure; HGS, *hand grip strength; $PaCO_2$, CO_2 partial pressure in arterial blood; F_IO_2, inspiratory oxygen fraction. p* value, between initial and 24h assessments; p# value, between initial and at discharge assessments.*

Table 4. Outcomes

Length of hospital stay (days), median (IQR)	6 (4:11)
New exacerbations, 90 days after discharge, No (%)	23 (46)
Readmissions, 90 days after discharge, No (%)	16 (32)
Mortality, 90 days after discharge, N (%)	1 (2)

Table 5. Inspiratory strength and a (a) new AECOPD episode, and (b) hospital Readmission (90 days after discharge)

a)

	Non AECOPD	New AECOPD	Total	p-value
	N = 27	N = 23	N = 50	
PI_{max} at admission (% pred)				0.050
Mean (SD)	56.6 (23.3)	45.0 (17.5)	51.2 (21.5)	
Median (Q1, Q3)	54.0 (47.0, 64.0)	41.0 (33.0, 57.0)	50.5 (38.0, 60.0)	
PI_{max} at 24h (% pred)				0.005
Mean (SD)	67.5 (26.8)	47.4 (17.7)	57.9 (24.8)	
Median (Q1, Q3)	66.0 (54.0, 77.5)	49.0 (36.0, 62.0)	54.5 (38.0, 72.0)	

b)

	Absence of Readmission	Hospital Readmission	Total	p-value
	N = 30	N = 20	N = 50	
PI_{max} at admission (% pred)				0.015
Mean (SD)	56.5 (23.3)	43.4 (15.8)	51.2 (21.5)	
Median (Q1, Q3)	54.5 (47.0, 64.0)	41.0 (35.0, 50.5)	50.5 (38.0, 60.0)	
PI_{max} at 24h (% pred)				0.012
Mean (SD)	65.9 (26.8)	47.5 (17.6)	57.9 (24.8)	
Median (Q1, Q3)	65.0 (53.0, 77.0)	49.0 (36.0, 59.0)	54.5 (38.0, 72.0)	

Abbreviations: PI_{max}, maximal inspiratory pressure measured at the mouth.

Table 6. Adjusted Odds Ratios for (a) a new AECOPD and (b) hospital Readmission (90 days after discharge). Multivariate logistic regression model.

a)

	OR	[95% CI]		p value
PI_{max} at 24h (% pred.)	0.93	0.88	0.98	0.005
AECOPD, previous year	1.75	1.10	2.80	0.018
Tobacco (packs/year)	0.99	0.96	1.02	0.350
Age (years)	1.05	0.93	1.17	0.441
BMI (kg/m^2)	0.94	0.77	1.14	0.532
FEV_1 (% pred.)	0.98	0.92	1.05	0.620
Sex				
M	1.00			
F	0.43	0.04	4.54	0.483
Charlson	0.91	0.49	1.70	0.762

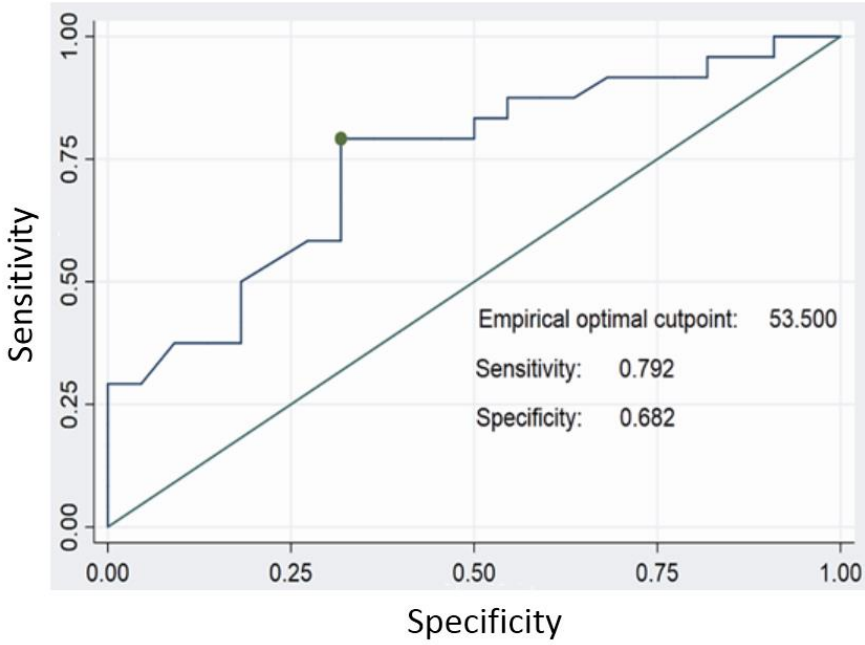
b)

	OR	[95% CI]		p value
Pi_{max} at 24h (% pred.)	0.90	0.83	0.97	0.005
AECOPD, previous year	2.23	1.27	3.94	0.005
BMI (kg/m^2)	0.82	0.63	1.05	0.117
FEV_1 (% pred.)	0.96	0.89	1.03	0.245
Sex				
M	1.00			
F	0.24	0.01	4.34	0.335
Charlson	1.20	0.59	2.43	0.612
Tobacco (packs/year)	1.00	0.97	1.04	0.817
Age (years)	1.01	0.88	1.15	0.924

Abbreviations: OR, odds ratio; CI, confidence interval; BMI, body mass index; FEV_1, forced expiratory volume in the first second; M, male; F, female.

Figure 1 legend.

Area under the ROC curve (0.7434) for PI_{max} at 24 h (% pred.) for the prediction of a new AECOPD, 90 days from admission



6. DISCUSIÓN

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6.1 Discusión estudio 1

En este estudio se analizaron y compararon tres grupos diferentes de pacientes hospitalizados por AEPOC. El primero compuesto por pacientes con AEPOC e infección por microrganismos resistentes al tratamiento convencional (MRCT) y los otros dos grupos control; uno de pacientes con AEPOC e infección por microorganismos sensibles a tratamiento convencional (MSCT) y el último grupo de pacientes con AEPOC pero con microbiología negativa y que no habían recibido tratamiento antibiótico previo.

Se objetivó que en situación previa basal, los pacientes con MRCT presentaban enfermedad más severa, medida por la escala de disnea, la escala COPDSS[60], el índice BODEx[61] y la historia de AEPOC en el año previo. Sin embargo, no hubo diferencias significativas entre los grupos en la gravedad de la exacerbación ni en el intercambio gaseoso en el momento del ingreso hospitalario. Tampoco se objetivaron diferencias en la purulencia del esputo ni en la clasificación de Anthonisen entre el grupo MRCT y el grupo MSCT.

El análisis reveló que los factores de riesgo independientes para presentar AEPOC por MRCT eran el tabaquismo no activo, la presencia de ≥ 2 AEPOC o de ≥ 1 ingreso hospitalario por AEPOC durante el año previo, y una baja respuesta inflamatoria al ingreso (medida por PCR). Los pacientes con MRCT tenían estancias hospitalarias más prolongadas. Sin embargo no se objetivó mayor mortalidad a los 3 años ni mayor número de agudizaciones posteriores que en los grupos controles.

Una respuesta inflamatoria baja (medida por PCR) fue un factor de riesgo para el aislamiento de MRCT en este estudio. Esto podría deberse a una virulencia más baja o bien a una disminución en la habilidad para producir reactantes de fase aguda en presencia de estos microorganismos. Resultados similares se han observado en pacientes con neumonía comunitaria o asociada a ventilación mecánica cuando el microorganismo aislado fue P. aeruginosa [62,63].

Se observó también una asociación entre el tabaquismo y el aislamiento de MRCT, específicamente a favor de ser no fumador en la actualidad. Es conocido que el humo del tabaco aumenta la colonización del tracto respiratorio superior por Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis y Streptococcus pyogenes [64], y que el tabaquismo facilita la colonización pulmonar por estas bacterias[13]. Este hecho está probablemente relacionado con la reducción de la capacidad fagocítica de los macrófagos alveolares y con la disminución de la respuesta de las citoquinas que se ha asociado con el tabaquismo[65,66]. La asociación encontrada en este estudio entre el estado de no fumador activo y el aislamiento de MRCT no debería, sin embargo, debilitar la recomendación para el cese del hábito tabáquico para todos los pacientes. Otra posible explicación a este punto podría ser que aquellos individuos que presentan una enfermedad más severa con más sintomatología respiratoria es más probable que abandonen el tabaquismo.

El papel del tratamiento antimicrobiano es controvertido en la AEPOC. Con la excepción de pacientes que requieren soporte ventilatorio ventilación mecánica, los beneficios de la antibioterapia son limitados y principalmente se observan en pacientes con esputo purulento o en aquellos con agudización de EPOC tipo I de la clasificación de Anthonisen[29-33]. Las consecuencias de utilizar un tratamiento antibiótico inadecuado en los pacientes con AEPOC no están bien definidas. En este estudio no se encontró ninguna diferencia en los principales outcomes clínicos entre pacientes con tratamiento antibiótico adecuado e inadecuado.

Las AEPOC son eventos que marcan la progresión de la enfermedad y son tan importantes como la limitación al flujo aéreo en el pronóstico de los pacientes[1,2] . Además, es evidente que hay pacientes que son susceptibles a exacerbaciones frecuentes; y , en este caso, el factor más importante conocido que predice las futuras exacerbaciones es la historia de AEPOC previas. Sin embargo, la asociación con los datos microbiológicos ha sido poco analizada hasta la fecha[11]. En nuestro estudio no se encontró que los pacientes con MRCT presentaran mayor riesgo de agudizaciones en el mes siguiente de la hospitalización.

Aunque hay datos controvertidos en los estudios previos acerca de la relación entre mortalidad y aislamiento de P. aeruginosa, en general han mostrado una tendencia a un aumento de mortalidad cuando se aísla este microorganismo en los cultivos [24-28] . En el presente estudio no se han encontrado diferencias en mortalidad entre los pacientes con P. aeruginosa, incluyendo aquellos con cepas multirresistentes (MDR). En nuestro estudio no encontramos diferencias en mortalidad entre los pacientes con P. aeruginosa, incluyendo aquellos con cepas multirresistentes (MDR) según la clasificación de Magiorakos et al[67]. En otras enfermedades respiratorias, como la fibrosis quística o las bronquiectasias, el aislamiento de P. aeruginosa y MRSA ha mostrado tener un papel importante en la progresión de la enfermedad[68-72]. Aunque la erradicación con antibioterapia pueda ser beneficiosa en estas enfermedades, no hay evidencia de que existan beneficios similares para pacientes con EPOC.

Los factores predictivos identificados en este estudio representan el primer paso en el desarrollo de un modelo de predicción, que deberá ser validado en posteriores estudios preferiblemente multicéntricos con un mayor número de pacientes.

En resumen, no se observaron diferencias ni en mortalidad ni en agudizaciones al comparar las AEPOC con MRCT o con MSCT. Sin embargo, la estancia hospitalaria fue mayor en el grupo MRCT. Este es un parámetro importante para ser tenido en cuenta y hacer esfuerzos en predecir y tratar estos microorganismos en la AEPOC.

6.1. a) Limitaciones potenciales

Este estudio tiene algunas limitaciones que deben ser tenidas en cuenta. En primer lugar, fue llevado a cabo en un único centro en España. En segundo lugar, al pequeño tamaño de la muestra puede limitar el análisis de factores específicos para MRCT. La información disponible acerca del aislamiento de estos microorganismos en pacientes con AEPOC es limitada, por lo que sería deseable una confirmación de estos resultados en estudios multicéntricos con mayor número de pacientes.

Finalmente, otra limitación de nuestro estudio podría ser el uso de cultivos de esputo para diagnóstico con lo que habría una potencial dificultad para distinguir entre colonización e infección. Sin embargo, es el método usado habitualmente tanto en la práctica clínica como en la mayoría de los estudios para diagnosticar infección de vía aérea en AEPOC, dada la dificultad de realizar una broncofibroscopia para toma de muestras microbiológicas en estos pacientes. Además, Soler et al validaron en un estudio previo cultivos de esputo en comparación con las muestras broncoscópicas[73].

6.2 Discusión estudio 2

El presente estudio confirma que los pacientes hospitalizados por una AEPOC presentan en ese momento una disfunción de su musculatura respiratoria y periférica, y que dicha alteración mejora progresivamente a lo largo de la hospitalización. La disfunción inicial más marcada se produce en los músculos respiratorios y se asocia al grado de atrapamiento aéreo.

El hallazgo más novedoso de nuestro estudio es que el nivel de dicha disfunción está asociado con el riesgo de padecer un nuevo episodio de AEPOC y de reingresar por dicho motivo. En concreto el nivel de PI_{max} a las 24 horas del ingreso se comporta como un factor de riesgo tanto de nueva AEPOC como de reingreso hospitalario a los 3 meses, pudiendo predecirse con un nivel razonable el riesgo de nueva AEPOC.

Diversos estudios han reportado previamente una elevada tasa de disfunción muscular inspiratoria en pacientes ingresados por AEPOC. Así, Vilaró et al observaron que los pacientes con exacerbación presentan un grado más importante de disfunción muscular, tanto respiratoria como periférica, que los enfermos en situación estable, siendo además un factor que predice futuras hospitalizaciones por AEPOC[51].

La mejoría en la fuerza muscular inspiratoria a lo largo de la propia hospitalización observada en nuestros pacientes también concuerda con lo observado en algún otro estudio previo. En este sentido Mesquita et al. también encontraron una alta prevalencia de disfunción muscular inspiratoria en el momento del ingreso en un reducido grupo de pacientes hospitalizados por AEPOC, con mejora progresiva durante el ingreso y al mes del alta[52]. También observaron que la afectación funcional de los músculos inspiratorios correlacionaba con el aumento de volúmenes pulmonares expresado como el inverso de la capacidad inspiratoria. Estos resultados son similares a los del presente estudio, donde además la determinación de la fuerza inspiratoria mediante maniobra estática se complementó con una maniobra dinámica (inhalación forzada), mucho más fácil de entender y ejecutar por parte de los pacientes ya que no requiere de aprendizaje ni de coordinación con el técnico[59,74].

Hasta ahora los valores de maniobra dinámica no habían sido utilizados para evaluar la fuerza muscular durante la AEPOC a pesar de que es una técnica más fácil de realizar. Sin embargo, aunque las determinaciones tanto de maniobra estática como dinámica mostraron evoluciones muy similares durante el ingreso, no hemos encontrado relación entre los valores de SNIP y los principales resultados clínicos (nueva AEPOC y reingreso).

Por otra parte, la mayor afectación de la musculatura inspiratoria comparada con la periférica, así como su relación con los volúmenes pulmonares estáticos nos indica que este último factor fue más determinante que los elementos de índole sistémica en la disfunción muscular de los pacientes. Es conocido que la longitud del diafragma, principal músculo inspiratorio, se acorta al aumentar los volúmenes pulmonares, alejándose de su longitud óptima de contracción y de su capacidad de generar fuerza[39,47]. Sin embargo, esto no descarta que otros factores, muchos de ellos de índole sistémica, puedan también estar implicados en la disfunción de los músculos respiratorios asociada a las AEPOC[39,45,48].

Respecto a la musculatura periférica medida mediante la determinación de la fuerza prensil de la mano, se hallaba ligeramente disminuida pero con mejoría progresiva a lo largo de la hospitalización. Como se ha comentado anteriormente, el déficit era

menor que el observado en los músculos respiratorios. Estos resultados confirman observaciones anteriores en que también se evidenció una pérdida de fuerza en las extremidades superiores y/o inferiores durante la exacerbación de la EPOC [53,55,57,58], con mejoría posterior tras el alta[53]. Las causas que se han invocado para dicha alteración incluyen principalmente el desuso, la inflamación sistémica, las alteraciones nutricionales y los tratamientos con efectos deletéreos sobre el músculo [45,75,76], factores que pueden incluso tener más relevancia durante las AEPOC [38,45,47, 77,78].

Una matización interesante respecto del presente estudio es que probablemente la fuerza de la extremidad no dominante es más representativa del estado sistémico de la fuerza muscular, ya que con relativa frecuencia ambas mediciones pueden diferir[79,80], y la mano del lado dominante se hallaría lógicamente sometido a una actividad superior en el día a día a la de otras regiones del organismo.

Finalmente, en nuestra serie la pérdida de masa muscular no parece que haya sido un factor relevante dados los valores del IMC medio y la baja presencia de bajo peso entre los pacientes. Esto es discrepante de otros estudios similares, en que las alteraciones nutricionales y/o la sarcopenia eran mucho más prevalentes, se asociaban a disfunción muscular más marcada y/o poseían una buena capacidad de predicción sobre los reingresos o la mortalidad [58,81,82]. Por contra, otros autores no han hallado este tipo de asociaciones en la predicción de resultados clínicos, como la posibilidad de reingreso[83]. Las discrepancias en cuanto a la prevalencia e impacto de las alteraciones nutricionales en los pacientes con EPOC son frecuentes y se han atribuido tanto a diferencias en los estilos de vida regionales como a los diferentes entornos del reclutamiento[84].

El hallazgo más novedoso de nuestro estudio es la asociación encontrada entre el grado de disfunción muscular inspiratoria al ingreso con las aparición de nuevos episodios de AEPOC e incluso reingreso por dicho motivo a los tres meses. Es más, se ha obtenido un valor que permite una aceptable predicción de una nueva AEPOC. Esto es muy relevante, dado el impacto que las AEPOC tienen sobre la salud de los pacientes y su pronóstico [1,85] y además de sobre la utilización y costes al sistema de salud[2]. Es más, algunos

enfermos son particularmente susceptibles a desarrollar AEPOC frecuentes y presentan una mayor morbi-mortalidad[2].

De hecho, la presencia de disfunción muscular inspiratoria mantenida u ocasional podría ser un factor de riesgo, aún no suficientemente estudiado, para padecer agudizaciones. De forma indirecta y a través de parámetros únicamente clínicos, como la utilización de músculos respiratorios accesorios en el curso de la AEPOC, diversos trabajos han demostrado también una capacidad pronóstica. Así, múltiples autores han observado que dicho signo contribuía a un mayor riesgo de muerte [82, 86-88], mientras que Liu et al. mostraron una asociación con el riesgo de un nuevo episodio de AEPOC[83]. En cuanto a mortalidad, dado que ésta ha sido muy baja en nuestro estudio (2%) no se ha podido establecer asociación con la disfunción muscular.

Por otra parte, diversos autores han estudiado la capacidad de predicción de la función de los músculos periféricos, fundamentalmente la capacidad prensil de la mano, respecto de las AEPOC, hospitalizaciones y/o mortalidad, con resultados poco concluyentes [46,89,90]. Aunque algunos autores han hallado asociaciones entre la función muscular periférica y el riesgo de futuras AEPOC [43,44,51], nunca se ha definido previamente un punto de corte que permita obtener una aceptable sensibilidad y especificidad.

Un aspecto importante es el de que la rehabilitación respiratoria antes, durante y con posterioridad al período de hospitalización, y en concreto el entrenamiento muscular o la estimulación eléctrica, podrían ayudar a prevenir o limitar la disfunción muscular ligada a la AEPOC [91-94].

6.2.a Limitaciones potenciales

Una limitación potencial del presente estudio es la ausencia de determinaciones de la función muscular previas al episodio agudo, con lo que no se puede afirmar con seguridad que los valores observados al inicio de la AEPOC sean completamente fruto de

esta. Sin embargo, el retorno a valores normales en el momento del alta hace presumir que sí sea así.

En el presente estudio no se ha determinado la fuerza de los músculos de las extremidades inferiores, lo que puede considerarse una limitación. Sin embargo, dicha fuerza es muy dependiente de un factor importante en la disfunción de los músculos periféricos, como es el nivel de actividad física cotidiano y el potencial decondicionamiento[76]. Probablemente la alteración detectada en el presente estudio en la extremidad superior no dominante refleje mejor factores sistémicos de otra índole, como la inflamación sistémica o el estrés oxidativo[3,76,95].

6.3. Discusión general

Como se ha descrito previamente, las AEPOC son eventos que marcan la progresión de la enfermedad y son tan importantes como la limitación al flujo aéreo en el pronóstico de los pacientes[1,2] . Los factores que predisponen a padecer AEPOC no están del todo aclarados y el factor más importante conocido hasta la actualidad que predice las futuras exacerbaciones es la historia de AEPOC previas. Sin embargo, el impacto tanto de los microorganismos resistentes como de la disfunción muscular en las en las AEPOC y en la evolución clínica de los pacientes tras ser hospitalizados por AEPOC no ha sido suficientemente estudiada hasta la fecha.

Nuestro trabajo muestra que los pacientes hospitalizados por AEPOC secundaria a MRCT tienen estancias hospitalarias más prolongadas, pero no se ha objetivado una mayor mortalidad ni asociación con las agudizaciones posteriores como otros trabajos habían mostrado, aunque con resultados contradictorios[23-27]. Se han encontrado factores de riesgo específicos para presentar MRCT y que pueden ser utilizados en la práctica clínica para adecuar la antibioterapia en estos pacientes.

Nuestro trabajo ha confirmado que la fuerza muscular respiratoria y periférica de los pacientes empeora con la AEPOC y que se recupera durante la propia hospitalización. Los pacientes con mayor disfunción muscular inspiratoria no presentaban más mortalidad ni estancias hospitalarias más prolongadas, pero sí un mayor riesgo de padecer futuras agudizaciones y reingresos hospitalarios. Además, se ha definido un punto de corte para PI_{max} con aceptable sensibilidad y especificidad para el riesgo de AEPOC y reingreso. La realización de la PI_{max} a las 24 horas del ingreso hospitalario por agudización podría ayudar a predecir el riesgo de padecer nuevas AEPOC. Además, la rehabilitación respiratoria podría ayudar a paliar la disfunción muscular de estos pacientes.

Sería necesaria la realización de estudios multicéntricos con mayor número de pacientes para confirmar estos resultados, validar el modelo predictivo para padecer MRCT y confirmar la capacidad de PI_{max} de predecir nuevas AEPOC y reingresos hospitalarios.

7. CONCLUSIONES

7. CONCLUSIONES

- Los factores de riesgo independientes para presentar AEPOC causada por un MRCT son el tabaquismo no activo, la presencia de ≥ 2 AEPOC o de ≥ 1 ingreso hospitalario por AEPOC durante el año previo, y una baja respuesta inflamatoria al ingreso.

- Los pacientes hospitalizados por AEPOC y aislamiento de MRCT no presentaban mayor mortalidad comparados con los controles, aunque sus estancias hospitalarias fueron más prolongadas y su enfermedad de base más severa.

- La fuerza muscular tanto respiratoria como periférica se halla disminuida en los pacientes hospitalizados por AEPOC, mejorando progresivamente durante la resolución de la misma. La afectación de la musculatura inspiratoria es superior que la periférica probablemente debido factores locales como el atrapamiento aéreo.

- La determinación temprana de la fuerza muscular inspiratoria durante la hospitalización por AEPOC es un buen predictor tanto de padecer una nueva AEPOC como de un reingreso hospitalario.

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