UNIVERSITAT DE BARCELONA

Les aguditzacions com a element crucial en el maneig no farmacològic de les bronquièctasis

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Memòria de Tesi Doctoral presentada per:

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Per optar al grau de Doctora per la Universitat de Barcelona

Directors:

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AUTORITZACIÓ DELS DIRECTORS DE TESI

El Dr. Antoni Torres Martí i la Dra. Elena Gimeno Santos certifiquen:

Que la memòria que duu per títol "**Les aguditzacions com a element crucial en el maneig no farmacològic de les bronquièctasis**", presentada per la Victoria Alcaraz Serrano per optar al grau de Doctor en Medicina, ha estat realitzada sota la nostra direcció. Un cop finalitzada, autoritzem la seva presentació per a ser avaluada pel tribunal corresponent.

I per a que quedi constància als efectes oportuns, signem la present a Barcelona, 17 d'Abril del 2021.

Dr. Antoni Torres Martí

Dra. Elena Gimeno Santos

A mis padres

AGRAÏMENTS

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Quan penso en la Tesi i en el moment que vaig decidir començar-la he de retrocedir a l'any 2011. En aquests 10 anys m'he format, crescut i he après al voltant de grans professionals i amics.

Per començar vull donar les gràcies als directors de la Tesi: el Dr. Antoni Torres i la Dra. Elena Gimeno. Dr. Torres gràcies per acollir-me al grup fa 9 anys, per haver confiat sempre en mi i lluitar pel creixement d'aquesta línia de recerca. Dra. Elena Gimeno gràcies per la teva paciència infinita i dedicació. És un plaer treballar amb tu i un privilegi que comptis amb mi com la teva mà dreta. Gràcies als dos per veure en mi les capacitats que en molts moments no he sabut veure.

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A mi familia, gracias por vuestro apoyo aún y estar a 600km de distancia, en especial a mis primas María y Ana Cristina, que son como las hermanas que nunca tuve, y a mi tía Encarna porque sé que allá donde esté nos cuida. A mis padres Amparo y Salvador, por vuestro amor, confianza y educación. Gracias por enseñarme a pelear por aquello que me he propuesto, por apoyarme siempre y creer en mi. Tengo una gran suerte por teneros como padres, os quiero. A mi familia política por vuestro apoyo y por cuidarme tanto.

Para terminar, quiero darle las gracias a mi compañero de viaje. Sergio, conocerte fue una gran suerte y que encima entendieras que hacía cosas raras con los mocos... Ni te cuento. Eres mi pilar fundamental, mi serenidad, mi hogar. Gracias por darme el mejor de todos los regalos: nuestra familia. Carla tú eres el motor de mi vida.

Sergio, Carla os quiero mucho.

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PRESENTACIÓ

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La Tesi Doctoral ha estat desenvolupada durant els anys 2016-2021 a la Fundació Clínic per la Recerca Biomèdica (Hospital Clínic de Barcelona). Ha estat dirigida pel Dr. Antoni Torres i la Dra. Elena Gimeno, i consisteix en un compendi d'articles on la doctoranda és co-autora, publicats segons la normativa aprovada per la Comissió de Doctorat de la Universitat de Barcelona.

Els treballs que formen part de la Tesi Doctoral pertanyen a la línia de recerca de bronquièctasis dins del grup d'investigació "recerca aplicada en infeccions respiratòries i malalt crític" liderat pel Dr. Antoni Torres, i pretenen estudiar l'impacte clínic de l'avaluació de l'activitat física i el sedentarisme, així com les característiques viscoelàstiques de l'esput dels pacients amb bronquièctasis.

La Tesi inclou una introducció general, hipòtesis i objectius, els resultats (3 estudis originals), una discussió general i les conclusions finals. Els resultats dels estudis realitzats han aportat informació rellevant i innovadora en aquest camp, i estan recollits en 3 manuscrits originals que han estat recentment publicats en revistes científiques d'àmplia difusió internacional.

Apart del treball realitzat per la present Tesi Doctoral, la doctoranda ha estat investigadora principal i col·laboradora de diferents projectes de recerca, tots relacionats a la línia de recerca de les bronquièctasis, que han resultat en altres manuscrits originals i contribucions a congressos (inclosos en un llistat a l'apèndix al final de la Tesi).

ABREVIATURES

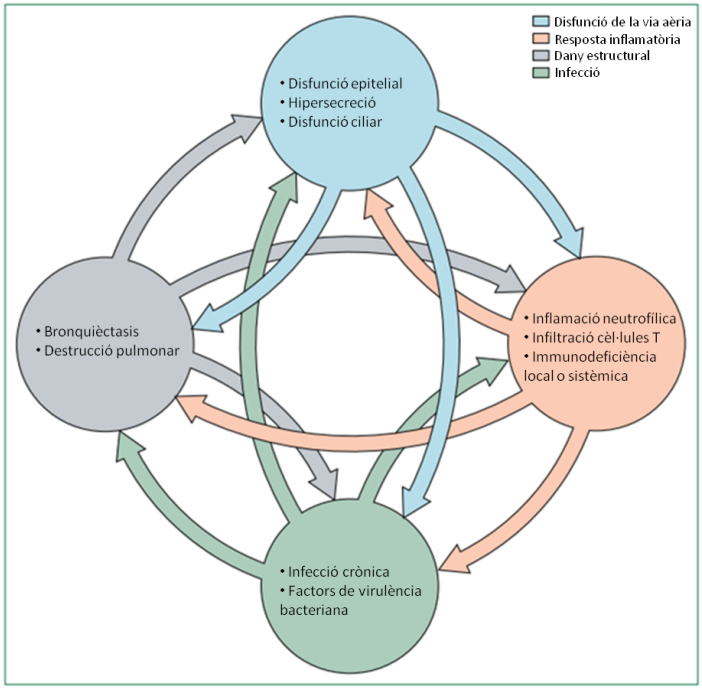
- AFMV: Activitat física moderada a vigorosa
- BSI: Bronchiectasis Severity Index
- BTS: British Thoracic Society
- FQ: Fibrosi Quística
- IC: Interval de Confiança
- IMC: Índex de Massa Corporal
- MET: Equivalent Metabòlic
- MRC: Medical Research Council
- mMRC: modified Medical Research Council
- MRC: Medical Research Council
- MPOC: Malaltia Pulmonar Obstructiva Crònica
- PAm: *Pseudomonas aeruginosa* mucoid
- PAnom: *Pseudomonas aeruginosa* no-mucoid
- TAC: Tomografia Axial Computada
- TACAR: Tomografia Axial Computada d'Alta Resolució
- VEF_1: Volum Expiratori Forçat en el primer segon

INTRODUCCIÓ

Definició de bronquièctasis

Les bronquièctasis és una malaltia respiratòria crònica caracteritzada radiològicament, per una destrucció i dilatació irreversible dels bronquis. Fisiopatològicament, aquestes deformacions provoquen l'activació d'un cercle d'infecció bronquial que es distingeix per un augment de la inflamació i problemes en l'aclariment mucociliar (**Figura 1**) [1-3]. Clínicament, es caracteritza per símptomes freqüents, com la tos acompanyada d'expectoració crònica, la dispnea i les aguditzacions recurrents de causa infecciosa. Altres símptomes comuns, però no tant freqüents són: la rinosinusitis, la fatiga, l'hemoptisi i el dolor toràcic [4], [5].

Figura 1. Model patogenètic de les bronquièctasis (adaptat de Flume PA, et al. [3])



Pel diagnòstic de les bronquièctasis cal realitzar una tomografia axial computada d'alta resolució (TCAR) per identificar les dilatacions bronquials de diferents morfologies: cilíndriques, varicoses i/o quístiques [6]. L'heterogeneïtat radiològica de les bronquièctasis és considerable i els allaus radiològics estan associats amb l'etiologia, els símptomes, la freqüència d'aguditzacions i el risc de mortalitat [7].

L'etiologia de les bronquièctasis es pot dividir en dos grans blocs: les que estan associades a fibrosi quística (FQ) i les que no. Les bronquièctasis no associades a FQ poden tenir una etiologia molt variada destacant la post-infecciosa, la idiopàtica i l'associada a altres malalties respiratòries com la malaltia pulmonar obstructiva crònica (MPOC) i l'asma (**Taula 1**) [8].

Taula 1. Etiologia i malalties associades a les bronquièctasis (adaptada de Martínez-García MA, et al. [8])

Etiologia, prevalença i malalties associades a les bronquièctasis	
Etiologia desconeguda (24,2-44,8%)	
Post-infeccioses (30%)	Bactèries, tuberculosi, MNT, virus i fongs
Associades a malaltia respiratòria crònica (6,3-13,7%)	MPOC (3,9-7,8%), asma bronquial (1,4-5,4%), dèficit d'alfa-1 antitripsina
Immunodeficiències (5-9,4%)	Primàries: dèficits quantitatius o qualitatius humorals, cèl·lules o combinats. Secundàries: neoplàsies, VIH, altres virus, tractament biològic i immunosupressors
Associades a malalties sistèmiques (1,4-3,8%)	Artritis reumatoide, lupus, síndrome de Sjögren, síndrome de Marfan, policondritis recidivant, sarcoïdosi, malaltia inflamatòria intestinal
Hipersensibilitat (0,9-2,6%)	Aspergil·losis broncopulmonar al·lèrgica
Discinèsies ciliars (2,5-2,9%)	Discinèsia ciliar primària, síndrome de Young
Causes locals (obstructives) (<1%)	Intrínseques (tumors, cossos estranys, estenosi). Extrínseques (tumors, adenopaties)
Post-transplantament pulmonar (<1%)	Bronquiolitis obliterant o malaltia d'empelt contra l'hoste
Pneumonitis post-inflamatòria (<1%)	Aspiració, reflux gastroesofàgic, radioteràpia, inhalació de gasos tòxics o drogues.
Altres (<1%)	Síndrome de les ungles grogues, panbronquiolitis difusa, defectes congènits de l'arbre tràqueo-bronquial, amiloïdosi, etc.
Abreviatures. MPOC: malaltia pulmonar obstructiva crònica; MNT: micobacteris no tuberculosos; VIH: virus de la immunodeficiència humana.	

Les bronquièctasis poden afectar tant a infants com a adults, sent la mitjana d'edat a Europa, als Estats Units i Austràlia de 60-70 anys, i augmentant la prevalença amb l'edat [9-11]. La prevalença actual de les bronquièctasis és encara confosa, ja que tot i que es considerava una malaltia òrfena [12], la millora en el diagnòstic per imatge en les últimes dècades ha incrementat el diagnòstic i, per tant, la prevalença [13]. L'any 2012, a Catalunya segons el "*Sistema de Información para el desarrollo de la Investigación en Atención Primaria*" es va estimar una prevalença de 36,2 casos per cada 10.000 habitants [14]. Un estudi realitzat al Regne Unit, va comparar la

prevalença de les bronquièctasis de l'any 2004 respecte el 2013 i es va detectar que tant en dones com en homes va créixer de manera important: de 350 per cada 100.000 habitants al 2004 a 566 al 2013, en dones; i de 301 a 485 en homes [10]. Per altra banda, a Alemanya, entre els anys 2005-2011 es va estimar una prevalença de 67 casos per cada 100.000 habitants [15], [16].

L'expectoració crònica és el símptoma més freqüent dels pacients diagnosticats per bronquièctasis, present en un 98% dels casos [4]. Les secrecions bronquials són una substància espessa que recobreix la superfície del sistema respiratori protegint-lo d'agents patògens, partícules i tòxics. En quantitats normals (10-100ml/dia en persones sanes), les secrecions es desplacen de manera fàcil mitjançant les cèl·lules ciliars i el flux d'aire expiratori, però en situacions patològiques com a les bronquièctasis, la hipersecreció bronquial provoca dificultats en el seu drenatge [17].

Propietats viscoelàstiques de l'esput

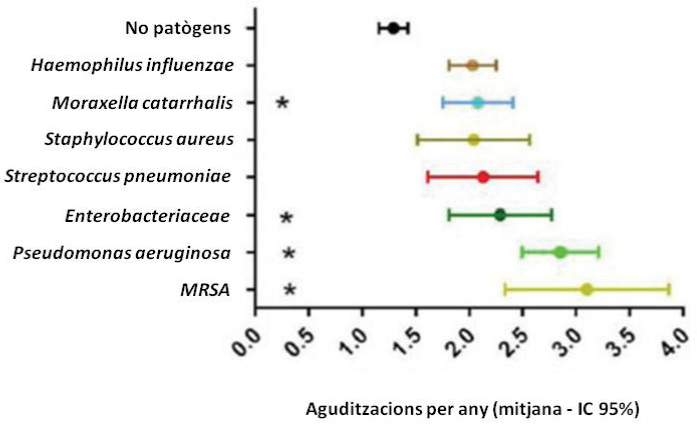
La reologia és la branca de la física que estudia la deformació i el fluir de la matèria. Dues de les característiques principals són: (i) l'elasticitat o mòdul d'emmagatzematge (G'), que mesura la tendència de la matèria a recuperar la seva forma original un cop s'ha deformat i, (ii) la viscositat o mòdul de pèrdua (G''), que és la resistència que oposa la matèria a fluir [18]. L'esput és un gel no-Newtonià amb un comportament viscoelàstic, amb una part sòlida (elàstic) i una líquida (viscós) [19]. Un estudi publicat per Voynow JA, et al. al 2009 va proposar que valors alts de viscositat ajuden a que les secrecions es quedin intactes en la seva posició, mentre que valors baixos d'elasticitat promouen la interacció aire – líquid evitant que les secrecions retornin a la seva posició inicial en ràfegues d'aire d'alta velocitat [20].

En pacients amb FQ i MPOC s'ha demostrat que l'elasticitat (G') i la viscositat (G'') augmenten quan l'esput és més purulent i en les fases agudes de la malaltia [21]. Específicament, els pacients amb FQ i colonitzats per *Pseudomonas aeruginosa* presenten un aclariment mucociliar disminuït (mesurat amb tècniques d'imatge nuclear) comparat amb els no colonitzats [22].

La majoria dels estudis en bronquièctasis s'han centrat en avaluar les propietats viscoelàstiques després de realitzar tècniques de fisioteràpia respiratòria o inhalació de fàrmacs [23-26]. A nivell descriptiu, s'ha identificat que l'esput dels pacients amb bronquièctasis té una elasticitat i viscositat més elevada que les persones sanes [27], però es desconeix si hi pot haver alguna associació entre la reologia i l'aïllament de *Pseudomonas aeruginosa* a l'esput.

La presència d'alguns tipus d'espècies i/o bactèries a l'esput pot influir directament en la simptomatologia del pacient, en el número d'aguditzacions i en la mortalitat. L'*Haemophilus influenzae* i la *Pseudomonas aeruginosa* són els microorganismes que s'aïllen de manera més freqüent en les bronquièctasis arreu del món, tot i que la proporció varia segons la població estudiada [28], [29]. Específicament, la *Pseudomonas aeruginosa* provoca més afectació clínica i pitjor pronòstic comparat amb l'*Haemophilus influenzae* [30-32]. La mitjana del número anual d'aguditzacions augmenta de 1,29±0,9 en pacients sense colonització bacteriana a l'esput, a 2,04±1,4 en presència d'alguns patògens respiratoris i a 2,85 ±1,5 quan hi ha presència de *Pseudomonas aeruginosa* (**Figura 2**).

Figura 2. Impacte de la microbiologia en la freqüència anual d'aguditzacions de bronquièctasis (adaptat de Chalmers JD, et al. [33])



Abreviatures. MRSA: *Staphylococcus aureus* resistent a meticil·lina

Un pacient es confirma com a colonitzat quan s'aïlla el mateix microorganisme en 2 o més mostres d'esput en el mateix any separades de 3 mesos entre elles [2]. La colonització per *Pseudomonas aeruginosa* s'associa amb un augment de la inflamació

crònica, deteriorament de la funció pulmonar, empitjorament de la qualitat de vida, i un augment significatiu de la morbiditat i mortalitat en els pacients amb bronquièctasis [34], [35]. Un meta-anàlisi publicat per Finch S, et al. al 2015 [36], on va incloure 3.683 adults amb bronquièctasis, va demostrar que els pacients colonitzats per *Pseudomonas aeruginosa* tenien aproximadament 3 vegades més risc de mortalitat, quasi 7 vegades més d'hospitalitzar i patien una agudització més per any respecte als que no presentaven colonització (**Taula 2**).

Taula 2. Resultats clínics de pacients amb bronquièctasis i colonització per *Pseudomonas aeruginosa* (adaptada de Finch S, et al. [36])

Variable	Odds ràtio	IC 95%	*p*-valor
Mortalitat	2,95	1,98-4,40	p<0,0001
Hospitalització	6,57	3,19-13,51	p<0,0001
Variable	**Diferència mitjana**	**IC 95%**	***p*-valor**
Aguditzacions	0,97/any	0,64-1,30	p<0,0001
Qualitat de vida	18,2 punts	14,7-21,8	p<0,0001
Abreviatures. IC: interval de confiança			

Una de les peculiaritats de la *Pseudomonas aeruginosa* és que té la capacitat de generar biofilms protegint-se del sistema immune i reduint la seva exposició als antibiòtics que s'administren per via sistèmica [37], [38]. D'aquesta manera té l'habilitat de colonitzar de manera més ràpida i desenvolupar resistències antimicrobianes [36].

Estudis en FQ i bronquièctasis no derivades de FQ han demostrat que la colonització per *Pseudomonas aeruginosa* comença amb un fenotip de tipus no-mucoid (PAnom), que conforme s'adapta al medi pulmonar i la malaltia progressa, muta el gen mucA adquirint un fenotip de tipus mucoid (PAm) [39-41]. Aquest fenotip mucoid té una major severitat, caracteritzat per la producció d'alginat exopolisacàrid, la resistència a la fagocitosi [42] i als antibiòtics [43], [44]. En FQ s'ha descrit que aquesta conversió és una senyal de colonització crònica [45], que no es pot erradicar amb els antibiòtics que hi ha a l'abast, provocant un pitjor pronòstic i un escurçament de la supervivència dels pacients [46], [47]. La detecció temprana de PAnom o PAm és un punt crític pel maneig i desenvolupament dels pacients amb FQ [48], hipotetitzant que també ho podria ser pels pacients amb bronquièctasis no derivades de FQ.

Gravetat i fenotips de les bronquièctasis

Les bronquièctasis es considera una malaltia multidimensional on el seu pronòstic no es pot adequar correctament tenint en compte una sola variable. A l'actualitat existeixen dues escales multidimensionals que han estat validades per classificar-ne la gravetat: el *Bronchiectasis Severity Index* (BSI) i el FACED. Ambdues escales inclouen aspectes clínics, funcionals, radiològics i microbiològics que són característics de la malaltia. El BSI [33] està format per 9 variables: edat, índex de massa corporal (IMC), percentatge del predit del volum expiratori forçat en el primer segon (VEF_1%), hospitalització prèvia, número d'aguditzacions l'any previ, percepció de dispnea mesurada amb l'escala *Medical Research Council* (MRC), colonització per *Pseudomonas aeruginosa*, colonització per altres microorganismes i severitat radiològica. La puntuació total es classifica en: lleu (0-4 punts), moderada (5-8 punts) i greu (≥9 punts); existint un risc més alt de mortalitat, hospitalització i agudització en els següents 1-4 anys com més alta sigui aquesta puntuació. Per altra banda, l'escala FACED [49] està formada per 5 ítems: edat, VEF_1% predit, colonització per *Pseudomonas aeruginosa*, severitat radiològica i percepció de dispnea relacionada amb les activitats de la vida diària mesurada amb l'escala modificada *Medical Research Council* (mMRC). La puntuació total es classifica en: lleu (0-2 punts), moderada (3-4 punts) i greu (5-7 punts); existint un risc més alt de mortalitat en els següents 5 anys com més alta és la puntuació final. Aquesta escala té una versió posterior anomenada Exa-FACED on s'inclou la variable d'aguditzacions i/o hospitalitzacions l'any previ, millorant d'aquesta manera la seva capacitat predictiva [50].

La població amb bronquièctasis és extremadament heterogènia amb una gran varietat d'etiologies, característiques clíniques, radiològiques i microbiològiques [1]. És per això, que la identificació de fenotips ajudaria a individualitzar-ne el maneig. Aliberti S, et al. al 2016 [51] van ser dels primers en categoritzar les bronquièctasis en diferents grups basant-se en el diagnòstic etiològic, l'extensió radiogràfica, la funció pulmonar i la presència o no d'infecció bronquial crònica. Els autors van agrupar les bronquièctasis en 4 grups diferents, sent el grup anomenat "*Pseudomonas*" (on tots els pacients estaven colonitzats per *Pseudomonas aeruginosa*) el que tenia la pitjor severitat,

afectació radiològica, paràmetres inflamatoris i estat funcional (**Taula 3**). Al mateix any, Martínez-García MA, et al. [52] van categoritzar les bronquièctasis en grups utilitzant variables demogràfiques, hàbit tabàquic, variables clíniques, microbiològiques, funcionals, radiològiques i etiològiques. En aquest cas també es van diferenciar 4 grups, sent l'anomenat "gran i amb aguditzacions freqüents" un grup de predomini masculí amb bronquièctasis moderades-greus, aguditzacions freqüents (≥3/any), colonització crònica i major mortalitat per causes respiratòries. Un dels missatges que emergeix quan s'examinen els fenotips identificats en ambdós estudis és que podrien no ser fenotips reals, ja que només la colonització per *Pseudomonas aeruginosa* i les aguditzacions freqüents van ser consistents en tots els anàlisis [7].

Una agudització s'estableix quan un pacient té un empitjorament d'almenys 3 dels següents signes/símptomes durant 48 hores: tos, volum de l'esput i/o consistència, purulència de l'esput, ofec i/o disminució de la tolerància a l'exercici, fatiga i/o malestar general, hemoptisi; i a més, un metge ha de determinar que es requereix un canvi en el tractament [53]. Les aguditzacions es poden dividir en lleus - moderades i greus. Les lleus - moderades són aquelles que es tracten amb antibiòtic oral i de manera ambulatòria, mentre que les greus requereixen d'hospitalització, antibiòtic per via intravenosa, admissió a unitats d'intensives i/o ventilació mecànica (invasiva o no) [54], [55].

La freqüència de les aguditzacions entre pacients és molt variable, podent ser entre 0 a 9 esdeveniments per any [56]. Un estudi europeu realitzat en una cohort de 1.310 pacients amb bronquièctasis va descriure que la freqüència anual d'aguditzacions era de 1,8-3 per pacient i per any, amb una taxa d'hospitalització del 26,6-31,4% [33].

Taula 3. Característiques dels quatre grups (adaptada de Aliberti S, et al. [51])

	Grup 1: "*Pseudomonas*" (n=179)	Grup 2: "Altre infecció crònica" (n=273)	Grup 3: "Esput diari" (n=373)	Grup 4: "Bronquièctasis seques" (n=307)	*p*-valor
Característiques demogràfiques					
Edat, anys	67 [56-75]	65 [56-73]	67 [57-74]	66 [55-74]	0,52
Homes	81 (45)	112(41)	148 (40)	109 (36)	0,19
Fumadors i ex-fumadors	56 (31)	90 (33)	165 (44)	121 (39)	0,005
Gravetat de la malaltia					
Escala BSI	14 [11-17]	7 [5-10]	6 [3-9]	5 [3-7]	0,0001
Escala FACED	4 [2-5]	2 [1-3]	2 [1-3]	1 [0-3]	<0,0001
Afectació radiològica					
Escala Reiff	6 [4-9]	4 [2-6]	3 [2-6]	3 [2-6]	0,0001
Característiques clíniques					
Tos diària	170 (95)	241 (88)	322 (86)	154 (50)	<0,0001
Esput diari	166 (93)	204 (75)	362 (97)	0 (0)	<0,0001
Escala dispnea MRC	3 [2-5]	2 [1-3]	2 [1-3]	1 [1-2]	0,0001
Aguditzacions l'any previ	3 [2-4]	2 [1-3]	2 [1-3]	2 [1-3]	0,0001
Hospitalització l'any previ	109 (61)	63 (23)	90 (24)	36 (12)	<0,0001
Funció pulmonar					
VEF_1 % predit	59 [46-78]	71 [55-93]	77 [57-95]	84 [68-101]	0,0001
Microbiologia					
Colonització *Pseudomonas aeruginosa*	179 (100)	0 (0)	0 (0)	0 (0)	<0,0001
Colonització altres patògens	0 (0)	273 (100)	0 (0)	0 (0)	<0,0001
Laboratori					
Proteïna C-Reactiva, mg/L	10,7 [4,0-36,0]	5,0 [3,7-9,0]	4,5 [2,0-7,7]	3,0 [1,2-7,2]	0,0001
Antibioteràpia a llarg termini					
Macròlids	97 (54)	103 (38)	119 (32)	37 (12)	<0,0001
Antibiòtic inhalat	64 (36)	15 (5,5)	7 (1,9)	2 (0,7)	<0,0001

Les dades es presenten com a n (%) o mediana (P_{25}-P_{75}). Abreviatures. BSI: Bronchiectasis Severity Index; MRC: Medical Research Council; VEF_1: volum expiratori forçat en el primer segon.

Un dels objectius principals en el maneig clínic de les bronquièctasis és identificar els pacients que tenen un risc a patir una agudització, per poder reajustar les teràpies preventives que siguin necessàries [7]. En aquest sentit, s'ha demostrat que el factor predictiu més important de futures agudtizacions és precisament la història prèvia d'agudtizacions, sent el risc més elevat, quan aquest número és més alt [55].

Conforme la freqüència de les agudtizacions augmenta es redueix el VEF_1, augmenta la severitat de la malaltia al TCAR i augmenta la infecció crònica per *Pseudomonas aeruginosa* i *Haemophilus influenzae* [57]. Per altra banda, quan específicament augmenta la freqüència de les agudtizacions severes, empitjora la qualitat de vida, augmenten el número d'hospitalitzacions, mortalitat i costos econòmics [33].

En el cas de les hospitalitzacions degudes a agudtizacions de les bronquièctasis la incidència anual a Espanya és de 15,5 per 100.000 habitants [58]; mentre que a altres països com Alemanya [15] o Estats Units [59] és de 9,4 i 16,5 respectivament. A Espanya, el cost d'una hospitalització per agudització de bronquièctasis és de 5.284,7€ [60].

Activitat física en bronquièctasis

Existeix una forta associació entre la percepció de dispnea relacionada amb les activitats de la vida diària [61] avaluada mitjançant l'escala MRC (o mMRC), i les futures hospitalitzacions, agudtizacions, qualitat de vida i mortalitat [33]. L'escala MRC puntua 1 quan no apareix dispnea al realitzar exercici o activitat física intensa i 5 quan la dispnea impedeix a la persona sortir de casa o apareix en activitats de baixa intensitat com vestir-se o desvestir-se. Els pacients colonitzats per *Pseudomonas aeruginosa* tenen els nivells més elevats en l'escala MRC segons Aliberti S, et al. [51] amb una mediana de 3 [2-5] (**Taula 3**)), per tant, presenten més limitacions a l'hora de realitzar activitats habituals com caminar en un terreny pla.

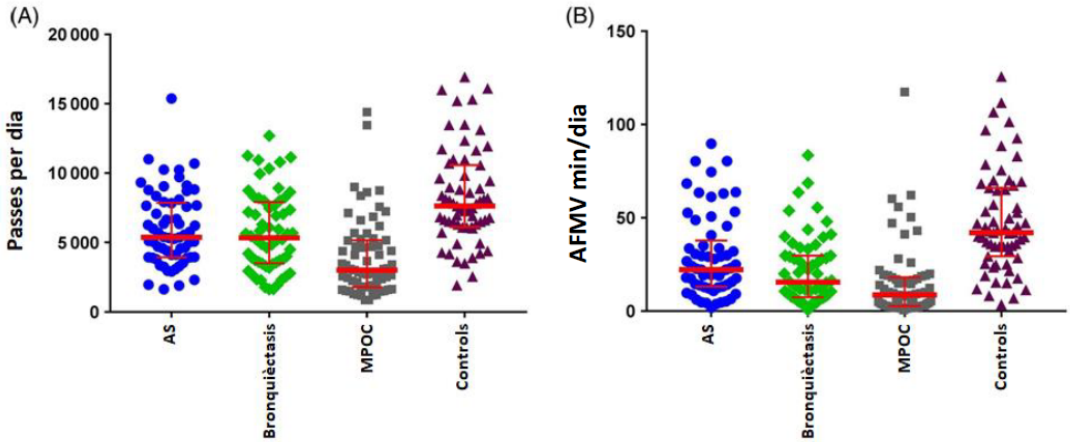
De manera general, l'activitat física es defineix com a "qualsevol moviment corporal provocat per la contracció muscular que genera un augment del cost energètic per sobre de nivells basals", que inclou exercici i activitats com a part de la feina, oci i desplaçament [62]. L'activitat física es classifica segons el nivell de cost energètic

requerit en: lleu (1.6 - <3.0 equivalents metabòlics (METs)), moderada (3.0 - <6.0 METs) i vigorosa (≥6.0 METs) [63], mentre que el comportament sedentari es defineix com a un cost energètic molt baix (<1.5 METs) que bàsicament suposa estar en sedestació o reclinat durant les hores de vigília [64], [65].

Els pacients adults amb bronquièctasis tenen nivells més baixos d'activitat física i més elevats de sedentarisme en comparació amb persones sanes de la mateixa edat, i una activitat física inferior al que recomanen les guies de pràctica clínica [66], [67]. Aquelles persones amb bronquièctasis que són més actives durant el dia, són les que tenen nivells més òptims de funció pulmonar, capacitat funcional i percepció de dispnea [68].

Quan es compara l'activitat física dels pacients amb bronquièctasis amb altres malalties pulmonars cròniques com la MPOC o l'asma severa es pot observar que la població amb asma severa i bronquièctasis tenen nivells semblants d'activitat física, que aquests són sempre inferiors si es compara amb persones sanes, però superiors si es compara amb els pacients que pateixen MPOC moderat – severa (**Figura 3**) [69].

Figura 3. Comparativa de l'AF entre pacients amb asma severa, bronquièctasis i MPOC (adaptat de Cordova-Rivera L, et al. [69])



Abreviatures. AS: asma severa; MPOC: malaltia pulmonar obstructiva crònica; AFMV: activitat física moderada a vigorosa

L'evidència científica actual en la MPOC demostra de manera consistent una associació amb l'activitat física, el sedentarisme i l'impacte de la malaltia. Els pacients amb MPOC i nivells baixos d'activitat física s'associen amb un pitjor pronòstic de la malaltia, un augment del risc de la mortalitat i hospitalitzacions degudes a aguditzacions de la malaltia [70-74].

Tot i així, la possible associació entre l'activitat física i el sedentarisme dels pacients amb bronquièctasis i altres variables d'alt impacte clínic, com poden ser les aguditzacions, és encara desconeguda.

HIPÒTESIS I OBJECTIUS

HIPÒTESIS

Hipòtesi general:

L'avaluació de l'activitat física i el sedentarisme, així com l'anàlisi de les característiques viscoelàstiques de l'esput dels pacients amb bronquièctasis, ens proporciona informació clínica rellevant pel maneig no farmacològic d'aquesta malaltia.

Hipòtesis específiques:

1. L'avaluació de les característiques viscoelàstiques de l'esput permet identificar i diferenciar aquells pacients amb bronquièctasis que tindran un pitjor aclariment mucociliar.
2. Els pacients amb bronquièctasis que se'ls hi aïlla el fenotip PAm tenen pitjors característiques viscoelàstiques de l'esput i més gravetat clínica comparat amb aquells que s'aïlla PAnom o flora mixta.
3. Existeix una associació entre colonització per *Pseudomonas aeruginosa*, característiques viscoelàstiques i variables clíniques indicadores de severitat de les bronquièctasis.
4. Presentar una baixa activitat física i un alt comportament sedentari s'associen amb les hospitalitzacions degut a una agudització de bronquièctasis.
5. Establir uns punts de tall per l'activitat física i el sedentarisme permet predir el risc d'hospitalitzacions per agudització de les bronquièctasis.
6. Algunes variables clíniques i/o sociodemogràfiques concretes poden estar relacionades amb un disminució de l'activitat física i un augment del sedentarisme en pacients amb bronquièctasis.

OBJECTIUS

Objectiu general:

Estudiar l'impacte clínic de l'avaluació de l'activitat física i el sedentarisme, així com les característiques viscoelàstiques de l'esput dels pacients amb bronquièctasis.

Objectius específics:

1. Avaluar les característiques viscoelàstiques de l'esput dels pacients amb bronquièctasis.
2. Determinar la relació entre els fenotips de la *Pseudomonas aeruginosa* (PAm i PAnom), les característiques viscoelàstiques de l'esput i variables de gravetat en pacients amb bronquièctasis.
3. Analitzar la possible associació entre colonització per *Pseudomonas aeruginosa*, les característiques viscoelàstiques i variables clíniques de severitat de les bronquièctasis.
4. Investigar l'associació entre: a) qualsevol variable d'activitat física (passes per dia, activitat física moderada i activitat física moderada a vigorosa (AFMV)), i b) temps en sedentarisme, amb les hospitalitzacions degudes a agudització en bronquièctasis.
5. Estimar punts de tall per: a) passes per dia i b) temps en sedentarisme, que puguin predir risc a hospitalitzar en pacients amb bronquièctasis.
6. Analitzar les característiques clíniques i sociodemogràfiques dels pacients amb bronquièctasis que es puguin associar a canvis en l'activitat física i el sedentarisme al cap d'un any.

ARTICLES ORIGINALS

La metodologia i els resultat dels estudis de la present Tesi Doctoral estan recollits en les següents publicacions:

1. **Alcaraz-Serrano V**, Fernández-Barat L, Scioscia G, Llorens-Llacuna J, Gimeno-Santos E, Herrero-Cortina B, Vàzquez N, Puig de la Bellacasa J, Gabarrús A, Amaro-Rodriguez R, Menéndez R, Torres A. Mucoid *Pseudomonas aeruginosa* alters sputum viscoelasticity in patients with non-cystic fibrosis bronchiectasis. **Respir Med 2019; 154:40-46**. Doi: 10.1016/j.rmed.2019.06.012.
   Factor d'impacte: 3.237. Quartil (Sistema Respiratori): 2

2. **Alcaraz-Serrano V,** Gimeno-Santos E, Scioscia G, Gabarrús A, Navarro A, Herrero-Cortina B, Amaro R, Fernández-Barat L, Torres A. Association between physical activity and risk of hospitalisation in bronchiectasis. **Eur Respir J 2020. 55(6): 1902138.** Doi: 10.1183/13993003.02138-2019.
   Factor d'impacte: 11.807. Quartil (Sistema Respiratori): 1

3. **Alcaraz-Serrano V,** Arbillaga-Etxarri A, Oscanoa P, Fernández-Barat L, Bueno L, Amaro R, Gimeno-Santos E, Torres A. Exacerbations and changes in physical activity and sedentary behavior in patients with bronchiectasis after 1 year. **J Clin Med 2021. 10(6): 1190.** Doi: 10.3390/jcm10061190.
   Factor d'impacte: 3.303. Quartil (Sistema Respiratori): 1

La doctoranda ha participat en el disseny dels estudis, reclutament dels pacients, treball de camp, anàlisi de les dades, redacció i publicació dels manuscrits originals, i difusió dels resultats en congressos nacionals i internacionals. Així queda reflectit en l'ordre i composició dels autors de cada un dels treballs.

ARTICLE 1

Mucoid *Pseudomonas aeruginosa* alters sputum viscoelasticity in patients with non-cystic fibrosis bronchiectasis.

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Mucoid *Pseudomonas aeruginosa* alters sputum viscoelasticity in patients with non-cystic fibrosis bronchiectasis

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ABSTRACT

Introduction and aim: *Pseudomonas aeruginosa* could acquire a mucoid phenotype due to mutations in mucA (mucoid *Pseudomonas aeruginosa* - mPA) that is a hallmark of poor prognosis in patients with bronchiectasis. Despite the higher prevalence of *Pseudomonas aeruginosa* in bronchiectasis, how mPA and non-mucoid *Pseudomonas aeruginosa* (non-mPA) phenotypes could affect viscoelastic properties of sputum is unknown. Our aim was to determine the relationship between *Pseudomonas aeruginosa* phenotypes isolation, the viscoelastic properties of sputum and the clinical outcomes in patients with bronchiectasis.

Methods: A cross-sectional study was conducted of sputum samples obtained by spontaneous expectoration and sent for microbiology and rheology analysis. Elasticity and viscosity were measured at two oscillatory frequencies (1 and 100 rad/s). Socio-demographic and clinical data were recorded.

Results: We analyzed 17 patients with mPA, 14 with non-mPA and 17 with no organism reported (NOR). Compared with the NOR group, the mPA group showed higher elasticity (median 10.30 vs. 5.70, p = 0.023), viscosity (2.40 vs. 1.50, p = 0.039), and stiffness (10.70 vs. 6.00, p = 0.024). Values in the mPA group tended to be higher compared with non-mPA. Clinically, the mPA group showed greater hospitalizations during the previous year and greater affected lobes than the non-mPA and NOR groups.

Conclusions: The mPA phenotype is associated with increased elasticity, viscosity and stiffness of bronchiectatic sputum. Viscoelastic properties could be used as a marker of poor mucociliary clearance in mPA, with potentially important clinical implications.

1. Introduction

Bronchiectasis is a chronic respiratory disease that can be caused by cystic fibrosis (CF) and other factors. Cases of non-CF bronchiectasis are characterized by radiological, pathological, and clinical features. Radiologically, there is irreversible destruction and dilatation of the bronchi, while pathologically, there is a cycle of chronic bronchial infection, inflammation, structural lung disease, and impaired mucociliary clearance [1–4]. Clinically, the disease is characterized by cough, sputum production, dyspnea, and chronic phlegm [5,6].

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Abbreviation list

BSI	Bronchiectasis severity index
CF	Cystic Fibrosis
δ	Phase angle
EPS	Extracellular polymeric substance
ERS	European Respiratory Society
G'	Storage modulus, elasticity
G''	Loss modulus, viscosity
|G*|	Stiffness
HRCT	High-resolution computed tomography
mPA	Mucoid *Pseudomonas aeruginosa*
MRC	Medical Research Council
non-mPA	Non mucoid *Pseudomonas aeruginosa*
NOR	No organism reported
PA	*Pseudomonas aeruginosa*

Whereas normal bronchial mucus (10–100 mL) is continuously produced and easily propelled by expiratory airflow and by the bronchial cilia, mucociliary clearance could be hindered due to excessive production and changes in the viscoelastic properties of mucus in patients with bronchiectasis [7,8].

Pseudomonas aeruginosa is among the most common bacteria detected in bronchiectasis [9]. The infection is associated with chronic inflammation, deterioration of lung function, and worsened quality of life, leading to significant increases in morbidity and mortality [10,11]. Longitudinal studies on CF have shown that initial *P. aeruginosa* colonization occurs by wild-type non-mucoid *P. aeruginosa* (non-mPA), but that as the disease progresses, there is adaptation to the lung environment. Thus, the non-mPA phenotype may acquire a mucoid *P. aeruginosa* (mPA) phenotype due to mutations in mucA, beginning to overproduce the exopolysaccharide alginate [12,13]. This conversion to the mPA phenotype is a hallmark of chronic infection and predicts a poor prognosis because of its recalcitrance to clearance by antibiotics and the immune response through the extracellular polymeric substance (EPS) of the biofilm [14].

The effect of changes to the EPS in the mPA biofilm on mucus viscoelasticity is a growth area of biofilm research. Characterization of the viscoelastic properties of mucus focuses on the elasticity (or storagemodulus, G') and viscosity (or loss modulus, G''), and together describe the rheology of complex biological fluids [15]. The elasticity measures the tendency for a material to recover its original shape following stress-induced deformation, whereas the viscosity, measures the extent to which the material resists the tendency to flow. A high viscosity allows mucus to remain intact, while low elasticity promotes airflow-mucus interactions by preventing mucus recoil during a burst of high-velocity air [16,17]. Pulmonary diseases, such as asthma, chronic obstructive pulmonary disease and CF, generally result in mucus hypersecretion and increased viscoelasticity, owing in part to reduced water content and an increased fraction of glycoproteins that impair mucociliary clearance [18]. However, how mPA and non-mPA phenotypes may affect viscoelastic properties in patients with bronchiectasis is still unknown.

The primary aim of this study was to evaluate the sputum viscolastic properties in patients with non-CF bronchiectasis. Second, we aimed to determine the relationship between different *P. aeruginosa* phenotypes (mPA or non-mPA) isolation, the viscoelastic properties of sputum, and severity outcomes. Finally, we analyzed the possible association between *P. aeruginosa* chronic colonization with viscoelastic properties and clinical outcomes.

2. Methods

2.1. Study design and patients

This cross-sectional study was conducted in the pulmonology service of a tertiary hospital. Patients were identified and enrolled consequently between October 2016 and July 2018. The inclusion criteria were as follows: (1) age ≥18 years; (2) a bronchiectasis diagnosis confirmed by high-resolution computed tomography (HRCT) and symptoms of the disease; (3) clinically stable disease (no exacerbation and no significant change in symptoms or therapy in the last four weeks); (4) good quality sputum sample provided for microbiology culture; and (5) ability to perform all clinical tests and to understand the process and purpose of the study. The following exclusion criteria were also applied: (1) positive microbiological result of any pathogenic bacteria other than *P. aeruginosa*; (2) any physical and psychological disorder that might interfere with protocol compliance; (3) diagnosis of CF, sarcoidosis, ciliary dyskinesia, pulmonary fibrosis, active tuberculosis, or non-tuberculosis mycobacterial infection; (4) exacerbation of any comorbidity; (5) participation in any clinical trial that included changes in pharmacological treatment in the preceding 6 months; and (6) respiratory insufficiency and/or oxygen therapy.

The study was approved by the Clinical Research Ethics Committee of the Hospital Clinic (Ethics Approval Reference: HCB/2016/0012). Written informed consent was obtained from all study participants.

2.2. Clinical measurements

Socio-demographic and clinical data were collected, such as the etiology of bronchiectasis, the current treatment, Comorbidity Charlson Index [19], number of exacerbations and hospitalizations due bronchiectasis in the previous year, and the lobes affected on HRCT. Exacerbation was defined as the deterioration in 3 or more of the following symptoms for at least 48 h: sputum volume and/or consistency; sputum purulence; breathlessness and/or exercise tolerance; fatigue and/or malaise; hemoptysis and a clinician determined that a change in bronchiectasis treatment was required [20]. Lung function was tested with an EaseOneTM WorldSpirometer (ndd Medical Technologies, Zurich, Switzerland) and was classified according to the guidelines of the American Thoracic Society/European Respiratory Society (ERS) [21]. Dyspnea was measured using the Medical Research Council (MRC) scale [22]. The bronchiectasis severity index (BSI) was calculated graded as mild (0–4 points), moderate (5–8 points), or severe (≥9 points) [23].

2.3. Microbiology

Sputum samples were collected from spontaneous expectorations into 50 mL sterile containers. Samples were divided, with one part used for microbiological culture and the other stored at −80 °C for rheological analysis. Microbiological cultures were analyzed at the microbiology laboratory, using only good quality sputum samples [24]. They were immersed in Sputolysin-Dithiothreitol (1:1) and sonicated in ultrasonic cleaning equipment (Branson 3510 E-MT, Bransonic, Danbury, USA) for 5 min at 40 kHz, as previously reported [25]. All samples were plated on blood, chocolate, MacConkey and Ziehl–Neelsen staining and Lowenstein and Mycobacteria Growth Indicator Tube (MGIT) liquid culture incubated in automatized BD BACTEC™ system were performed. The cultures were evaluated for growth after 48 h, and Lowenstein cultures (for *Mycobacterium* spp.) after 6 weeks. Susceptibility testing was performed using disc diffusion, E-test when needed, and samples were classified as sensitive, intermediate or resistant according to the criteria published by the EUCAST [26]. Microorganisms were identified by MALDI-TOF [27] and were classified as potential pathogenic microorganisms (PPMs), which included *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Moraxella catarrhalis*, Gram-negative bacilli,

Pseudomonas aeruginosa and *Staphylococcus aureus*, and non-potential pathogenic microorganisms (non-PPMs), which included normal flora such as: *Streptococcus viridans*, *Neisseria* spp, *Candida* spp, *Corynebacterium* spp, *Haemophilus parainfluenzae* and *Staphylococcus epidermidis*. *Pseudomonas aeruginosa* were classified primarily as mPA and non-mPA phenotypes, with "no organism reported" (NOR) used when normal saprophytic flora grew. Chronic colonization was defined according to the ERS guidelines as two or more isolates of the same organism at least 3 months apart in 1 year [2]. Sputum color was classified using the Murray scale [28] as mucoid, muco-purulent, and purulent.

2.4. Rheology

Rheological analysis was done at the Chemical Engineering department of the Barcelona University. Each sample was processed using a rheometer (HAAKE MARS III, Thermo Scientific, Germany), with a plate-plate spindle diameter of 35 mm and gap of 0.4 mm, under a temperature of 37 °C. Two oscillation frequencies were used: 1 and 100 rad/s (simulating ciliary movement and cough, respectively). At 1 rad/s 10 repetitions were measured and at 100 rad/s 40. The mean of the storage modulus (elasticity, G′) and loss modulus (viscosity, G″) were measured and the magnitude of the complex modulus (stiffness, |G*|) and phase angle (δ) were calculated. The phase angle (G″/G′) characterized mucus as $\delta = 0^{\circ}$ for a Hookean solid, $\delta = 90^{\circ}$ for a pure viscous liquid; $\delta < 45^{\circ}$ for a viscoelastic solid, and $\delta > 45^{\circ}$ for a viscoelastic liquid [15].

$$|G^*| = \sqrt{G'^2 + G''^2} \qquad \delta^{o} = \tan - 1(G''/G') \cdot 180/\pi$$

In order to reduce potential sources of bias, the rheological and microbiological analysis were done by two independent analysts.

2.5. Statistical analysis

We report the number and percentage of patients for categorical variables, the mean and standard deviation for normally distributed data, and the median with the first and third quartile for non-normally distributed data. The assumption of normality was checked by Shapiro–Wilk tests. Categorical variables were compared using chi-square or Fisher exact tests, two continuous variables were compared using the *t*-test or the non-parametric Mann–Whitney test, and more than two continuous variables were compared by analysis of variance or the Kruskal–Wallis test. If the overall analysis of variance or Kruskal–Wallis test result was significant, we could then carry out post-hoc pairwise comparisons via Bonferroni testing to control for the experiment-wise error rate. The level of significance was set at 0.05 (two-tailed). All analyses were performed using IBM SPSS Version 23.0 (Armonk, New York, USA).

3. Results

Of the 57 stable patients with bronchiectasis enrolled, 9 (16%) were not considered because these patients had sputum positive for other pathogens but *P. aeruginosa* (Fig. 1). The study population therefore comprised 48 patients, which were classified in three groups according to the sputum culture: 31 (65%) *P. aeruginosa* (17 (35%) mPA, 14 (29%) non-mPA) and 17 (35%) NOR.

No differences were found in baseline characteristics between study groups but in severity variables (Table 1). Compared with the non-mPA group, the mPA group had more hospitalizations in the previous year and more lobes affected on HRCT. Additionally, the mPA group had greater exacerbations and greater hospitalizations in the last year, more affected lobes, and more purulent sputum than the NOR group; by contrast, the non-mPA and NOR groups did not differ.

In terms of the viscoelastic properties of the sputum, at 1 rad/s, the mPA group showed higher median G′ (10.30 [8.30–17.46] vs. 5.70 [4.63–8.84]), G″ (2.40 [1.95–3.40] vs. 1.50 [1.20–2.30]), and |G*| (10.70 [8.56–17.58] vs. 6.00 [4.83–9.11]), compared with the NOR group (p values of 0.023, 0.039, and 0.024, respectively; Fig. 2A).

There were no differences in rheology between the non-mPA vs. NOR groups and mPA vs. non-mPA groups although there was a trend to higher viscosity, elasticity, and stiffness in the mPA group compared to the non-mPA group.

There were no differences between any group at 100 rad/s (Fig. 2B), and there were no differences in delta values between any group at either 1 or 100 rad/s.

Of all the patients, 36 (75%) had chronic *P. aeruginosa* colonization and 12 (25%) did not (Table 2). The chronic *P. aeruginosa* group presented poorer lung function, higher dyspnea scores, and increased BSI severity scores compared with the non-chronic *P. aeruginosa* group (81% vs. 36%, $p < 0.001$) (Fig. 3), but no differences were found in sputum viscoelasticity between these two groups.

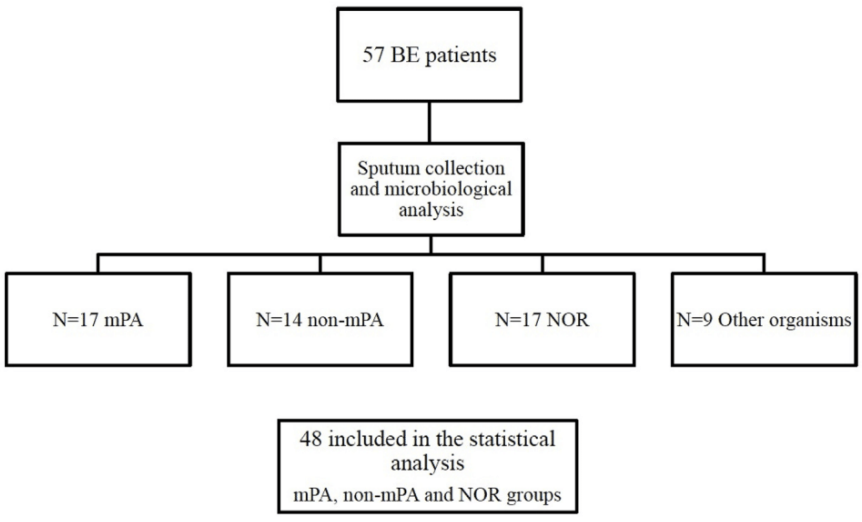

Fig. 1. Flow chart
Abbreviations: BE, bronchiectasis; mPA, mucoid *Pseudomonas aeruginosa*; non-mPA, non-mucoid *Pseudomonas aeruginosa*; NOR, no organism reported.

Table 1
Population baseline characteristics.

	All patients	PA		NOR	p value
		mPA	Non-mPA		
	N = 48	N = 17 (35%)	N = 14 (29%)	N = 17 (35%)	
Baseline characteristics					
Female sex, n (%)	31 (64)	13 (76)	7 (50)	11 (65)	0.389
Age, mean (SD), years	68.5 (16)	61.7 (18.4)	71.8 (11.4)	72.5 (15.6)	0.096
BMI, mean (SD), Kg/m^2	24 (3.29)	24 (3.8)	23.8 (3.5)	24.2 (2.7)	0.925
Former smokers, n (%)	14 (29)	2 (12)	7 (50)	5 (29)	0.067
Smoking habit, mean (SD), packs/year	39 (32)	44.5 (51.6)	47.6 (29.8)	32.8 (34)	0.880
Chronic colonization, n (%)	36 (75)	15 (88)	13 (93)	8 (47)	0.003
Pseudomonas aeruginosa	34 (95)	15 (88)	13 (93)	6 (86)	< 0.001
Haemophilus influenza	2 (5)	0 (0)	0 (0)	2 (12)	0.419
Dyspnea (MRC Scale, 1–5), median [Q1; Q3]	2 [2; 3]	2 [2; 3]	3 [2; 3]	2 [2; 2.5]	0.118
Etiology, n (%)					0.114
Post-infectious	19 (40)	6 (35)	6 (43)	7 (41)	0.905
Idiopathic	13 (27)	8 (47)	2 (14)	3 (18)	0.081
Others	16 (33)	3 (17)	6 (43)	7 (41)	0.083
CCI Index, n (%)					0.357
Low (1–2 points)	36 (75)	12 (70)	13 (93)	11 (65)	0.179
Moderate (3–4 points)	8 (16)	4 (23)	0 (0)	4 (24)	0.144
High (≥5 points)	4 (8)	1 (6)	1 (7)	2 (12)	0.814
Therapy, n (%)[a]					
Oral Antibiotic	14 (25)	4 (23)	4 (28)	6 (86)	0.426
Nebulized Antibiotic	12 (21)	5 (29)	4 (28)	3 (17)	0.426
Bronchodilators	40 (83)	15 (88)	12 (86)	13 (76)	0.642
Nebulized Saline Solutions	6 (12)	2 (12)	1 (7)	3 (17)	0.751
Variables of severity					
Exacerbations last year, median [Q1; Q3]	2 [2; 3]	2 [2; 4]	2 [1; 3]	2 [1.5; 2]	0.031[b]
Hospitalizations last year, median [Q1; Q3]	0 [0; 1]	1 [0; 1]	0 [0; 0]	0 [0; 0]	0.021[bc]
Lobes affected (HRCT), median [Q1; Q3]	3 [3; 5]	5 [3.5; 5.5]	3 [2.75; 4]	3 [2; 4]	0.015[bc]
BE severity (BSI stages), n (%)					0.527
Mild: 0–4	4 (8)	0 (0)	1 (7)	3 (17)	0.172
Moderate: 5–8	11 (23)	5 (29)	3 (21)	3 (17)	0.691
Severe: ≥9	31 (65)	11 (65)	10 (71)	10 (59)	0.867
Sputum color, n (%)					
Mucoid	1 (1)	0 (0)	0 (0)	1 (5)	0.402
Mucopurulent	19 (39)	4 (23)	5 (35)	10 (59)	0.108
Purulent	28 (58)	13 (76)	9 (64)	6 (35)	0.048[b]
Pulmonary Function, mean (SD)					
FEV_1, % predicted	66 (23)	66 (20)	58 (19)	75 (28)	0.137
FEV_1, L	1.62 (0.72)	1.63 (0.59)	1.53 (0.72)	1.83 (0.86)	0.531
FVC, % predicted	76 (17)	77 (16)	71 (16)	81 (20)	0.317
FVC, L	2.62 (0.85)	2.54 (0.75)	2.57 (0.97)	2.74 (0.89)	0.793
FEV_1/FVC, %	70 (19)	73 (18)	62 (17)	75 (20)	0.128

Abbreviations. mPA: mucoid *Pseudomonas aeruginosa*; Non-mPA: Non-mucoid *Pseudomonas aeruginosa*; NOR: no organism reported; SD: standard deviation; BMI: body mass index; MRC: medical research council; Q1: first quartile; Q3: third quartile; COPD: chronic obstructive pulmonary disease; CCI: comorbidity Charlson index; HRCT: high-resolution computed tomography; BE: bronchiectasis; BSI: bronchiectasis severity index; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; SD: standard deviation.
Percentages calculated on non-missing data.
[a] Could have more than 1 medication.
[b] $p < 0.05$ for comparison between mPA and NOR.
[c] $p < 0.05$ for comparison between mPA and Non-mPA.

4. Discussion

To the best of our knowledge, this is the first study to measure the sputum viscoelasticity in adult patients with non-CF bronchiectasis and to associated them among *P. aeruginosa* phenotypes (mucoid and non-mucoid), and the clinical and severity outcomes in these patients. As previous results in CF population, in our study we confirmed that non-CF bronchiectasis patients with mPA phenotype infection had worse severity outcomes compared with the non-mPA and NOR ones (e.g., increased number of hospitalizations in the previous year and a greater number of affected lobes). For the first time, we demonstrated that mPA caused poor viscoelastic properties of sputum (e.g. elasticity, viscosity and stiffness) implying a reduced mucociliary clearance. Finally, we analyzed the possible associations among the sputum viscoelasticity, clinical outcomes, and chronic *P. aeruginosa* colonization and we showed that chronic colonized patients had poorer lung function, greater dyspnea, and an increased disease severity (BSI) compared with non-chronic ones, but there were no differences in terms of viscoelastic properties.

In healthy subjects, the viscoelasticity of mucus maintains a balance that promotes clearance by cough and mucociliary mechanisms [29]. In lung disease such as CF, hypersecretion and a change in the viscoelastic properties of mucus alter this balance. Our findings provide evidence that the mPA phenotype is not only a marker of disease severity, determined by more advanced disease on HRCT and higher number of hospitalizations, but it is also associated with a trend of poorer viscoelastic properties than non-mPA phenotype. We assume that the lack of significance in rheology measures between mPA and non-mPA phenotypes is due to the lower number of samples. Further larger investigation is needed to confirm this result. Moreover, compared to NOR group, mPA had poor elasticity, viscosity and stiffness at ciliary velocity (1 rad/s) but not at cough velocity (100 rad/s). We could relate

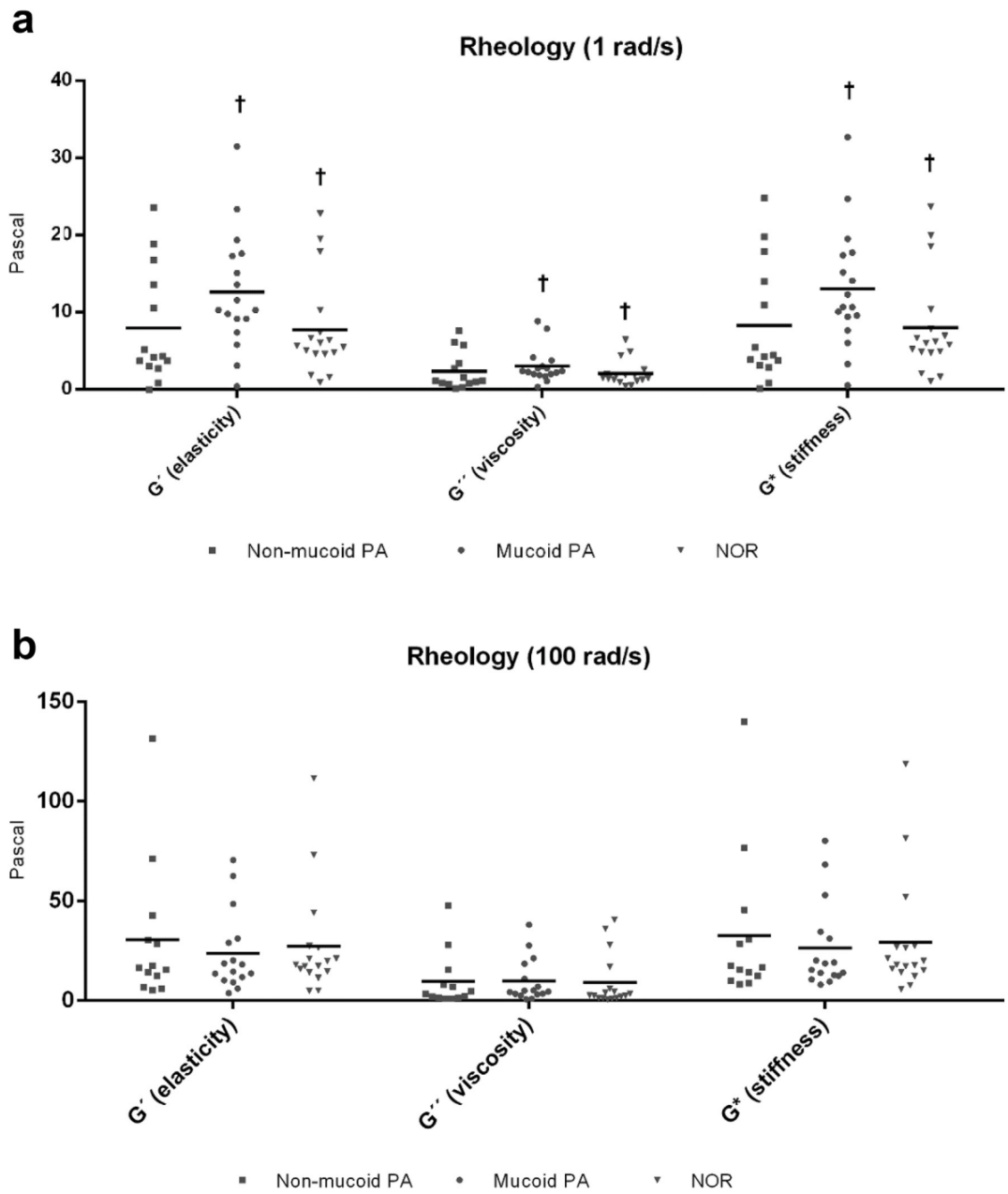

Fig. 2. (A) Viscoelastic results at 1 rad/s. (B) Viscoelastic results at 100 rad/s.
Abbreviations: non-mPA, non-mucoid *Pseudomonas aeruginosa*; mPA, mucoid *Pseudomonas aeruginosa*; NOR, no organism reported. (A): the mPA storage modulus (elasticity; G′), loss modulus (viscosity; G″), and magnitude of the complex modulus (stiffness; |G*|) were 10.30 (8.30–17.46), 2.40 (1.95–3.40), and 10.70 (8.56–17.58), respectively. The NOR G′, G″, and |G*| were 5.70 (4.63–8.84), 1.50 (1.20–2.30), and 6.00 (4.83–9.11).

this last finding to the mutation of the mPA phenotype that causes the overproduction of exopolysaccharide alginate that is probably responsible for the poor mucociliary clearance but it not affect the cough mechanisms. Finally, the non-mPA phenotype did not differ by the NOR patients in terms of viscoelastic properties and severity outcomes.

Our results are consistent with those of previous studies in patients with CF [30]. One study in a pediatric population indicated that the presence of mPA was associated with a decline in lung function, and that it was a marker of progressive transition to more severe disease stages [31]. In a dynamic assessment, Gloag et al. [17] demonstrated how the viscoelastic properties of the exopolysaccharide *P. aeruginosa* matrix change from early to mature mucoid biofilms, suggesting that this contributes to decreases in mucociliary and cough clearance as CF progresses [32,33].

Previous studies have shown that patients colonized by *P. aeruginosa* had poor quality of life [34], worse lung function [11], higher inflammatory responses [35], more exacerbations [36] and increased mortality [37]. In our study, chronic colonization with mPA or non-mPA was associated with poor lung function, greater dyspnea, and more severe BSI score, despite a similar number of exacerbations between the groups. Similarly, Lee et al. [38] correlated the colonization status of *P. aeruginosa* to disease severity using the FACED scoring system [39]. They found that, despite *Haemophilus influenzae* being the most commonly isolated genus, it was significantly more abundant in

Table 2
Clinical characteristics of chronic PA vs non-chronic colonization subjects.

	CHRONIC PA	NON-CHRONIC	p value
	N = 36 (75%)	N = 12 (25%)	
Microbiologic result, n (%)			0.004
Mucoid PA	15 (41.6)	2 (16.7)	
Non-mucoid PA	13 (36.1)	1 (8.3)	
No organism reported	8 (22.2)	9 (75)	
Clinical Characteristics, median [Q1; Q3]			
Exacerbations last year	2 [2; 3]	2 [2; 2]	0.462
Hospitalizations last year	0 [0; 1]	0 [0; 0]	0.254
Lobes affected (HRCT)	4 [3; 5]	3 [2.25; 3.75]	0.227
Dyspnea (MRC Scale, 1–5)	2 [2; 3]	2 [1.25; 2]	0.006
Pulmonary Function, mean (SD)			
FEV_1, % predicted	59.09 (18.6)	85.29 (23.55)	< 0.001
FEV_1, L	1.52 (0.6)	2.02 (0.9)	0.029
FVC, % predicted	73.06 (16.5)	84.79 (17.24)	0.033
FVC, L	2.59 (0.83)	2.69 (0.92)	0.704
FEV_1/FVC, %	66.45 (19)	80.57 (15)	0.017

Abbreviations. PA: *Pseudomonas aeruginosa*: Q1: first quartile; Q3: third quartile; HRCT: high-resolution computed tomography; MRC: medical research council; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; SD: standard deviation.
Percentages calculated on non-missing data.

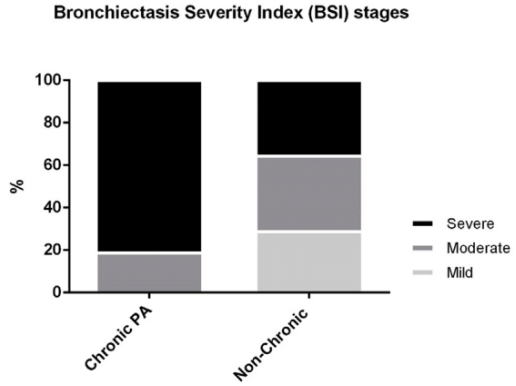

Fig. 3. Chronic colonization and severity.
Abbreviations: PA, *Pseudomonas aeruginosa*.
N (%) are represented.

patients with mild bronchiectasis, whereas *Pseudomonas* was more prevalent in the moderate/severe group.

In patients with CF, Locke et al. reported that those with chronic *P. aeruginosa* colonization had a reduced mucociliary clearance (MCC) compared with those who had non-chronic colonization [40]. In contrast to this finding, we identified no correlations between chronic *P. aeruginosa* colonization and the viscoelastic parameters. However, our data did strongly indicate that viscoelasticity was increased in the presence of the mPA phenotype. The fact that we found similar frequencies of colonization by mPA (41.6%) and non-mPA (36.1%) phenotypes might have been responsible for this lack of correlation between viscoelasticity and *P. aeruginosa* colonization. We suggest that it is recommendable to identify the *P. aeruginosa* phenotype responsible for the colonization because it represents significant information about the severity of the disease. In the colonized group, we also found patients with sputum cultures labelled as NOR (22.2%). Therefore, although sputum should provide a representative sample of the content of the lower respiratory tract [41], it is possible that these samples were obtained from the upper airways.

The results of this study may justify the application of rheological analysis in clinical practice to analyze sputum viscoelasticity of bronchiectasis patients. However, rheological analysis needs specific equipment and technical formation, which may difficult its implementation. We believe that the evaluation of the sputum viscoelasticity as an outcome could be useful in clinical practice to personalize the therapeutic approach to the patient with bronchiectasis. Our findings could suggest that patients infected by mPA phenotype may benefit from physiotherapy strategies and/or use of hyperosmolar nebulized agents in order to fluidize sputum but, further longitudinal investigations and randomized clinical trials are needed to confirm this suggestion.

The main limitation of this research was the low number of samples included in the study. Secondly, the samples were stored at −80 °C before performing the rheological analyses. Previous research has shown that different storage durations (2, 10, 30, and 90 days) and two temperatures (−20 °C and −80 °C) did not affect the viscoelastic properties [42]. Finally, further investigation is needed so as to compare viscoelastic properties between mPA vs. other pathogens in order to confirm if mPA phenotype is the only organism causing poor viscoelastic properties of sputum.

5. Conclusions

In conclusion, the mPA phenotype is associated with worse severity outcomes and increased sputum purulence, elasticity, viscosity, and stiffness in patients with bronchiectasis. Our preliminary results suggest that viscoelasticity assessment with rheology could be a new clinical tool in order to optimize and personalize bronchiectasis management, but further investigation is needed to confirm our hypothesis.

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Contributions

VAS had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. VAS designed and developed the study protocol. VAS and JLL analyzed the viscoelasticity of the sputum samples. LFB, NV, and JPB participated in the microbiological analysis. VAS, LFB, AG, and GS participated in the statistical analysis and data interpretation. VAS, LFB, and GS participated in the writing of the manuscript. All authors read the final version of the manuscript, fully approve it, and qualify for authorship.

Declarations of interest

None.

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ARTICLE 2

Association between physical activity and risk of hospitalisation in bronchiectasis.

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Association between physical activity and risk of hospitalisation in bronchiectasis

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Adult patients with bronchiectasis and reduced physical activity (<6290 steps·day^{-1}) or high sedentary behaviour (≥7.8 h·day^{-1}) have a higher than average risk of hospital admission due to exacerbation after 1-year follow-up http://bit.ly/2wX2Y2D

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ABSTRACT

Background: Patients with bronchiectasis have a less active lifestyle than healthy peers, but the association with hospital admission has not been explored. The aim of this study was to investigate the association between 1) any physical activity variable; and 2) sedentary time, with hospitalisation due to exacerbation in adults with bronchiectasis.

Methods: In this prospective observational study, baseline lung function, quality of life, exercise tolerance, severity of bronchiectasis and physical activity were recorded. Physical activity was objectively assessed over a week using a SenseWear armband and the results were expressed in steps·day^{-1} and sedentary time. Number of hospitalisations due to a bronchiectasis exacerbation and time to first event were recorded after 1-year follow-up.

Results: Sixty-four patients with bronchiectasis were analysed, of whom 15 (23%) were hospitalised during the follow-up. Hospitalised patients showed poor baseline clinical and severity outcomes, fewer steps walked per day and more sedentary behaviour than the non-hospitalised group. Patients who walked ≤6290 steps·day^{-1} or spent ≥7.8 h·day^{-1} in sedentary behaviour had an increased risk of hospital admission due to bronchiectasis exacerbation at 1-year follow-up. Specifically, ≥7.8 h·day^{-1} of sedentary behaviour was associated with a 5.9-fold higher risk of hospital admission in the following year.

Conclusions: Low levels of physical activity and high sedentary time at baseline were associated with a higher risk of hospitalisation due to bronchiectasis exacerbation. If these findings are validated in future studies, it might be appropriate to include physical activity and sedentary behaviour as an item in severity scores.

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Introduction

In adults with non-cystic fibrosis bronchiectasis, the pathogenic vicious circle of persistent infection, neutrophilic inflammation and impaired mucociliary clearance leads to an increase in bacterial load and recurrent exacerbations, which in turn raises healthcare costs [1, 2]. Moreover, the presence of comorbidities and a history of hospitalisations increase the risk of further hospital admission due to bronchiectasis exacerbation [3, 4]. In Spain [5], the annual incidence of hospitalisations due to bronchiectasis exacerbations is reported to be around 15.5 per 100 000 population, while in Germany [4] and the United States [6] it is 9.4 and 16.5, respectively. These hospitalisations are associated with higher mortality, as well as a decline in respiratory function and poor quality of life (QoL) [7, 8]. The current disease burden and hospitalisation trends due to bronchiectasis exacerbation are steadily increasing and appear to be related to age and disease severity [3].

Longitudinal studies in patients with chronic obstructive pulmonary disease (COPD) have consistently demonstrated the association between low levels of physical activity and a higher risk of both mortality and hospitalisation due to exacerbation [9–12]. Similarly, patients with cystic fibrosis (CF) who regularly participate in physical activity programmes have shown better prognostic outcomes, increased respiratory function, elevated QoL and enhanced clearance of sputum [13, 14].

Physical activity can be defined as "any bodily movement produced by the contraction of a skeletal muscle that increases energy expenditure above a basal level", which includes exercise and activity as part of work, leisure or movement [15]. Physical activity is often classified as being of light, moderate or vigorous, according to the level of energy expenditure required [16]. For its part, sedentary behaviour is defined by low energy expenditure (less than 1.5 metabolic equivalent tasks (METs)) in a sitting or reclining posture during waking hours [17].

Although it has been demonstrated that only 11% of the bronchiectasis population met the recommended physical activity guidelines of ⩾150 min of at least moderate activity per week [18], the current evidence on physical activity and sedentary behaviour, and their association with bronchiectasis hospitalisations, is scarce. We hypothesised that steps·day^{-1} and sedentary time would be strongly associated with the presence of hospital admission due to a bronchiectasis exacerbation at 1-year follow-up.

Therefore, the principal aim of this longitudinal study was to investigate the association between 1) any physical activity variable (steps·day^{-1}, moderate physical activity and moderate-to-vigorous physical activity (MVPA)); and 2) sedentary time, with hospital admission due to exacerbation in adults with bronchiectasis. The secondary aim was to estimate cut-off points for steps·day^{-1} and sedentary time that might indicate the risk of hospital admission.

Methods

Study design and subjects

This was a prospective observational study conducted at the pulmonology service of a tertiary care hospital in Barcelona, Spain. Subjects who met the selection criteria were included in the study consecutively between March 2016 and August 2017. Inclusion criteria were as follows: 1) adults (⩾18 years of age) diagnosed with bronchiectasis, as confirmed by computed tomography (CT) and with symptoms of the disease; 2) clinical stability (no exacerbations and no significant change in symptoms and/or medication in the last 4 weeks); 3) the ability to perform all the clinical tests and understand the process and the purposes of the study; 4) willing to give informed consent. Exclusion criteria were: 1) any physical or psychological disorder that might interfere with protocol compliance; 2) diagnosis of CF, sarcoidosis, pulmonary fibrosis, active tuberculosis (TB) or non-TB mycobacterial infection in treatment; 3) participation in a pulmonary rehabilitation (PR) programme in the last year; 4) respiratory insufficiency and/or oxygen therapy.

The study was approved by the Clinical Research Ethics Committee of the Hospital Clínic de Barcelona (Ethics Approval Reference: HCB/2016/0012).

Measurements

Baseline clinical and physical activity measurements

Socio-demographic and clinical data were collected at baseline, including the aetiologic diagnosis of bronchiectasis, current treatment, comorbidities (using the Charlson Comorbidity Index (CCI) [19]), the presence and number of exacerbations that did not require hospitalisation and hospitalisations due to bronchiectasis in the 12 months prior to the study. Exacerbations were defined according to the international consensus statement [7]. Disease severity was calculated using the Bronchiectasis Severity Index (BSI) [20] score. Dyspnoea was measured using the Medical Research Council (MRC) scale [21]. Lung function was assessed with an EasyOne™ World Spirometer (ndd Medical Technologies, Zurich, Switzerland) and was classified according to the European Respiratory Society (ERS)/American Thoracic

Society (ATS) guidelines [22]. Exercise capacity was measured using the 6-min walk test (6MWT) [23]. QoL was assessed using the Quality of Life Bronchiectasis Questionnaire (QoL-B) [24] and the impact of coughing on QoL by the Leicester Cough Questionnaire (LCQ) [25].

Physical activity was the independent variable and was measured using the tri-axial accelerometer SenseWear Armband (BodyMedia Inc., Pittsburgh, PA, USA). Participants were asked to wear the armband for the maximum period of time over 7 days, except during water-based activities. It was worn in the triceps area, at the back of the dominant arm.

Intensity of physical activity was reported in relation to METs and classified as sedentary (⩽1.5 METs), light (1.6 to <3.0 METs), moderate (3.0 to <6.0 METs) and vigorous (⩾6.0 METs) [26]. The mean time (in min) spent at each level of intensity was recorded. MVPA was calculated with the mean of minutes spent in moderate and vigorous physical activity on the valid days. Sedentary time was analysed considering the number of minutes that the patient spent at an intensity of ⩽1.5 METs.

Follow-up data collection

The follow-up period lasted 12 months. The number of patients hospitalised at least once during the follow-up period due to a bronchiectasis exacerbation and the time to first hospitalisation were recorded prospectively through the revision of the medical dataset. The dependent variable was the presence of hospitalisation due to an exacerbation of bronchiectasis during the 12 months of follow-up.

The need for hospitalisation and discharge were defined by an independent medical doctor who was not involved in the study. The authors checked that all exacerbations met the consensus definition [7]. Patients were classified into hospitalised *versus* non-hospitalised groups depending on the presence or absence of hospitalisation due to a bronchiectasis exacerbation during the follow-up period.

Patients who participated in a PR and/or physical activity programme during the follow-up period were excluded from the final analysis.

Statistical analysis

Prior to any analysis we calculated whether the number of patients included would allow the identification of significant differences in physical activity and sedentary time between hospitalised *versus* non-hospitalised groups. Calculations were performed using GRANMO 7.10 [27], with an accepted alpha risk of 0.05, in a two-sided test with 15 subjects in the hospitalised group and 49 in the non-hospitalised group. The statistical power needed to recognise a statistically significant difference was 94% in physical activity and 96% in sedentary time.

Data are presented as n (%) for categorical variables, as mean±SD for normally distributed data and as median (P_{25}–P_{75}) (1st and 3rd percentiles) for non-normally distributed data. The assumption of normality was checked by means of Shapiro–Wilk tests.

In accordance with previous research for reducing the noise in physical activity analyses [28], the data were considered valid if patients presented ⩾8 h of waking hours (08:00 to 22:00) per day for ⩾4 weekdays during the assessment period. A sensitivity analysis was performed including weekend data.

A receiver operating characteristic (ROC) curve was constructed to determine the best cut-off point in steps·day^{-1} for the presence of bronchiectasis hospitalisation (hospitalisation "yes" or "no") and also for sedentary time, moderate physical activity and MVPA. Youden's index [29] was defined for all points along these ROC curves and the maximum values of these indices were used as criteria in selecting the optimum cut-off points. Kaplan–Meier analysis was used to compare the association of steps·day^{-1} and sedentary time with time to first hospitalisation due to an exacerbation of bronchiectasis. The probabilities of hospitalisation in the two groups were analysed using the log-rank test. Univariate and multivariable logistic regression analyses were performed to identify variables associated with bronchiectasis hospitalisation. Due to the limited number of patients in the hospitalised and non-hospitalised groups, and in order to exclude bias related to overestimation or underestimation of regression coefficient variance, the only variables analysed in the univariate analysis were age, gender, chronic colonisation by *Pseudomonas aeruginosa*, hospitalisations 12 months prior to the study, MRC dyspnoea scale, % predicted forced expiratory volume in 1 s (FEV_1), BSI stage and 6-min walk distance. Factors showing an association in the univariate analyses ($p<0.10$) were entered into two multivariable regression models, the first adjusted for steps·day^{-1} and the second for sedentary time. The final variable selection was performed using the backward stepwise selection method (likelihood ratio; $p_{in}<0.05$, $p_{out}>0.10$), except for age and gender which had to appear in both models. Odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated. The Hosmer–Lemeshow goodness-of-fit test was performed to assess the overall fit of the final model. The areas under the curve (AUCs) for the ROC curves of the multivariable models for hospitalisation due to bronchiectasis were then calculated.

The internal validity of the final models was assessed using ordinary non-parametric bootstrapping with 1000 bootstrap samples and bias-corrected, accelerated 95% CIs.

We used the multiple imputation method [30] for missing data in the multivariable analyses. The level of significance was set at 0.05 (two-tailed). All analyses were performed using IBM SPSS Statistics version 25.0 (Armonk, NY, USA).

Results

Baseline clinical and physical activity data

Of the 72 patients with bronchiectasis recruited at baseline, 64 were included in the follow-up analysis (figure 1). The study population was classified into two groups according to the presence of hospitalisation due to an exacerbation during the 1-year follow-up: 1) hospitalised patients (n=15, 23%); and 2) non-hospitalised patients (n=49, 77%). Baseline clinical and physical activity characteristics are shown in table 1. Hospitalised patients were more likely to have chronic colonisation by *Pseudomonas aeruginosa*, more hospitalisations in the 12 months prior to the study, poor dyspnoea, worse lung function, worse QoL, a higher CCI score and a more severe BSI score.

The number of patients with COPD and bronchiectasis overlap was low. Of all patients, four (6%) had a smoking history of >10 packs·year^{-1} and a FEV_1/forced vital capacity (FVC) ratio of <70%. Distribution did not differ significantly between hospitalised (n=2, 13%) and non-hospitalised groups (n=2, 4%) (p=0.455).

In terms of physical activity, hospitalised patients took fewer of steps·day^{-1}, spent more time sedentary and had lower levels of MVPA than non-hospitalised patients. Light physical activity and exercise capacity did not differ between groups.

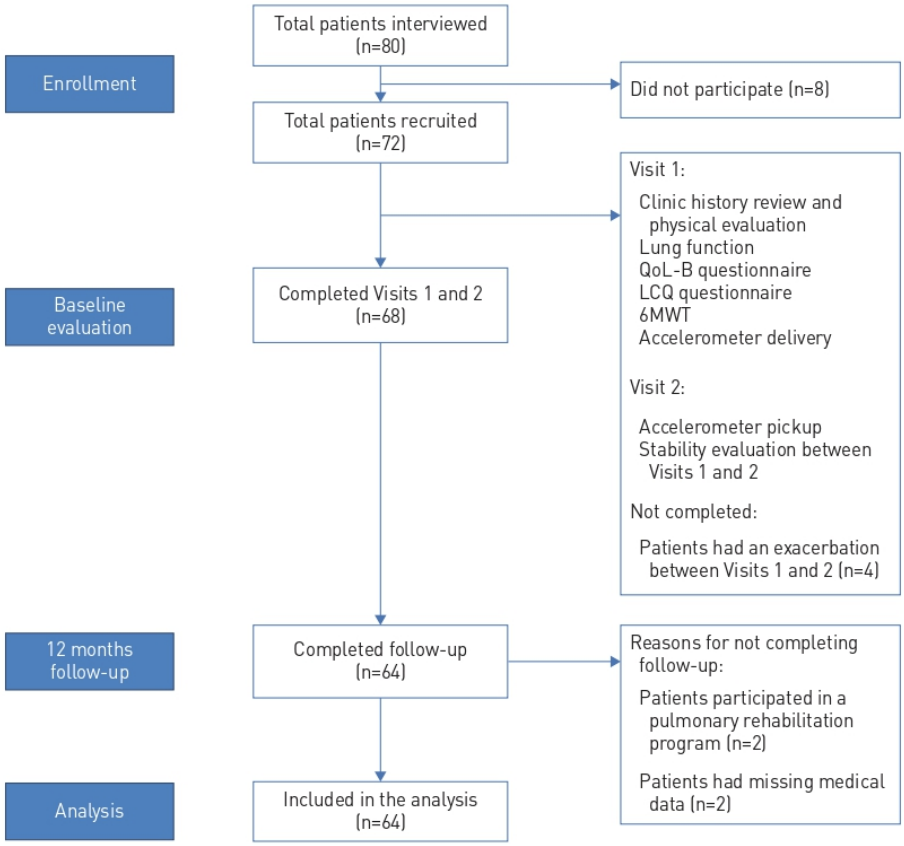

FIGURE 1 Enrolment flow chart. QoL-B: Quality of Life Bronchiectasis Questionnaire; LCQ: Leicester Cough Questionnaire; 6MWT: 6-min walk test.

TABLE 1 Baseline characteristics of hospitalised *versus* non-hospitalised bronchiectasis patients

Characteristics	All patients (n=64)	Hospitalised (n=15)	Non-hospitalised (n=49)	p-value
Demographics				
Male	21 (33)	6 (40)	15 (31)	0.501
Age years	62.9±14.9	64.3±17.4	62.2±14.5	0.510
BMI kg·m^{-2}	24.6±4.3	24.3±4.1	24.6±4.5	0.924
Retired	41 (64)	11 (73)	30 (61)	0.550
Former smoker	20 (31)	5 (33)	15 (31)	0.923
Smoking habit packs·year^{-1}	30 (8.5–60)	40 (25.5–86.5)	19.2 (7–60)	0.119
Chronic colonisation	23 (36)	11 (73)	12 (24)	**0.001**
Pseudomonas aeruginosa	19 (29)	10 (66)	9 (18)	**0.000**
Haemophilus influenza	2 (3)	0 (0)	2 (4)	0.430
Staphylococcus aureus	2 (3)	1 (6)	1 (2)	0.371
Dyspnoea (MRC scale 1–5)	2 (2–2)	2 (2–3)	2 (2–2)	**0.004**
Exacerbations and hospitalisations[#]				
Exacerbated patients	45 (70)	11 (73)	34 (70)	0.772
Number of exacerbations	1 (0–2)	2 (0–4)	1 (0–2)	0.171
Hospitalised patients	13 (20)	7 (47)	6 (12)	**0.004**
Number of hospitalisations	0 (0–0)	0 (0–1)	0 (0–0)	**0.004**
Aetiology				
Post-infectious	29 (45)	6 (40)	23 (47)	0.639
Idiopathic	14 (22)	5 (33)	9 (18)	0.224
Associated with COPD	4 (6)	2 (13)	2 (4)	0.455
Other	17 (26)	2 (13)	15 (30)	–
Severity				
CCI stage				**0.031**
Mild	51 (79)	9 (60)	42 (86)	
Moderate	9 (14)	4 (26)	5 (10)	
High	4 (6)	2 (13)	2 (4)	
BSI stage				**0.001**
Mild	23 (36)	2 (13)	21 (43)	
Moderate	22 (34)	3 (20)	19 (39)	
Severe	19 (29)	10 (66)	9 (18)	
Pulmonary function and exercise capacity				
FEV_1 % predicted	72±19.8	62.1±18.7	75.2±19.9	**0.020**
FEV_1 L	1.94±0.81	1.82±0.94	1.99±0.78	0.366
FVC % predicted	80.6±17.1	72.7±15.3	83.1±17.7	**0.026**
FVC L	2.82±0.83	2.6±0.75	2.89±0.86	0.342
FEV_1/FVC %	86±18.6	82±22.1	86.92±17.7	0.495
6MWT m	512.7±93.5	467.7±116	522.7±83	0.063
Respiratory medication[¶]				
Inhaled steroids	45 (70)	11 (73)	34 (69)	0.772
LABA	48 (75)	12 (80)	36 (73)	0.612
LAMA	28 (44)	12 (80)	16 (32)	**0.001**
Antibiotics	11 (17)	3 (20)	8 (16)	0.743
QoL				
QoL-B				
Physical function	57.3±33.8 (0–100)	53.3±35.2 (0–100)	58.5±33.7 (0–100)	0.588
Role function	75.5±28 (0–100)	53.3±32.9 (0–100)	82.3±22.7 (33.3–100)	**0.001**
Vitality	58.6±25.5 (0–100)	45.6±33.6 (0–100)	62.6±21.4 (16.7–100)	**0.033**
Emotional function	73.7±28.6 (0–100)	64.4±30.1 (0–100)	76.5±27.8 (0–100)	0.140
Social function	68.2±31.7 (0–100)	54.4±35.9 (0–100)	72.4±29.4 (0–100)	0.072
Treatment burden	69.8±40.6 (0–100)	75.5±36.6 (0–100)	68.0±41.9 (0–100)	0.670
Health perceptions	52.9±26.5 (0–100)	35.5±30.8 (0–100)	58.2±22.8 (0–100)	**0.007**
Respiratory symptoms	76.3±22.6 (33.3–100)	67.8±22.4 (33.3–100)	78.9±22.5 (33.3–100)	0.052
LCQ	15.8 (11.8–19.4)	15 (10.4–18.7)	16.6 (12.4–19.5)	0.292
Physical	15.3 (12–18.4)	14.2 (11.2–16.9)	15.7 (12–18.4)	0.115
Psychological	15.6 (11.1–19.3)	14.6 (9.4–18.4)	16.7 (12–19.9)	0.243
Social	18 (13–21)	18 (11.2–19.5)	18.7 (13.1–21)	0.582
Physical activity				
Light (1.6 to <3.0 METs) min·day^{-1}	211.4±79	186±42.5	222.3±87.5	0.178
Moderate (3.0 to <6.0 METs) min·day^{-1}	117±82	81.9±63	127.3±83.4	**0.015**
Vigorous (6.0 to <8.7 METs) min·day^{-1}	0.78±1.86	0.55±1.6	0.9±2	0.546

Continued

TABLE 1 Continued

Characteristics	All patients (n=64)	Hospitalised (n=15)	Non-hospitalised (n=49)	p-value
MVPA min·day^{-1}	115.5±78.5	82.4±64.2	125.3±78.6	**0.015**
Number of steps steps·day^{-1}	6880±3447	4740±3196	7563±3382	**0.003**
Sedentary time h·day^{-1}	7.17±1.8	8.22±1.48	6.83±1.74	**0.005**

Data are presented as n (%), mean±SD, median (interquartile range), or mean±SD (range). p-values in bold are statistically significant. BMI: body mass index; MRC: medical research council; COPD: chronic obstructive pulmonary disease; CCI: Charlson Comorbidity Index; BSI: Bronchiectasis Severity Index; PFT: pulmonary function test; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; 6MWT: 6-min walk test; LABA: long-acting β-agonist; LAMA: long-acting muscarinic antagonist; QoL: quality of life; QoL-B: Quality of Life Bronchiectasis Questionnaire; LCQ: Leicester Cough Questionnaire; MET: metabolic equivalent task; MVPA: moderate-to-vigorous physical activity. #: exacerbations and hospitalisations in the 12 months prior to the study; ¶: patients may have had more than one medication.

Cut-off points (steps·day^{-1} and sedentary time) and hospitalisation risk

Table 2 presents the best cut-off points for steps·day^{-1}, sedentary time, moderate physical activity and MVPA for predicting hospital admission during follow-up. Light and vigorous physical activity had very low sensitivity and specificity, without presenting statistically significant differences. Kaplan–Meier curves evaluating the time to first hospitalisation due to bronchiectasis exacerbation (according to steps·day^{-1} and sedentary time) are represented in figure 2. Patients with ⩽6290 steps·day^{-1} or ⩾7.8 h·day^{-1} of sedentary behaviour had a higher risk of hospital admission due to bronchiectasis exacerbation at 1-year follow-up than patients with more steps·day^{-1} or less sedentary time ($p<0.001$).

Association between physical activity outcomes and hospitalisation due to an exacerbation of bronchiectasis

In accordance with the proposed cut-off values, the logistic regression model showed a higher risk of hospitalisation for bronchiectasis patients with low levels of physical activity (⩽6290 steps·day^{-1}) and high sedentary behaviour (⩾7.8 h·day^{-1}). After adjusting for all relevant confounders (age, gender, chronic colonisation by *Pseudomonas aeruginosa* and hospitalisations during the 12 months prior to the study), sedentary behaviour raised the risk of hospitalisation by 5.91 times (table 3 and supplementary table S1). When the final model was adjusted for gender and BSI, sedentary behaviour also raised the risk of hospitalisation by 5.34 times (supplementary table S1). After excluding patients with a smoking history of ⩾10 packs·year^{-1} and after adjusting for all relevant confounders, low physical activity (⩽6290 steps·day^{-1}) raised the risk of hospitalisation by 8.7 times (supplementary table S2).

The sensitivity analyses including weekend data showed reductions in the cut-off points and the size of the associations, although the significance of the effect remained unchanged with regard to the analyses including only weekdays (supplementary tables S3–S5 and supplementary figures S1a and S1b). Internal validation of the final models was conducted using bootstrapping with 1000 samples. All variables remained significant after a bootstrapping procedure, with small 95% CIs around the original coefficients.

Discussion

To our knowledge, this is the first study to investigate the association between physical activity, sedentary time and risk of hospitalisation in patients with bronchiectasis. We confirmed that patients hospitalised for an exacerbation of bronchiectasis during the 1-year follow-up period presented poor clinical characteristics, higher severity and lower levels of physical activity at baseline compared than those not hospitalised. This study is the first to propose cut-off points for number of steps (⩽6290 steps·day^{-1}) and time spent in sedentary behaviour (⩾7.8 h·day^{-1}) in order to objectively identify patients with bronchiectasis who are at a higher risk for hospital admission in the next year. Finally, the risk for

TABLE 2 Cut-off points for hospitalisation variables (number of steps, sedentary time and physical activity)

Variable	AUC (95% CI)	Sensitivity %	Specificity %	Best cut-off value	p-value
Number of steps steps·day^{-1}	0.75 (0.60–0.89)	61	73	6290	0.003
Sedentary time h·day^{-1}	0.74 (0.59–0.88)	73	74	7.8	0.005
Moderate physical activity min·day^{-1}	0.71 (0.55–0.87)	67	73	84.4	0.015
MVPA min·day^{-1}	0.71 (0.55–0.87)	85	53	66.3	0.015

AUC: area under the curve; CI: confidence interval; MVPA: moderate-to-vigorous physical activity.

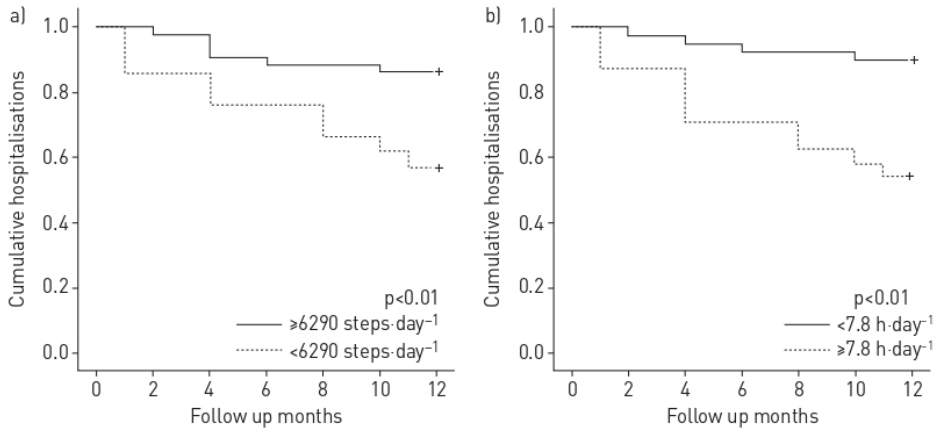

FIGURE 2 Kaplan–Meier graphics according to receiver operating characteristic (ROC) curve cut-off points: a) 6290 steps·day^{-1}; b) 7.8 h·day^{-1} of sedentary behaviour.

hospitalisation in patients with bronchiectasis due to exacerbation was significantly higher (5.91 times) in those who spent ⩾7.8 h·day^{-1} in sedentary behaviour.

Little is known about physical activity behaviour in bronchiectasis populations. In a recent study, José *et al.* [31] measured physical activity with a pedometer and demonstrated that patients with bronchiectasis showed lower physical activity levels than healthy controls. They also concluded that patients affected by bronchiectasis who appeared to be more active in daily life were the ones with better pulmonary function, functional capacity and lower dyspnoea. In fact, this Brazilian bronchiectasis population was surprisingly active (with a mean 8007 steps·day^{-1} *versus* 10 994 steps·day^{-1} in healthy peers).

In 2015, Bradley *et al.* [18] analysed physical activity in 63 patients with bronchiectasis using an ActiGraph GT3X+ accelerometer (ActiGraph, Pensacola, FL, USA). The mean was 6001 steps·day^{-1} *versus* 6880 steps·day^{-1} in our population and the mean time spent in sedentary behaviour in those subjects was 10.5 h·day^{-1} compared to 7.2 h·day^{-1} in our study. We stress that this finding is unlikely to be related to disease severity, as the population analysed by Bradley *et al.* presented lower severity levels (BSI score: 49% mild, 33% moderate and 18% severe) than ours (BSI score: 36% mild, 35% moderate and 29% severe). A point to be considered is that the patients with lower physical activity levels were the ones with greater severity. Consequently, lower physical activity may have been due to physical impairment in the more severe patients, who in turn had more exacerbations.

Regarding BSI [20], the item "hospitalisations in the previous 2 years" had the highest score of all, and is a recognised predictor of 4-year mortality, further hospital admissions, exacerbations and worse QoL. The history of hospitalisations due to a bronchiectasis exacerbation is an important clinical outcome because of

TABLE 3 Crude and adjusted associations between level of physical activity (measured in steps) and sedentary time, and bronchiectasis hospitalisations

Variable	n	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Number of steps[#] steps·day^{-1}					
High physical activity (⩾6290)	43	1.00		1.00	
Low physical activity (<6290)	21	4.62 (1.36–15.68)	0.014	4.20 (0.82–21.47)	0.085
Sedentary time[¶] h·day^{-1}					
Not sedentary (<7.8)	40	1.00		1.00	
Sedentary (⩾7.8)	24	7.62 (2.06–28.18)	0.002	5.91 (1.26–27.81)	0.024

Data are shown as estimated odds ratios (ORs) (95% confidence intervals (CIs)) of the explanatory variables in the low physical activity group. The OR represents the odds that low physical activity will occur given exposure to the explanatory variable, compared to the odds of the outcome occurring in the absence of that exposure. The p-values are based on the null hypothesis that all ORs relating to an explanatory variable are equal to unity (no effect). [#]: multivariable model adjusted for age, gender, chronic colonisation by *Pseudomonas aeruginosa* and hospitalisations in the 12 months prior to the study. A Hosmer–Lemeshow goodness-of-fit test is used (p=0.85). For the receiver operating characteristic (ROC) curve, the area under the curve (AUC)=0.86 (95% CI 0.76–0.97). [¶]: multivariable model adjusted for age, gender, chronic colonisation by *Pseudomonas aeruginosa* and hospitalisations in the 12 months prior to the study. A Hosmer–Lemeshow goodness-of-fit test is used (p=0.78). For the ROC curve, the AUC=0.87 (95% CI 0.76–0.97).

its negative consequences for the prognosis of the disease. In a recent cohort of 651 patients, 23.2% were defined as "frequent exacerbators" and presented poorer severity scores, more systemic inflammation and a greater use of antibiotic and anti-inflammatory therapies. The authors concluded that a history of at least 2 exacerbations·year^{-1} or 1 hospitalisation·year^{-1} was the variable with the best prognostic value for 5-year all-cause mortality (AUC 0.75, 95% CI 0.69–0.81; p<0.001) [32]. However, no information was available about physical activity levels in that population.

Considering our results, the groups did not differ in terms of exercise capacity or light physical activity, and time spent in sedentary behaviour was the only factor that raised the risk of hospitalisation (by 5.91 times). Although the differences in exercise capacity were not statistically significant, they were greater than the minimal important difference defined for patients with bronchiectasis [33]. We believe that breaking the sedentary habit in the population with bronchiectasis might have a significant clinical impact on reducing the number of hospitalisations and on improving QoL.

Previous studies have sought to find cut-off points for time spent in sedentary behaviour and steps·day^{-1} in chronic respiratory diseases. In 2017, Furlanetto *et al.* [12] were the first to propose an objective cut-off point for sedentarism in subjects affected by COPD and to investigate the association of this variable with long-term mortality. They demonstrated that the mortality risk was 4.09 times higher in patients who spent ⩾8.5 h·day^{-1} seated (with AUC=0.76, sensitivity=84% and specificity=65%). It has also been shown that the longer the time spent in sedentary behaviour per day, the higher the number of COPD exacerbations, although this was not analysed in terms of hospitalisation [34]. Our results are in line with previous studies in patients with COPD, perhaps due to similarities in physical activity behaviour in patients with these two chronic respiratory diseases. The risk of hospitalisation during follow-up in our population remained in the same direction after excluding patients who had a smoking history of >10 packs·year^{-1}. However, these findings should be interpreted carefully, as after excluding these patients the sample size fell by 25%.

It is well known that increased sedentary behaviour is associated with worsened health effects, which may differ from those caused by reduced physical activity in daily life [35], in both healthy subjects and patients with chronic respiratory diseases [10]. Strategies for reducing sedentary behaviour and for increasing physical activity will be key components of future bronchiectasis management in order to improve outcomes such as QoL and to reduce the risk of hospitalisation.

The main strengths of our study were the fact that physical activity was measured with an objective and validated tool such as an accelerometer, and the reduction of bias due to seasonality thanks to the inclusion and follow-up of patients over a whole year. One limitation of our study might be the analyses of the physical activity parameters on weekdays; however, since the significance of the effect remained unchanged with regard to the analyses including weekends, we are confident that the magnitude of the association was not overestimated. Another possible limitation is the fact that the number of hospitalisations was calculated using only medical history data and we might have missed some patients hospitalised at different centres.

Future studies should consider the inclusion of patients with bronchiectasis from other countries and other ethnicities in order to compare and contrast the results reported here. It will also be important to determine whether reducing the time spent in sedentary behaviour can significantly lower the percentage of hospitalised patients.

Conclusions

For the first time we demonstrate an association between hospitalisation due to bronchiectasis exacerbation and physical activity behaviour. Hospitalised bronchiectasis patients had lower physical activity and higher sedentary behaviour than their non-hospitalised counterparts. Patients who walked ⩽6290 steps·day^{-1} or spent ⩾7.8 h·day^{-1} in sedentary behaviour increased the risk of hospitalisation during 1-year follow-up. Moreover, sedentary behaviour alone increased the risk of hospital admission by 5.91 times. Objectively measured sedentary behaviour could be an independent predictor of hospitalisation due to an exacerbation in patients with bronchiectasis. If this finding is validated in future studies, it may be appropriate to include physical activity and sedentary behaviour as an item in severity scores.

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Author contributions: V. Alcaraz-Serrano had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. V. Alcaraz-Serrano designed and developed the study protocol. V. Alcaraz-Serrano and A. Navarro collected the data from patients. V. Alcaraz-Serrano, E. Gimeno-Santos and A. Gabarrus participated in the statistical analysis and data interpretation. V. Alcaraz-Serrano, E. Gimeno-Santos and G. Scioscia participated in the writing of the manuscript. All the authors have read the final version of the manuscript, fully approve it and qualify for authorship.

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ONLINE MATERIAL

Manuscript: Association between physical activity and risk of hospitalisation in bronchiectasis

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Online Table S1. Crude and adjusted associations between level of physical activity in steps per day and sedentary time with bronchiectasis hospitalisations.

	N	Crude OR (95% CI)	p value	Adjusted OR (95% CI) [a]	p value	Adjusted OR (95% CI) [b]	p value	Adjusted OR (95% CI) [c]	p value	Adjusted OR (95% CI) [d]	p value
Steps per day						-	-			-	-
High physical activity (≥6,290 steps per day)	43	1.00		1.00		-	-	1.00		-	-
Low physical activity (<6,290 steps per day)	21	4.62 (1.36 to 15.68)	0.014	4.20 (0.82 to 21.47)	0.085	-	-	3.37 (0.85 to 13.39)	0.085	-	-
Sedentary time				-	-			-	-		
Sedentary (≥7.8h)	24	7.62 (2.06 to 28.18)	0.002	-	-	5.91 (1.26 to 27.81)	0.024	-	-	5.34 (1.29 to 22.46)	0.020
No sedentary (<7.8h)	40	1.00		-	-	1.00		-	-	1.00	
Age (+1 year)	64	1.01 (0.97 to 1.05)	0.646	0.99 (0.94 to 1.04)	0.681	0.99 (0.94 to 1.05)	0.804	-	-	-	-
Gender											
Male	21	1.00		1.00		1.00		1.00		1.00	
Female	43	0.66 (0.20 to 2.19)	0.500	0.55 (0.13 to 2.42)	0.432	0.83 (0.19 to 3.68)	0.802	0.76 (0.18 to 3.37)	0.715	1.14 (0.27 to 4.77)	0.861
Pseudomonas aeruginosa								-	-	-	-
No	45	1.00		1.00		1.00		-	-	-	-
Yes	19	8.89 (2.44 to 32.43)	0.001	5.83 (1.35 to 25.16)	0.018	6.82 (1.56 to 29.94)	0.011	-	-	-	-
Hospitalisations 12 months prior to the study								-	-	-	-
No	51	1.00		1.00		1.00		-	-	-	-
Yes	13	6.27 (1.66 to 23.62)	0.007	6.70 (1.38 to 32.65)	0.018	5.65 (1.12 to 28.44)	0.036	-	-	-	-
MRC Dyspnoea Scale			0.347	-	-	-	-	-	-	-	-
1	12	1.00		-	-	-	-	-	-	-	-
2	39	2.41 (0.27 to 21.81)	0.435	-	-	-	-	-	-	-	-
3	10	7.33 (0.66 to 81.36)	0.105	-	-	-	-	-	-	-	-

4	3	-	-	-	-	-	-	-	-	-	-	-
FEV_1 (+1 %)	64	0.97 (0.94 to 1.00)	0.034	-	-	-	-	-	-	-	-	-
BSI stage			0.004	-	-	-	-		0.022		0.035	
Mild	23	1.00		-	-	-	-	1.00		1.00		
Moderate	22	1.66 (0.25 to 11.02)	0.601	-	-	-	-	1.46 (0.20 to 10.43)	0.707	1.99 (0.27 to 14.5)	0.495	
Severe	19	11.67 (2.12 to 64.33)	0.005	-	-	-	-	8.35 (1.43 to 48.71)	0.018	8.79 (1.47 to 52.5)	0.017	
6MWT (+1 meter)	64	0.99 (0.99 to 1.00)	0.056	-	-	-	-	-	-	-	-	-

Abbreviations. OR: odds-ratio; CI: confidence interval; h: hours; MRC: medical research council; FEV_1: forced expiratory volume in one second; BSI: bronchiectasis severity index; 6MWT: 6 minutes walking test.

Data are shown as estimated ORs (95% CIs) of the explanatory variables in the low level of physical activity group. The OR represents the odds that low level of physical activity will occur given exposure to the explanatory variable, compared to the odds of the outcome occurring in the absence of that exposure. The P-values are based on the null hypothesis that all ORs relating to an explanatory variable are equal to unity (no effect).

[a] Initial multivariable model comprised age, gender, chronic colonisation by *Pseudomonas aeruginosa*, hospitalisations 12 months prior to the study, MRC Dyspnoea Scale, FEV_1 %predicted, BSI stage and 6MWT. Final multivariable model was adjusted for age, gender, chronic colonisation by *Pseudomonas aeruginosa* and hospitalisations 12 months prior to the study. Hosmer–Lemeshow goodness-of-fit test for the multivariable model, p = 0.85. Area under the ROC curve for the multivariable model, AUC = 0.86 (0.76 to 0.97).

[b] Initial multivariable model comprised age, gender, chronic colonisation by *Pseudomonas aeruginosa*, hospitalisations 12 months prior to the study, MRC Dyspnoea Scale, FEV_1 %predicted, BSI stage and 6MWT. Final multivariable model was adjusted for age, gender, chronic colonisation by *Pseudomonas aeruginosa* and hospitalisations 12 months prior to the study. Hosmer–Lemeshow goodness-of-fit test for the multivariable model, p = 0.78. Area under the ROC curve for the multivariable model, AUC = 0.87 (0.76 to 0.97).

[c] Initial multivariable model comprised gender and BSI stage. Final multivariable model was adjusted for gender and BSI. Hosmer–Lemeshow goodness-of-fit test for the multivariable model, p = 0.986. Area under the ROC curve for the multivariable model, AUC = 0.80 (0.67 to 0.94).

[d] Initial multivariable model comprised gender and BSI stage. Final multivariable model was adjusted for gender and BSI. Hosmer–Lemeshow goodness-of-fit test for the multivariable model, p = 0.606. Area under the ROC curve for the multivariable model, AUC = 0.81 (0.67 to 0.95).

Online Table S2. Crude and adjusted associations between level of physical activity in steps per day and sedentary time excluding patients with ≥10 pack/year of tobacco.

	N	Crude OR (95% CI)	p value	Adjusted OR (95% CI) [a]	p value	Adjusted OR (95% CI) [b]	p value
Steps per day						-	-
High physical activity (≥6,290 steps per day)	36	1.00		1.00		-	-
Low physical activity(<6,290 steps per day)	12	4.43 (1.00 to 19.58)	0.050	8.7 (1.16 to 65.01)	0.035	-	-
Sedentary time				-	-		
Sedentary (≥7.8h)	14	5.62 (1.27 to 24.86)	0.023	-	-	5.54 (0.77 to 40.01)	0.089
No sedentary (<7.8h)	34	1.00		-	-	1.00	
Age (+1 year)	48	0.983 (0.94 to 1.03)	0.450	0.94 (0.88 to 1.00)	0.056	0.95 (0.88 to 1.02)	0.169
Gender							
Male	15	1.00		1.00		1.00	
Female	33	1.07 (0.24 to 4.90)	0.924	1.34 (0.17 to 10.46)	0.778	1.19 (0.15 to 9.65)	0.870
Pseudomonas aeruginosa				-	-		
No	34	1.00		-	-	1.00	
Yes	14	10.3 (2.13 to 50.26)	0.004	-	-	8.50 (1.14 to 63.39)	0.037
Hospitalisations 12 months prior to the study							
No	37	1.00		1.00		1.00	
Yes	11	9.90 (2.05 to 47.89)	0.004	19.3 (2.39 to 155.6)	0.005	15.93 (1.60 to 158.3)	0.018
FEV_1 (+1 %)	48	0.97 (0.94 to 1.00)	0.217	-	-	-	-
BSI stage			0.071	-	-	-	-
Mild	15	1.00		-	-	-	-
Moderate	19	2.62 (0.24 to 28.19)	0.426	-	-	-	-

Severe	14	10.5 (1.06 to 103.5)	0.044	-	-	-	-
6MWT (+1 meter)	48	0.99 (0.98 to 1.00)	0.336	-	-	-	-

Abbreviations. OR: odds-ratio; CI: confidence interval; h: hours; MRC: medical research council; FEV_1: forced expiratory volume in one second; BSI: bronchiectasis severity index; 6MWT: 6 minutes walking test.

Data are shown as estimated ORs (95% CIs) of the explanatory variables in the low level of physical activity group. The OR represents the odds that low level of physical activity will occur given exposure to the explanatory variable, compared to the odds of the outcome occurring in the absence of that exposure. The P-values are based on the null hypothesis that all ORs relating to an explanatory variable are equal to unity (no effect).

[a] Initial multivariable model comprised age, gender, chronic colonisation by *Pseudomonas aeruginosa*, hospitalisations 12 months prior to the study, MRC Dyspnoea Scale, FEV_1 %predicted, BSI stage and 6MWT. Final multivariable model was adjusted for age, gender, chronic colonisation by *Pseudomonas aeruginosa* and hospitalisations 12 months prior to the study. Hosmer–Lemeshow goodness-of-fit test for the multivariable model, p = 0.76. Area under the ROC curve for the multivariable model, AUC = 0.87 (0.75 to 0.98).

[b] Initial multivariable model comprised age, gender, chronic colonisation by *Pseudomonas aeruginosa*, hospitalisations 12 months prior to the study, MRC Dyspnoea Scale, FEV_1 %predicted, BSI stage and 6MWT. Final multivariable model was adjusted for age, gender, chronic colonisation by *Pseudomonas aeruginosa* and hospitalisations 12 months prior to the study. Hosmer–Lemeshow goodness-of-fit test for the multivariable model, p = 0.35. Area under the ROC curve for the multivariable model, AUC = 0.89 (0.78 to 1.00).

Online Table S3. Physical activity baseline characteristics of hospitalised vs. non-hospitalised bronchiectasis patients including weekend data.

	All patients	Hospitalised	Non-hospitalised	p value
	N=64	N=15 (23%)	N=49 (77%)	
Physical Activity				
Light PA, 1.6 - <3.0 MET-min/day	211.4 (75.9)	184.3 (37.0)	220.2 (82.8)	0.110
Moderate PA, 3.0 - <6.0 MET-min/day	112.9 (80	84.4 (64)	121.6 (82.8)	0.050
Vigorous PA, 6.0 - <8.7 MET-min/day	0.81 (2.17)	0.4 (1.1)	0.9 (2.4)	0.486
MVPA, min/day	113.9 (80.6)	85.1 (64.5)	122.7 (83.5)	**0.047**
Steps per day	6,933 (3,345)	5,156.11 (3464)	7,477.4 (3,146)	**0.019**
Sedentary time, hours per day	7.51 (1.77)	8.53 (1.52)	7.21 (1.74)	**0.018**

Data are presented as n (%), mean (SD) or median (P_{25};P_{75}). *Data presented as mean (SD), and range.

Abbreviations. BMI: body mass index; MRC: medical research council; COPD: chronic obstructive pulmonary disease; BSI: bronchiectasis severity index; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; 6MWT: 6 minutes walking test; PA: physical activity; MET: metabolic equivalent tasks; MVPA: moderate-to-vigorous physical activity.

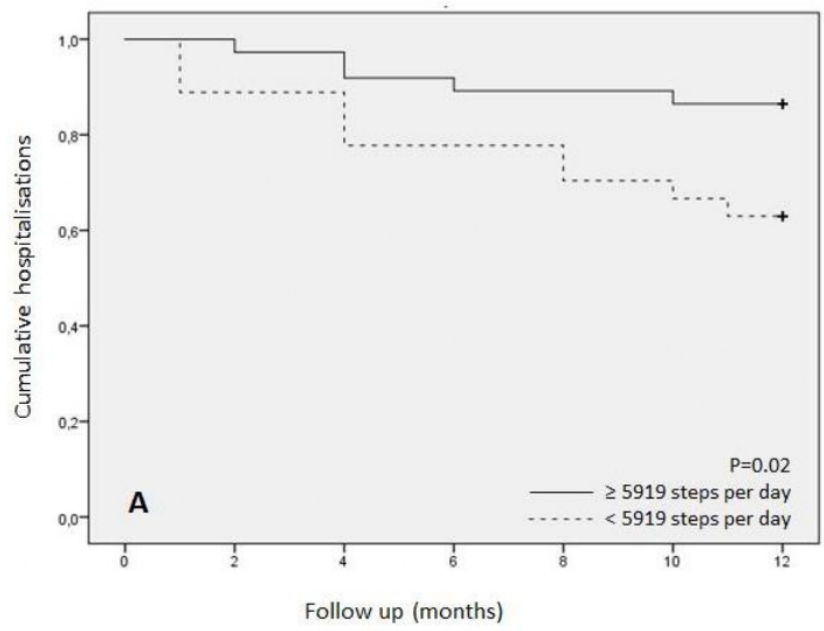
[a] Could have more than one medication.

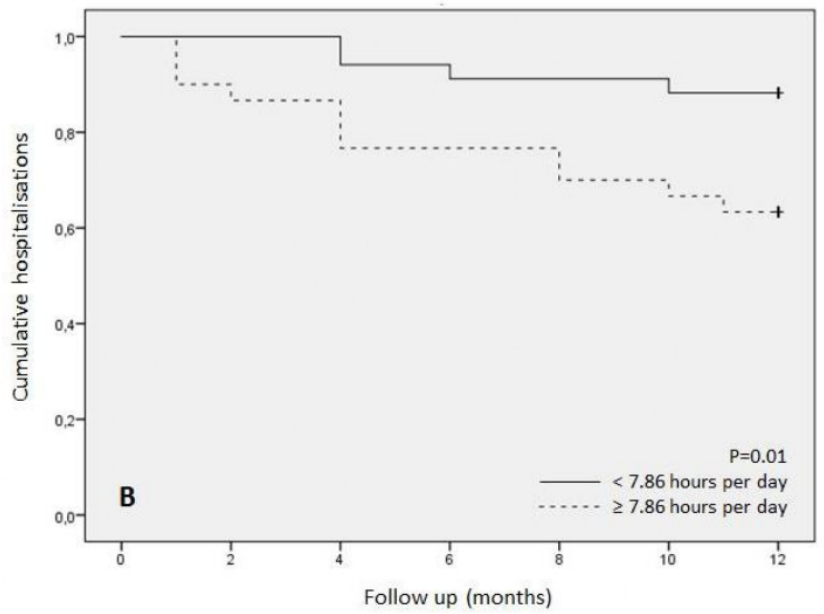
Online Table S4. Steps per day, sedentary time, moderate PA and MVPA cut-off points for hospitalisation including weekend data.

Hospitalisation variable	AUC (95% CI)	Sensitivity (%)	Specificity (%)	Best Cut-off	p value
Steps per day	0.71 (0.54 to 0.87)	65	67	5,919	0.017
Sedentary time (hours)	0.72 (0.57 to 0.87)	73	63	7.86	0.009
Moderate PA (min)	0.67 (0.50 to 0.84)	61	60	89.6	0.050
MVPA (min)	0.67 (0.50 to 0.84)	61	60	89.9	0.047

Abbreviations. AUC: area under the curve; CI: confidence interval; PA: physical activity; min: minutes; MVPA: moderate-to-vigorous physical activity.

Figure S1. Kaplan-Meier graphics according to ROC curve cut-off points including weekend data.
1A. <5919 steps per day; 1B. ≥7.86 hours of sedentary behaviour.





Online Table S5. Crude and adjusted associations between level of physical activity in steps per day and sedentary time and bronchiectasis hospitalisations including weekend data.

	N	Crude OR (95% CI)	p value	Adjusted OR (95% CI) [a]	p value	Adjusted OR (95% CI) [b]	p value
Steps per day						-	-
High physical activity (≥5,919 steps per day)	37	1.00		1.00		-	-
Low physical activity (<5,919 steps per day)	27	3.76 (1.11 to 12.80)	0.034	4.75 (0.89 to 25.48)	0.069	-	-
Sedentary time				-	-		
Sedentary (≥7.8h)	34	4.34 (1.21 to 15.63)	0.025	-	-	2.96 (0.66 to 13.30)	0.158
Non-sedentary (<7.8h)	30	1.00		-	-	1.00	
Age (+1 year)	64	1.01 (0.97 to 1.05)	0.646	0.99 (0.94 to 1.04)	0.717	1.00 (0.95 to 1.05)	0.977
Gender			0.500		0.429		0.592
Male	21	1.00		1.00		1.00	
Female	43	0.66 (0.20 to 2.19)		0.55 (0.12 to 2.44)		0.68 (0.16 to 2.84)	
Pseudomonas aeruginosa			0.001		0.014		0.007
No	45	1.00		1.00		1.00	
Yes	19	8.89 (2.44 to 32.43)		6.12 (1.44 to 26.04)		7.17 (1.72 to 29.79)	
Hospitalisations 12 months prior to the study			0.007		0.013		0.028
No	51	1.00		1.00		1.00	
Yes	13	6.27 (1.66 to 23.62)		8.22 (1.55 to 43.62)		5.57 (1.21 to 25.75)	
MRC Dyspnoea Scale			0.347	-	-	-	-
1	12	1.00		-	-	-	-
2	39	2.41 (0.27 to 21.81)	0.435	-	-	-	-

3	10	7.33 (0.66 to 81.36)	0.105	-	-	-	-
4	3	-	-	-	-	-	-
FEV_1 (+1 %)	64	0.97 (0.94 to 1.00)	0.034	-	-	-	-
BSI stage			0.004	-	-	-	-
Mild	23	1.00		-	-	-	-
Moderate	22	1.66 (0.25 to 11.02)	0.601	-	-	-	-
Severe	19	11.67 (2.12 to 64.33)	0.005	-	-	-	-
6MWT (+1 meter)	64	0.99 (0.99 to 1.00)	0.050	-	-	-	-

Abbreviations. OR: odds-ratio; CI: confidence interval; h: hours; MRC: medical research council; FEV_1: forced expiratory volume in one second; BSI: bronchiectasis severity index; 6MWT: 6 minutes walking test.

Data are shown as estimated ORs (95% CIs) of the explanatory variables in the low level of physical activity group. The OR represents the odds that low level of physical activity will occur given exposure to the explanatory variable, compared to the odds of the outcome occurring in the absence of that exposure. The P-values are based on the null hypothesis that all ORs relating to an explanatory variable are equal to unity (no effect).

[a] Initial multivariable model comprised age, gender, chronic colonisation by *Pseudomonas aeruginosa*, hospitalisations 12 months prior to the study, MRC Dyspnoea Scale, FEV_1 %predicted, BSI stage and 6MWT. Final multivariable model was adjusted for age, gender, chronic colonisation by *Pseudomonas aeruginosa* and hospitalisations 12 months prior to the study. Hosmer–Lemeshow goodness-of-fit test for the multivariable model, p = 0.27. Area under the ROC curve for the multivariable model, AUC = 0.86 (0.75 to 0.97).

[b] Initial multivariable model comprised age, gender, chronic colonisation by *Pseudomonas aeruginosa*, hospitalisations 12 months prior to the study, MRC Dyspnoea Scale, FEV_1 %predicted, BSI stage and 6MWT. Final multivariable model was adjusted for age, gender, chronic colonisation by *Pseudomonas aeruginosa* and hospitalisations 12 months prior to the study. Hosmer–Lemeshow goodness-of-fit test for the multivariable model, p = 0.14. Area under the ROC curve for the multivariable model, AUC = 0.84 (0.72 to 0.96).

ARTICLE 3

Exacerbations and changes in physical activity and sedentary behaviour in patients with bronchiectasis after 1 year.

Victoria Alcaraz-Serrano, Ane Arbillaga-Etxarri, Patricia Oscanoa, Laia Fernández-Barat, Leticia Bueno, Rosanel Amaro, Elena Gimeno-Santos, Antoni Torres.

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Article

Exacerbations and Changes in Physical Activity and Sedentary Behaviour in Patients with Bronchiectasis after 1 Year

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Abstract: Background: Low physical activity and high sedentary behaviour in patients with bronchiectasis are associated with hospitalisation over one year. However, the factors associated with longitudinal changes in physical activity and sedentary behaviour have not been explored. We aimed to identify clinical and sociodemographic characteristics related to a change in physical activity and sedentary behaviour in patients with bronchiectasis after one year. Methods: This was a prospective observational study during which physical activity measurements were recorded using a SenseWear Armband for one week at baseline and at one year. At each assessment point, patients were classified as active or inactive (measured as steps per day) and as sedentary or not sedentary (measured as sedentary time). Results: 53 patients with bronchiectasis were analysed, and after one year, 18 (34%) had worse activity and sedentary levels. Specifically, 10 patients became inactive and sedentary. Multivariable analysis showed that the number of exacerbations during the follow-up period was the only outcome independently associated with change to higher inactivity and sedentary behaviour (odds ratio (OR), 2.19; 95% CI, 1.12 to 4.28). Conclusions: The number of exacerbations in patients with bronchiectasis was associated with changes in physical activity and sedentary behaviour. Exacerbation prevention may appear as a key factor in relation to physical activity and sedentary behaviour in patients with bronchiectasis.

Keywords: bronchiectasis; physical activity; sedentary behaviour; exacerbation

1. Introduction

Bronchiectasis is a chronic respiratory disease characterised by chronic productive cough, dyspnoea, and frequent exacerbations [1]. An exacerbation is defined as a person with bronchiectasis with a deterioration in three or more of the following key symptoms for at least 48 h: cough, sputum volume and/or consistency, sputum purulence, breathlessness and/or exercise tolerance, fatigue and/or malaise, haemoptysis; and a clinician determines that a change in treatment is required [2]. Exacerbations increase the severity of microbiological, radiological, and functional outcomes [3], being differentiated into mild, when patients are treated with oral antibiotics as outpatients, and moderate to severe, when they require hospitalisation and intravenous therapy [4]. Furthermore, a higher frequency of exacerbations is associated with an increased risk of mortality [5].

It is known that in patients with chronic obstructive pulmonary disease (COPD), high levels of physical activity and low time in sedentary behaviour are at a reduced risk of exacerbations and reduced health care utilisation, which leads to various cost savings [6,7]. By contrast, there is limited knowledge of the relation between physical activity, sedentary behaviour, and exacerbations in patients with bronchiectasis. It was recently described that patients with bronchiectasis who spent ≥7.8 h/day in sedentary behaviour were at a 5.9 times greater risk of future severe exacerbations [8]. Physical activity is a complex behaviour structured in variables according to different intensities and outcomes [9]. Although steps per day and time spent in sedentary behaviour are strongly correlated, they should be considered independently because they each have their own peculiarities and associated factors [10]. To date, the factors associated with the modification in physical activity and sedentary behaviour after one year have not been explored for either measure in patients with bronchiectasis.

Therefore, the aim of this study was to analyse the clinical and sociodemographic characteristics associated with a change in physical activity and sedentary behaviour after one year in patients with bronchiectasis.

2. Materials and Methods

2.1. Study Design

This was a prospective observational study conducted at the pulmonology service of a tertiary care hospital in Barcelona, Spain. Physical activity and sedentary behaviour measurements were performed at baseline and at one year follow-up to study the distribution of groups (active/inactive and sedentary/not sedentary) and their longitudinal modification. We also investigated the clinical and sociodemographic factors potentially related to a shift between physical activity and sedentary behaviour levels. The inclusion criteria were as follows: (1) adults (≥18 years of age) diagnosed with bronchiectasis, as confirmed by computed tomography and with symptoms of the disease; (2) clinical stability (no exacerbations and no significant change in symptoms and/or medication in the last four weeks); (3) the ability to perform all the clinical tests and understand the process and the purposes of the study; (4) willing to give informed consent. Exclusion criteria were: (1) any physical or psychological disorder that might interfere with protocol compliance; (2) diagnosis of cystic fibrosis, sarcoidosis, pulmonary fibrosis, active tuberculosis (TB), or non-TB mycobacterial infection in treatment; (3) participation in a pulmonary rehabilitation (PR) programme in the last year; 4) respiratory insufficiency and/or oxygen therapy; (5) missing data after 12 months of follow-up.

The study was approved by the Clinical Research Ethics Committee of the Hospital Clinic (Ethics Approval Reference: HCB/2016/0012). Informed consent was obtained from all subjects involved in the study.

2.2. Measurements

Patients were assessed at baseline and after one year, with no intervention provided during this year. Dyspnoea was measured using the modified Medical Research Council (mMRC) scale [11]. Lung function was assessed with an EasyOne™ World Spirometer (NDD Medical Technologies, Zurich, Switzerland) and classified according to the American Thoracic Society/European Respiratory Society Guidelines [12]. Exercise capacity was measured using the 6-min walking test (6MWT) [13]. Quality of life was assessed using the Quality-of-Life Bronchiectasis questionnaire (QoL-B) [14], while the impact of coughing on the quality of life was assessed with the Leicester Cough Questionnaire (LCQ) [15]. Bronchiectasis severity was assessed using the Bronchiectasis Severity Index (BSI) Score [16]. We recorded the number of exacerbations and hospitalisations in the medical dataset during the follow-up based on a consensus definition [2]. Frequency of exacerbations for subanalysis was divided into 0, 1–2, and ≥3 exacerbations during the follow-up [17].

Physical activity and sedentary behaviour were measured using a tri-axial accelerometer, the SenseWear Armband (SWA) (BodyMedia Inc., Pittsburgh, PA, USA). Participants

were asked to wear the SWA for the maximum time possible over seven days, except during water-based activities. It was worn in the triceps area, on the rear of the dominant arm [18]. Intensity of physical activity was reported as metabolic equivalents (METs) and classified into sedentary (≤1.5 MET), light (1.6 to <3.0 MET), moderate (3.0 to <6.0 MET), and vigorous (≥6.0 MET) [19]. The mean time (in minutes) spent at each intensity level was recorded. Moderate-to-vigorous physical activity (MVPA) was calculated as the mean number of minutes spent in moderate and vigorous physical activity on the valid days. Sedentary time was analysed as the number of minutes the patient spent at ≤1.5 MET intensity.

Patients were classified into four groups according to their physical activity and sedentary behaviour levels at baseline and at one year. The cut-off for being active was ≥6290 steps per day and for being sedentary ≥7.8 h per day spent in sedentary behaviour [8]. The groups were labelled from the best to worst, as follows: 'active + not sedentary', 'active + sedentary', 'inactive + not sedentary', 'inactive + sedentary'. The dependent variable was the change, after one year follow-up, to the worst group 'inactive + sedentary'.

2.3. Statistical Analysis

Data are presented as numbers (%) for categorical variables, as means ± standard deviations (SD) for normally distributed data and as medians (P_{25}–P_{75}) (1st and 3rd quartiles) for non-normally distributed data. The assumption of normality was checked by means of Shapiro–Wilk tests. Comparisons of categorical variables were performed using the chi-square test. Comparisons between continuous variables were performed by analysis of variance (ANOVA) or the Kruskal–Wallis test. If the overall ANOVA (or Kruskal–Wallis) result was significant, we conducted post-hoc pairwise comparisons with Bonferroni correction to control for the experiment-wise error rate.

Logistic regression analyses [20] were used to examine the associations between the change to 'inactive + sedentary' and the various risk factors. In the first step, each risk factor, together with the numbers of hospitalisations and exacerbations during the follow-up, were tested individually. We included age, 6-min walking distance, and forced expiratory volume in the first second predicted (FEV_1%) as risk factors. In the second step, all risk factors that showed an association in the univariate model ($p < 0.10$) were added to the multivariable model. Finally, a backward stepwise selection (likelihood ratio) (pin < 0.05, pout > 0.10) was used to determine factors associated with change to the 'inactive + sedentary' group after one year [21]. Multicollinearity was assessed by calculating the variance inflation factor, and we calculated the odds ratios (ORs) and their 95% confidence intervals (CIs). The Hosmer–Lemeshow goodness-of-fit test was performed to assess the overall fit of the final model. The internal validity of the final model was assessed using ordinary non-parametric bootstrapping with 1000 bootstrap samples and bias-corrected, accelerated 95% CIs.

The level of significance was set at 0.05 (two-tailed) for all analyses, which were performed using IBM SPSS Statistics 26.0 (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Baseline Data

Of the 72 patients with bronchiectasis who we recruited, 53 (37 females, mean age 62 ± 16 years) were included in the analysis (Figure 1).

Their baseline sociodemographic and clinical characteristics are shown in Table 1, with 24 in the 'active + not sedentary' group, 3 in the 'active + sedentary' group, 11 in the 'inactive + not sedentary' group, and 15 in the 'inactive + sedentary' group. There were only differences in physical activity outcomes where the group 'inactive + sedentary' had the lowest values of light and moderate physical activity, MVPA and steps per day, as well as the highest value for sedentary time.

Table 1. Baseline characteristics by physical activity and sedentary behaviour classification.

	All Patients	'Active + Not Sedentary'	'Active + Sedentary'	'Inactive + Not Sedentary'	'Inactive + Sedentary'	*p* Value
	N = 53	24 (45)	3 (6)	11 (21)	15 (28)	
Demographics						
Female	37 (70)	19 (79)	1 (33.3)	7 (63.6)	10 (66.6)	0.368
Age, years	62.3 (15.9)	58.7 (14.9)	62.7 (6.4)	64.6 (21.9)	66.1 (13.9)	0.523
BMI, Kg/m^2	24.3 (4.1)	23.8 (3.9)	29.4 (5.1)	23.9 (2.9)	24.1 (4.6)	0.174
Work activity						0.263
Active	19 (36)	12 (50)	1 (33.3)	2 (18.2)	4 (26.7)	
Retired	34 (64)	12 (50)	2 (66.6)	9 (81.8)	11 (73.3)	
Smoking habit						0.538
Active smoker	1 (2)	1 (4.2)	0 (0)	0 (0)	0 (0)	
Former smokers	14 (26)	4 (16.6)	2 (66.6)	3 (27.2)	5 (33.3)	
Non-smoker	38 (71.7)	19 (79.2)	1 (33.3)	8 (72.7)	10 (66.6)	
Chronic colonisation	20 (37)	5 (20.8)	1 (33.3)	6 (51.5)	8 (53.3)	0.121
Pseudomonas aeruginosa	16 (30)	3 (60)	1 (100)	5 (83.3)	7 (87.5)	0.081
Dyspnoea (mMRC Scale, 0–4)	1 [1,1]	1 [0,1]	1 [1,1]	1 [1,2]	1 [1,2]	0.263
No. exacerbations previous year	1 [0,1,2]	1 [0,1,2]	1 [0,1]	2 [0,1,2]	1 [0,1,2,3,4]	0.283
No. hospitalizations previous year	0 [0,0]	0 [0,0]	0 [0,0]	0 [0,0]	0 [0,1]	0.653
Number of lobes affected in CT scan	3.62 (1.6)	3.50 (1.7)	2.33 (0.6)	3.91 (1.3)	3.86 (1.7)	0.350
Aetiology						
Post-infectious	24 (45)	15 (62.5)	0 (0)	6 (54.5)	3 (20)	0.022
Idiopathic	13 (24)	3 (12.5)	2 (66.6)	2 (18)	6 (40)	0.074
Others	16 (30.2)	6 (25)	1 (33.3)	3 (27.3)	6 (40)	0.789
Severity						
BSI stages	2 [1,2,3]	2 [1,2]	2 [1,2]	2 [2,3]	3 [1,2,3]	0.086
Pulmonary function						
FEV1, % predicted	73.2 (20)	80.9 (18.2)	67 (5.56)	68.9 (23.1)	65.4 (19.9)	0.086
FVC, % predicted	81 (18.3)	87.2 (16.4)	90.3 (38.6)	72.36 (14.3)	75.6 (16.5)	0.059
FEV1/FVC, %	85.9 (18)	89.1 (17.2)	73 (17.7)	84.9 (19.4)	84.2 (18.6)	0.490
6MWT, metres	516.8 (97.8)	534.3 (80.03)	564.8 (40.5)	512.8 (103.4)	482.3 (122.01)	0.345
Physical activity						
Light (min per day)	216.7 (77)	237.2 (71.6)	138.8 (64.4)	256.6 (91.9)	170.2 (37.6)	0.002 [a,b]
Moderate (min per day)	112 (76)	143.3 (91.1)	97.2 (24.5)	117.5 (57.4)	60.8 (30.1)	0.008 [a]
Vigorous (min per day)	0.66 (1.7)	1.1 (2.3)	0 (0)	0.26 (0.31)	0.44 (1.0)	0.445
MVPA (min per day)	112.5 (77)	144 (92.1)	97.2 (24.5)	117.7 (57.5)	61.2 (30.5)	0.009 [a]
Steps per day	6759 (3530)	9441 (3014)	8912 (549)	4840 (1120)	3444 (1563)	<0.001
Sedentary time (min)	430 (99.8)	374.4 (75.7)	487.5 (18.4)	384.9 (79.8)	541 (46.6)	<0.001 [a,b]
Quality of Life Bronchiectasis Questionnaire						
Physical Function	60.4 (32.7)	62.3 (33.3)	55.5 (19.2)	45.5 (34.2)	64.4 (32)	0.382
Role Function	76.7 (26.6)	83.3 (26)	66.6 (0)	75.7 (26.2)	68.9 (29.5)	0.367
Vitality	59.4 (26.8)	62.5 (24.7)	55.6 (19.2)	65.2 (24)	51.1 (33)	0.521
Emotional Function	74.2 (28.9)	75.7 (27.4)	61.1 (25.4)	69.7 (34)	77.8 (30)	0.771
Social Function	69.8 (30.8)	76.4 (24.5)	55.6 (38.5)	65.2 (36.9)	65.6 (34.7)	0.530
Treatment Burden	72.9 (39.8)	72.2 (42.5)	66.7 (57.7)	69.7 (37.8)	77.7 (37)	0.948
Health Perceptions	53.1 (26.7)	61.8 (28.4)	50 (16.7)	51.5 (24.1)	41.4 (24.3)	0.129
Respiratory Symptoms	76.7 (23.2)	77.7 (23.4)	66.7 (33.3)	78.8 (22.5)	75.6 (23.5)	0.981
Leicester Cough Questionnaire						
Total	15.3 (4.64)	16.04 (4.2)	12.9 (7.2)	15.1 (5.5)	14.8 (4.5)	0.678
Physical	4.9 (1.34)	5.2 (1.2)	4.37 (2.3)	5.03 (1.3)	4.74 (1.5)	0.616
Psychological	5.01 (1.74)	5.2 (1.6)	4.19 (2.4)	4.78 (2.2)	5.04 (1.6)	0.773
Social	5.44 (1.8)	5.67 (1.6)	4.41 (2.7)	5.3 (2.2)	5.4 (1.6)	0.710

Abbreviations: 6MWT, 6-min walking test; BMI, body mass index; BSI, bronchiectasis severity index; CT: computed tomography; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; Kg, kilogram; m, metre; min: minutes; mMRC, modified Medical Research Council scale; MVPA, moderate-to-vigorous physical activity. Data are presented as n (%), mean ± SD or median (P_{25}–P_{75}). [a] $p < 0.05$ for comparison between 'active + not sedentary' vs. 'inactive + sedentary'. [b] $p < 0.05$ for comparison between 'inactive + sedentary' vs. 'inactive + not sedentary'.

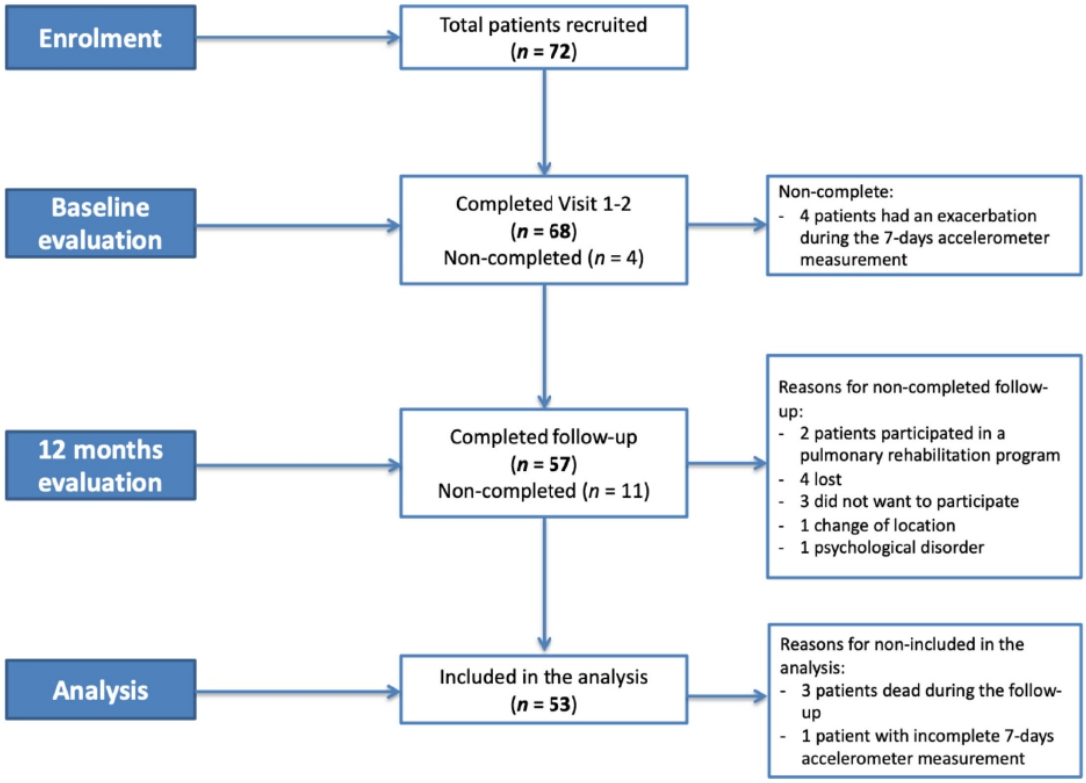

Figure 1. Enrolment flow-chart.

3.2. Follow-Up Assessment at 1 Year

After one year follow-up, the number of patients in each group changed to 18 in the 'active + not sedentary' group, 7 in the 'active + sedentary' group, 8 in the 'inactive + not sedentary' group, and 20 in the 'inactive + sedentary' group. In total, 27 (51%) patients changed to a different group, of whom only 9 (17%) improved from a sedentary and/or inactive group to a not sedentary and/or active group. The other 18 (34%) patients deteriorated, and 10 of these shifted to the worst group ('inactive + sedentary'). At this time, the 'inactive + sedentary' group had more exacerbations, lower physical activity levels, and worse quality of life (Table 2).

Table 2. Follow-up characteristics by physical activity and sedentary behaviour classification.

	All Patients	'Active + Not Sedentary'	'Active + Sedentary'	'Inactive + Not Sedentary'	'Inactive + Sedentary'	*p* Value
	N = 53	18 (34)	7 (13)	8 (15)	20 (38)	
Demographics						
BMI, Kg/m^2	24.2 (4.3)	25.1 (4.2)	24.2 (4.6)	21.6 (4.1)	24.7 (4.4)	0.287
Dyspnoea (mMRC Scale, 0–4)	1 [0,1]	1 [0,1,2]	1 [0.75–2.25]	2 [0,1,2,3]	3 [2,3,4]	0.075
No. exacerbations during FUP	2 [1,2,3]	1 [0,1,2]	1 [0.75–2.25]	2 [0,1,2,3]	3 [2,3,4]	<0.001
No. hospitalisations during FUP	0 [0–0.5]	0 [0,0]	0 [0,0]	0 [0–0.75]	0 [0,1]	0.125
Pulmonary function						
FEV_1, % predicted	69.5 (20.4)	75.5 (19.4)	73.8 (22.4)	64.1 (23.2)	66.7 (19.1)	0.363
FVC, % predicted	77.7 (17.8)	82.4 (16.6)	77.4 (13.5)	72.7 (23.1)	76.5 (18.2)	0.256
FEV_1/FVC, %	83.7 (18.3)	83.9 (14.8)	93 (20.5)	87.4 (30.7)	81.9 (13.3)	0.532

Table 2. *Cont.*

	All Patients	'Active + Not Sedentary'	'Active + Sedentary'	'Inactive + Not Sedentary'	'Inactive + Sedentary'	*p* Value
6MWT, metres	520.4 (98.5)	540.3 (77.2)	582.9 (81.2)	505.4 (73.9)	470.8 (111.8)	0.068
Physical activity						
Light (min per day)	205.4 (75.5)	248.2 (86.1)	164.8 (37.1)	206.1 (86.4)	179.2 (53.7)	0.016 [a]
Moderate (min per day)	107.6 (84.2)	160.2 (95.7)	86.2 (36.3)	155.7 (88.8)	49.8 (24.6)	<0.001 [a,c]
Vigorous (min per day)	0.89 (2.51)	1.9 (3.9)	1.14 (2.3)	0.5 (0.67)	0.04 (0.14)	0.123
MVPA (min per day)	108.5 (85.1)	162.2 (96.6)	87.3 (37.4)	156.2 (89.4)	49.9 (24.6)	<0.001
Steps per day	6781 (5799)	10443 (2681)	8073 (1624)	4383 (1764)	3983 (1484)	<0.001 [a,c]
Sedentary time (min)	441.2 (115.6)	337.9 (72.1)	501.3 (30.3)	372.6 (117.1)	540.2 (53.3)	<0.001
Quality of Life Bronchiectasis Questionnaire						
Physical Function	53.14 (31.8)	61.1 (23.6)	72.2 (25.1)	50 (34.7)	35.1 (32.3)	0.026
Role Function	72.01 (29.56)	81.5 (23.5)	94.4 (13.6)	61.9 (12.6)	57 (35.7)	0.012 [a,b]
Vitality	59.4 (22.98)	61.1 (21.4)	63.8 (16.4)	66.7 (21.5)	50.8 (25.7)	0.215
Emotional Function	74.5 (27.5)	73.1 (24.3)	88.9 (17.2)	80.9 (26.2)	66.7 (33.3)	0.295
Social Function	64.5 (31.4)	78.7 (23.4)	75 (20.4)	54.7 (20.9)	48.2 (37.6)	0.030 [a]
Treatment Burden	69.9 (37.8)	75.9 (35.8)	72.2 (44.3)	52.4 (42.4)	68.4 (37.6)	0.590
Health Perceptions	55.3 (28.8)	62.9 (27.1)	63.9 (6.8)	57.1 (26.9)	42.1 (32.6)	0.101
Respiratory Symptoms	74.8 (23.5)	77.8 (19.8)	72.2 (13.6)	85.7 (17.8)	66.7 (29.4)	0.164
Leicester Cough Questionnaire						
Total	15.5 (4.4)	15.9 (4.4)	17.3 (2.2)	16.1 (3.8)	14.2 (5.1)	0.348
Physical	4.98 (1.4)	5.24 (1.2)	5.6 (0.8)	5.1 (1.3)	4.5 (1.6)	0.238
Psychological	5.23 (1.7)	5.4 (1.7)	5.8 (0.8)	5.4 (1.5)	4.7 (1.9)	0.426
Social	5.36 (1.6)	5.5 (1.5)	5.9 (0.9)	5.6 (1.3)	4.9 (1.8)	0.348

Abbreviations: 6MWT, 6-min walking test; BMI, body mass index; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; FUP, follow-up; Kg, kilogram; m, metre; min: minutes; mMRC, modified Medical Research Council scale; MVPA, moderate-to-vigorous physical activity. Data are presented as n (%), mean ± SD or median (P_{25}–P_{75}). [a] $p < 0.05$ for comparison between 'active + not sedentary' vs. 'inactive + sedentary'. [b] $p < 0.05$ for comparison between 'inactive + sedentary' vs. 'active + sedentary'. [c] $p < 0.05$ for comparison between 'inactive + not sedentary' vs. 'inactive + sedentary'.

3.3. Factors Associated with the Shift to Reduced Activity Levels

Results from the multivariable analysis showed that the number of exacerbations during the follow-up (OR, 2.19; 95% CI, 1.12 to 4.28) was independently associated with change to the 'inactive + sedentary' group (Table 3). Internal validation of the logistic regression model using bootstrapping with 1000 samples demonstrated robust results for the variable included in the model, with small 95% CIs around the original coefficients.

Table 3. Significant risk factors for inactivity and sedentary behaviour in the logistic regression analyses.

Variable	Univariate [a]			Multivariable [b]		
	OR	95% CI	*p* Value	OR	95% CI	*p* Value
Age (+1 year)	1.003	0.96 to 1.05	0.906	-	-	-
6-min walking distance (+1 m)	0.998	0.99 to 1.00	0.518	-	-	-
FEV_1 (+1% predicted)	1.005	0.97 to 1.04	0.796	-	-	-
Number of hospitalisations during FUP (+1 unit)	1.200	0.80 to 1.793	0.089	-	-	-
Number of exacerbations during FUP (+1 unit)	1.540	1.23 to 2.65	0.045	2.192	1.12 to 4.28	0.021

Abbreviations: CI, confidence interval; FEV_1, forced expiratory volume in 1 s; FUP, follow-up; OR, odds ratio. The OR represents the odds that the change of group to 'inactive + sedentary' will occur with exposure to the explanatory variable, against the odds of the outcome occurring in the absence of that exposure. The *p*-value is based on the null hypothesis that all ORs relating to an explanatory variable equal unity (i.e., no effect).[a] The variables analysed in the univariate analysis were age, 6-min walking distance, FEV_1% predicted, number of hospitalisations during the follow-up and number of exacerbations during the follow-up.[b] Hosmer–Lemeshow goodness-of-fit test, $p = 0.76$.

3.4. Relationship between Baseline and Follow-Up Activity Levels by Number of Exacerbations

In the final cohort, 11 (21%) patients had 0 exacerbations, 25 (47%) had 1–2 exacerbations, and 17 (32%) had ≥3 exacerbations. The physical activity and sedentary behaviour variables at baseline and at one year, together with the ***p***-trend for each parameter, are

shown in Figure 2. At both evaluations, the group with ≥3 exacerbations had the lowest MVPA, lowest number of steps per day and the highest sedentary time compared with the other two groups (i.e., 0 or 1–2 exacerbations).

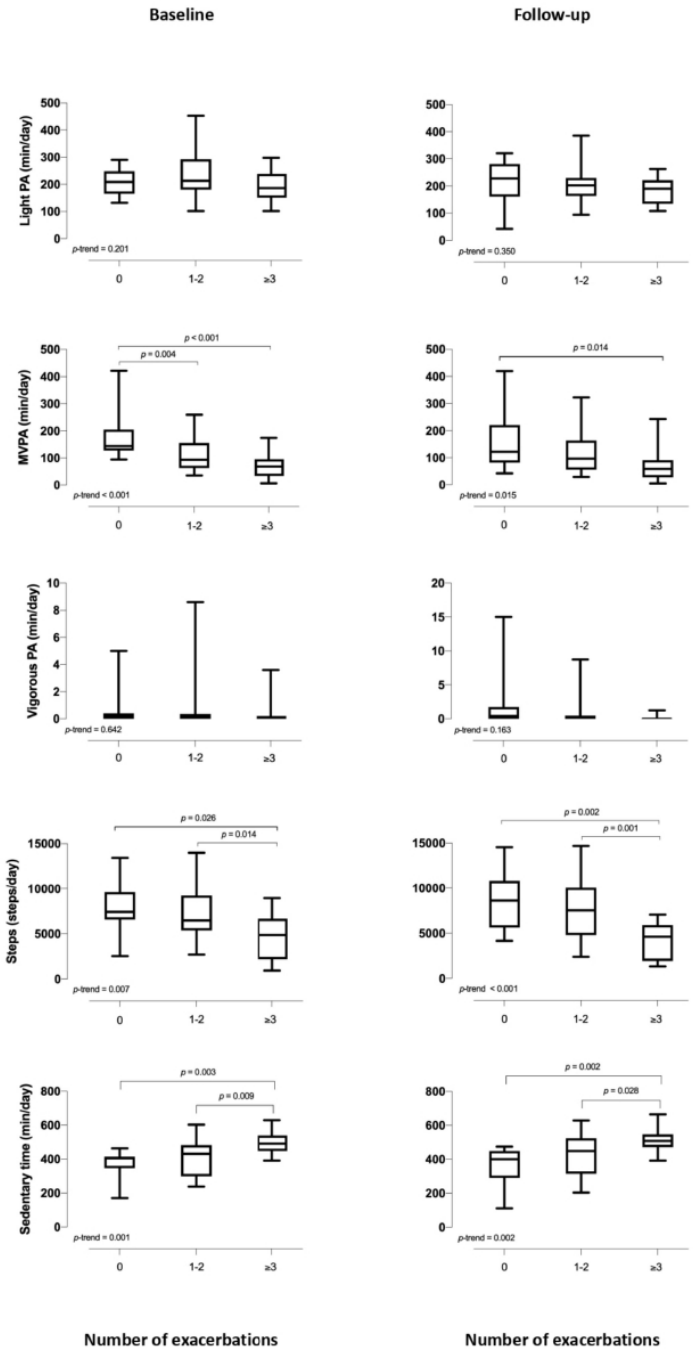

Figure 2. Physical activity and sedentary behaviour at baseline and follow-up according to number of exacerbations. The box and whisker plots show the mean ± SD for each physical activity variable and sedentary time by the number of exacerbations (0, 1–2, and ≥3). The left and right figures show the data for baseline and one year, respectively. Abbreviations: min, minutes; MVPA, moderate-to-vigorous physical activity; PA, physical activity.

4. Discussion

To the best of our knowledge, this is the first study to have (1) evaluated and categorised patients with bronchiectasis by their physical activity and sedentary levels at baseline and one year, (2) identified and characterised those patients who deteriorated to become most 'inactive + sedentary' after one year, and (3) associated this shift to the number of exacerbations during the follow-up.

In our previous study, patients with bronchiectasis who walked ≤6290 steps day and/or spent ≥7.8 h in sedentary behaviour were at higher risk of hospitalisation in the following year; concluding that physical activity and sedentary behaviour were a determinant for hospitalisation of bronchiectasis [8]. In the present study, the number of exacerbations during the follow-up was a determinant for changing physical activity and sedentary behaviour in patients with bronchiectasis. Likewise, Bradley et al. [22] reported that patients with bronchiectasis and low physical activity levels showed increased severity, which may have been related to their physical impairment, thereby more exacerbations. Martínez-García et al. [5] also showed that there is a specific group of patients with bronchiectasis who are characterised by a high frequency of exacerbations (at least two) or a hospitalisation per year; specifically, it was shown that these patients had a worse five-year all-cause mortality independent to the initial severity of bronchiectasis. These data, combined with the present results, indicate that a high frequency of exacerbations may be associated with declining physical activity levels and increasing sedentary behaviour over time rather than with the severity of exacerbations (reflected by hospitalisation).

In similar populations, such as COPD, Moy et al. [23] showed that lower daily step count was associated with significantly higher rates of acute exacerbations and hospitalisations. Donaire et al. [24] also reported that an increase of 1000 steps daily, performed at low average intensity, reduced the risk of hospitalisation by 20%, whereas Nguyen et al. [25] reported that there was a significant risk reduction (34%) in 30-day readmissions among patients with COPD who reported engaging in any physical activity. Regarding sedentary behaviour, this has been associated with more exacerbations [26] and higher mortality [27]. Previous observational studies have consistently shown that physical inactivity is associated with an increased risk of hospitalisations and mortality in patients with COPD [28–32]. According to our results, the pattern of decline in physical activity and increase in sedentary behaviour was associated with the number of exacerbations in bronchiectasis; hence, we hypothesise that this may be strongly associated with a worse prognosis. Therefore, these findings highlight the necessity of including assessments for both physical activity and sedentary behaviour in routine clinical practice. PR programs have demonstrated improvements in exercise capacity and health related quality of life in patients with bronchiectasis. However, there is no evidence related to the sustainability of the effects achieved by the exercise training and the importance of the behaviour change as a challenge in the management of patients with bronchiectasis [33]. Hence, more observational and interventional studies are also needed to describe and improve physical activity and sedentary behaviour in the bronchiectasis population. In terms of physical activity intensity, the group with ≥3 exacerbations were least active (lowest MVPA and steps per day, with the highest sedentary time) compared with the groups that had 0 or 1–2 exacerbations during follow-up. There was no difference when assessing light physical activity and exercise capacity. This finding is consistent with our previous study where hospitalised patients walked fewer steps per day, spent more time being sedentary, and had lower levels of MVPA compared with their peers who were not hospitalised. Although the intensity of physical activity seems related to a reduction in exacerbation risk and disease severity, more studies are needed for clarification. Bradley et al. [21] reported that MVPA in bouts of ≥10min correlated with QoL-B Social Functioning and that patients with moderate/severe disease spent significantly less time in daily total MVPA. In our study, social, physical, and role function domains of the QoL-B were statistically different between groups at follow-up, and these differences were greater than the minimal

important difference [34]. It seems that low physical activity and high sedentary behaviour could be associated with a higher decline in quality of life after one year of follow-up.

Exacerbations, with or without hospitalisation, hasten acute physical activity deterioration and inactivity in patients with COPD [35–40]. However, the determinants of physical activity change over time are poorly understood [5]. In our longitudinal analysis, 18 patients (34%) switched from more active or non-sedentary groups to more inactive and/or sedentary groups over one year. Among those patients, 10 (55%) switched directly to the worst group, and except for the number of exacerbations, not other clinical or functional characteristic (i.e., BSI score, lung function, dyspnoea, or exercise capacity) was associated with this change. Likewise, Bradley et al. [21] reported that neither lung function (FEV_1% predicted) nor disease severity (BSI score) was correlated with sedentary behaviour in patients with bronchiectasis. Data collected from patients with COPD have shown that physical activity decliners vary from 35% to 59% over time [41,42], but the clinical characteristics could not predict or explain the subsequent patterns of decline, included the number of exacerbations [42–45]. This indicates that the common clinical and functional assessments are unsuitable for use as indicators of risk of physical activity decline and/or increase in sedentary behaviour, which further highlights the need for further longitudinal and objective assessment in clinical settings. Moving forward, the whole spectrum of those behaviours must be included, accounting for the potential impacts of psychological, interpersonal, social, and environmental correlates in the assessment [5,42,46].

A major strength of our study is the use of validated and objective devices to assess physical activity and sedentary behaviour over a one year follow-up period. The results provide novel and valuable information that will require allied respiratory health professionals to design interventions that can enhance physical activity and reduce sedentary behaviour in patients with bronchiectasis.

However, the study also has limitations. The sample size ($n = 53$) may result in a large type II error and conclusions that can be drawn are limited. This limitation notwithstanding, the rigorous approach to the study underpins our confidence in its findings and their clinical relevance. In addition, possible over-fitting and instability of the variables due to the limited sample size in the logistic regression model evaluating the change in physical activity and sedentary behaviour after one year in patients with bronchiectasis, was measured by internal validation using ordinary nonparametric bootstrapping, which demonstrated robust results. Other measurements related to physical activity and sedentary behaviour, such as muscle strength, were missing and may have improved the analysis. This should be addressed in future research. Considering the heterogeneity of physical activity and sedentary behaviour levels among countries and cultures, the study results may not be generalizable to other settings. Further studies are, therefore, needed, with larger number of patients included that target different bronchiectasis populations in other regions or medical settings.

5. Conclusions

In this broad assessment of clinical, functional, and sociodemographic factors, a decline in physical activity levels and increase in sedentary behaviour over one year in patients with bronchiectasis was independently associated with the number of exacerbations. Exacerbation prevention may appear as a key factor in relation to physical activity and sedentary behaviour in patients with bronchiectasis.

Author Contributions: V.A.-S. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. V.A.-S. designed, developed the study protocol and collected the data from patients. V.A.-S., A.A.-E. and E.G.-S. participated in the statistical analysis, data interpretation and in the writing of the manuscript. V.A.-S, A.A.-E, P.O., L.F.-B., L.B., R.A., E.G.-S., and A.T. have read the final version of the manuscript, fully approve it and qualify for authorship.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Clinical Research Ethics Committee of the Hospital Clinic (Ethics Approval Reference: HCB/2016/0012).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

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DISCUSSIÓ

La següent discussió general complementa les discussions de cada un dels manuscrits que conformen la present Tesi Doctoral, amb l'objectiu de proporcionar una interpretació més àmplia e integrada dels resultats obtinguts en els diferents projectes de recerca duts a terme. La discussió general s'articula en relació a: (i) les aguditzacions com a element crucial en les bronquièctasis, i (ii) el paper de la fisioteràpia respiratòria en el maneig de les bronquièctasis.

Les aguditzacions com a element crucial en les bronquièctasis

Les aguditzacions són una pedra angular en les bronquièctasis per l'elevat cost sanitari i l'impacte negatiu en el pronòstic de la malaltia [75]. Específicament, quan s'aïlla *Pseudomonas aeruginosa* a l'esput (12-27% dels pacients amb bronquièctasis) s'associa a un pitjor pronòstic de la malaltia, augmentant el risc a morir, hospitalitzar i aguditzar [2], [36]. La detecció avançada de la *Pseudomonas aeruginosa* seguit d'un tractament adequat, podria reduir la colonització bronquial i, per tant, millorar el pronòstic de la malaltia. En aquesta direcció, les tècniques microbiològiques de diagnòstic ràpid, la identificació de biofilms així com la presència d'un fenotip mucoid o no mucoid, són i seran essencials en el maneig dels pacients amb bronquièctasis. L'avaluació de la viscoelasticitat de l'esput, tot i que necessita d'una formació i equipament específics, pot associar-se com a factor de virulència de la generació de biofilms [76] i com a marcador d'infecció de la *Pseudomonas aeruginosa* [77]. Tal i com s'esmena a l'article 1, la incorporació, en un futur, de les mesures viscoelàstiques dels esputs dels pacients amb bronquièctasis sembla ser una eina útil que podria ajudar en el diagnòstic i personalització del tractament, afectant directament al pronòstic de la malaltia.

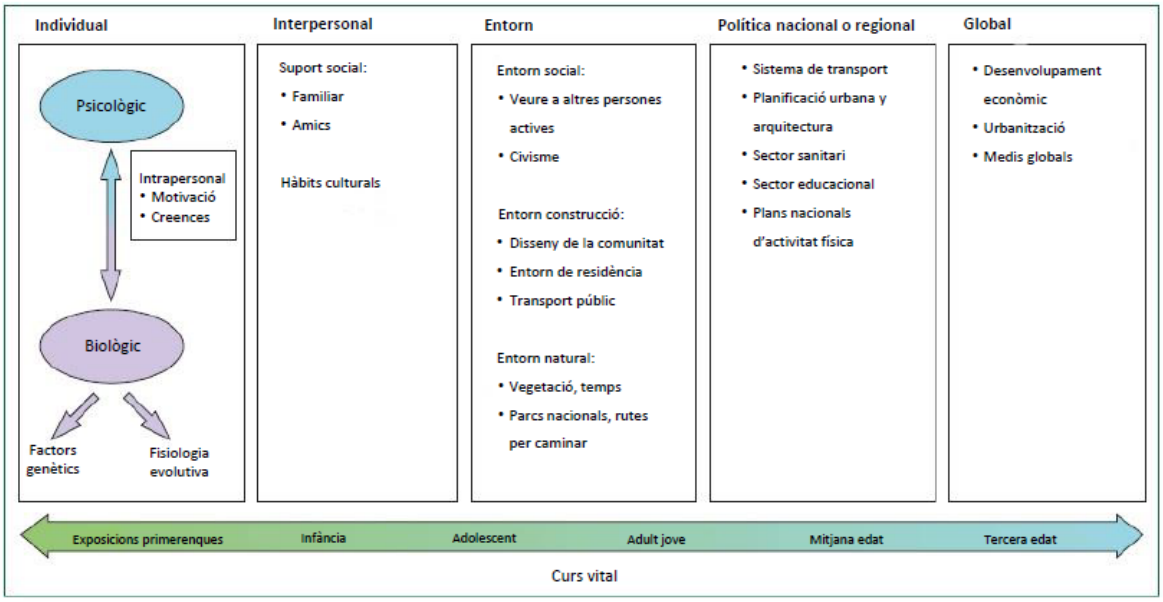
Un dels principals objectius clínics i de recerca és el de reduir el número, la severitat i espaiar els episodis d'agudització dels pacients amb bronquièctasis; ja que estan relacionats amb un augment de la morbimortalitat [78]. Segons els articles 2 i 3 de la present Tesi Doctoral, s'ha pogut descriure per primera vegada una associació entre l'activitat física, el sedentarisme i les aguditzacions (tant lleus com greus). Caminar <6.290 passes per dia o tenir un comportament sedentari ≥7,8 hores per dia incrementa el risc d'hospitalitzar per una agudització de bronquièctasis al cap d'un

any. Específicament el comportament sedentari incrementa quasi 6 cops aquest risc (article 2). Davant la manca d'evidència o estudis similars en bronquièctasis, no es pot analitzar la consistència de les troballes però aquests resultats estan en línia amb altres estudis realitzats en malalties similars, com la MPOC, on s'ha descrit que existeix una clara relació entre els efectes de l'activitat física amb el risc a aguditzar i la mortalitat [70]. Els pacients amb bronquièctasis són més actius i menys sedentaris que els pacients amb MPOC, però comparteixen la característica que són menys actius i més sedentaris que la població sana [69], [79]. Per tant, com passa amb els pacients amb MPOC, podria existir una impacte entre l'activitat física i el sedentarisme dels pacients amb bronquièctasis i variables clíniques com la pèrdua de funció pulmonar i la mortalitat. Estudis longitudinals que avaluïn aquesta possible associació poden donar resposta a aquesta manca d'evidència.

Entendre els determinants que estan relacionats amb la realització o no d'activitat física, és essencial pel desenvolupament d'intervencions, per guiar projectes de recerca i per millorar el maneig dels pacients [70]. Bauman A, et al. [80] va descriure que per entendre l'activitat física cal tenir en compte no tant sols els determinants individuals sinó també els interpersonals, de l'entorn, així com les polítiques regionals i nacionals, incloent els determinants globals (**Figura 4**). Tot i així, esbrinar quins són és un procediment complex i moltes vegades esbiaixat per una recollida de dades limitada. D'acord amb l'article 3 de la present Tesi, l'únic determinant clínic relacionat amb un canvi conductual en activitat física i sedentarisme en els pacients amb bronquièctasis és el número d'aguditzacions durant l'any de seguiment. De nou, si es compara amb els pacients amb MPOC, aquests resultats concorden amb els de Demeyer H, et al. [81], on després d'un any de seguiment, els pacients amb MPOC que van tenir ≥2 aguditzacions o una hospitalització són els que van tenir una pèrdua més significativa en les passes caminades per dia en comparació amb els que es van aguditzar < 2 vegades. Un estudi recent publicat per Cordova-Rivera L, et al. [79] va observar que els pacients amb bronquièctasis tenien un nivell de sedentarisme semblant als que pateixen asma severa però inferior al dels pacients amb MPOC. A més, tenir nivells baixos en conducta sedentària es va associar a una millor capacitat a l'exercici, estat de salut i menys dispnea en els pacients amb bronquièctasis i en MPOC

moderada-severa. Aquests resultats afegeixen informació rellevant sobre el comportament dels pacients amb bronquièctasis en comparació a dues malalties respiratòries cròniques d'alt impacte clínic com la MPOC i l'asma, però cal tenir present que el disseny de l'estudi era transversal i, per tant, no podem determinar si és la conducta sedentària la que afecta a les variables de salut o si és al contrari. Per tant, calen estudis on s'incloguin altres variables del model sòcio-ecològic proposat per Bauman, per entendre quins altres determinants poden modificar el comportament actiu i sedentari en pacients amb bronquièctasis.

Figura 4. Model sòcio-ecològic dels determinants d'activitat física (adaptat de Bauman A, et al. [80])

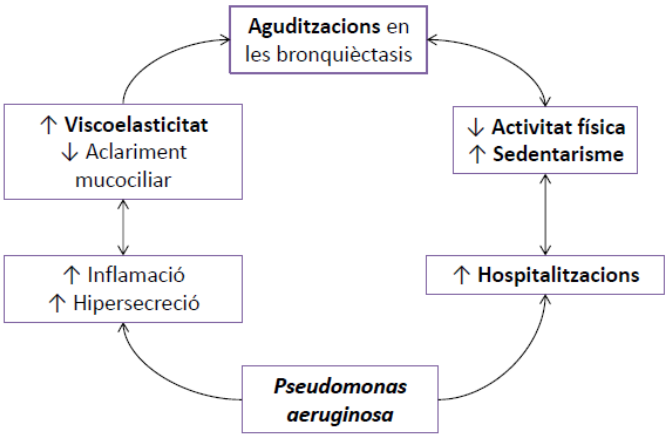


Segons els resultats dels articles 2 i 3 podem dir que en pacients amb bronquièctasis (a) l'activitat física i el sedentarisme són determinants per hospitalitzar degut a una agudització, i (b) les aguditzacions són un determinant per alterar negativament l'activitat física i el sedentarisme. Per tant, sembla ser que hi ha una relació bidireccional entre l'activitat física i el sedentarisme amb les aguditzacions dels pacients amb bronquièctasis. Aquest fet fa pensar en la necessitat d'incorporar l'avaluació objectiva de l'activitat física i el sedentarisme durant la pràctica clínica

habitual, ja que podria ser essencial donada la relació establerta de manera indirecta amb el pronòstic de la malaltia.

Dels resultats de la present Tesi Doctoral se'n pot derivar una proposta de cercle viciós (**Figura 5**) que emmarcaria els allaus més rellevants i el seu impacte clínic en aquests pacients. El qual caldria corroborar i validar amb nous estudis [82].

Figura 5. Proposta de cercle viciós segons els resultats de la present Tesi Doctoral



El paper de la Fisioteràpia respiratòria en el maneig de les bronquièctasis

La tos productiva crònica pot afectar a un 98% de la població amb bronquièctasis [4], sent capaç de generar obstrucció de la via aèria i taps mucosos, afavorint la colonització bacteriana [83].

La guia publicada al 2019 per la *British Thoracic Society* (BTS) [84] incorpora la Fisioteràpia respiratòria com a part del tractament en tots aquells pacients amb bronquièctasis que: 1) estan en fase estable, 2) tenen agudització freqüents (≥3), 3) tenen una evolució clínica deteriorada i/o 4) estan en fase d'agudització. Segons aquests criteris, es podria dir que tots els pacients amb bronquièctasi haurien d'estar, almenys avaluats, per un fisioterapeuta expert en Fisioteràpia respiratòria. L'evidència científica demostra i recomana la inclusió de la figura del fisioterapeuta expert en Fisioteràpia respiratòria com una part indispensable dels equips multidisciplinaris que aborden els pacients amb bronquièctasis, per l'avaluació, seguiment i tractament dels

mateixos però malauradament, la implementació de la mateixa en algunes parts del món és molt baixa. Per exemple, destaca un 50 i 25% dels pacients d'Europa i Estats Units qui realitzen Fisioteràpia respiratòria de manera regular [81], [82] comparat amb els 81-100% dels pacients d'Austràlia i Nova Zelanda [83].

Segons la nova proposta de cercle viciós, quan existeix la presència de *Pseudomonas aeruginosa* a l'esput, el cercle viciós d'inflamació – infecció crònica – agudització, podria veure's augmentat de manera significativa (**Figura 5**) [38]. Específicament el fenotip PAm s'associa a un augment de la severitat (en termes d'aguditzacions, hospitalitzacions i afectació radiològica) i pitjors propietats viscoelàstiques de l'esput (article 1). Aquests resultats concorden amb estudis on han descrit que en altres malalties pulmonars cròniques com la MPOC, l'asma o la FQ, la hipersecreció bronquial està associada a un augment de la viscoelasticitat, una disminució en l'aclariment mucociliar [85] i per tant un augment del risc de la colonització bacteriana [86] i un augment del risc a aguditzar. Així doncs, la Fisioteràpia respiratòria podria ser útil per facilitar el drenatge de secrecions d'aquells pacients que: a) se'ls hi aïlla PAm a l'esput i/o b) se'ls identifica un pitjor aclariment mucociliar (degut a un augment de la viscoelasticitat a l'esput); d'aquesta manera s'aconseguiria reduir la càrrega bacteriana i millorar el control de la malaltia. Tot i així, falten estudis que demostrin l'efecte d'aquesta associació en pacients amb bronquièctasis.

Per altra banda les guies de la BTS mencionen que millorar el comportament actiu i reduir el sedentarisme, podria tenir un efecte directe en aquells pacients que tenen aguditzacions freqüents [84]. Aquesta suposició podria veure's recolzada segons els resultats de la present Tesi Doctoral, on a) intervencions que milloren el comportament actiu i redueixen el sedentarisme podrien reduir el número d'hospitalitzacions (article 2) i b) intervencions que milloren el comportament actiu i redueixen el sedentarisme en pacients aguditzats podrien evitar modificacions conductuals (article 3); però calen més estudis per confirmar aquestes hipòtesis.

L'anamnesi dels pacients amb bronquièctasis ha de ser holística, incloent la figura del fisioterapeuta expert en Fisioteràpia respiratòria dins l'equip multidisciplinari. És per això, i derivat dels resultats de la present Tesi Doctoral, que pel maneig dels pacients

amb bronquièctasis caldria tenir en compte altres mesures com l'estudi de la viscoelasticitat de l'esput, l'activitat física i el sedentarisme, ja que poden tenir una repercussió directe en el maneig i el pronòstic de la malaltia.

Limitacions i fortaleses de la Tesi Doctoral

Tot i que les limitacions dels estudis s'han detallat a cada un dels articles originals, cal destacar-ne algunes de la present Tesi Doctoral. Les dades utilitzades en els articles provenen d'un estudi que no tenia com a objectiu principal respondre les hipòtesis per aquesta Tesi Doctoral. Tot i això, i previ a qualsevol anàlisi estadística, es van establir les hipòtesis que es volien comprovar i es va fer un càlcul de la mostra i/o potència estadística per assegurar que la mostra era suficient com per respondre els objectius de cada article. També cal remarcar que la mida de la mostra era petita i els pacients es van reclutar en un sol centre, cosa que podria haver donat lloc a un biaix de selecció i lògicament els resultats no es poden generalitzar.

Com a fortaleses cal destacar que els tres estudis aporten resultats innovadors i pioners en el món de les bronquièctasis, on s'ha fet ús de tècniques d'avaluació objectives i avançades, com la reologia per l'estudi de l'esput i l'accelerometria per l'estudi de l'activitat física i el sedentarisme. A més, el seguiment longitudinal dels pacients ha permès veure relacions entre variables després d'un any. Aquesta Tesi Doctoral proporciona una nova aplicació clínica de l'avaluació de l'activitat física i la viscoelasticitat de l'esput en pacients amb bronquièctasis.

Futures línies de recerca

Els resultats de la present Tesi Doctoral, accentuen la necessitat de seguir investigant en l'abordatge de les bronquièctasis. Futures línies de recerca es podrien centrar en: (a) avaluar l'aplicabilitat clínica de l'anàlisi de les propietats viscoelàstiques de l'esput per optimitzar i personalitzar el tractament de les bronquièctasis; (b) avaluar l'impacte de l'activitat física i el sedentarisme amb el deteriorament d'altres variables clíniques, com la funció pulmonar, la qualitat de vida i la mortalitat, (c) avaluar l'impacte d'altres variables del model sòcio-ecològic com a determinant d'activitat física dels pacients amb bronquièctasis, i (d) investigar l'eficàcia de la implementació de programes que incrementin el comportament actiu i redueixin el sedentarisme, en el número d'aguditzacions en bronquièctasis.

CONCLUSIONS

Els resultats dels tres manuscrits inclosos en la present Tesi Doctoral han permès obtenir les següents conclusions:

- En pacients amb bronquièctasis, l'aïllament del fenotip PAm s'associa amb un augment de la purulència, elasticitat, viscositat i rigidesa de l'esput comparat amb els que s'aïlla PAnom o flora mixta. A més, els pacients amb PAm presenten un perfil clínic més sever, amb un número més elevat d'aguditzacions i hospitalitzacions l'any previ; i més lòbuls afectats al TAC.

- En pacients amb bronquièctasis, existeix una associació entre les hospitalitzacions degudes a una agudització de la malaltia i l'activitat física. Els pacients que hospitalitzen són menys actius i tenen un comportament sedentari més elevat comparat amb els que no hospitalitzen. A més, els pacients que caminen ≤6.290 passos/dia o estan ≥7,8 hores/dia en conducta sedentària, tenen un risc més elevat d'hospitalitzar l'any següent. Independentment, tenir una conducta sedentària de ≥7,8 hores/dia augmenta el risc d'hospitalitzar 5,91 cops.

- La disminució de l'activitat física i l'augment del sedentarisme al cap d'un any, s'associa de manera independent amb les aguditzacions dels pacients amb bronquièctasis.

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APÈNDIX

APÈNDIX 1. Llistat de manuscrits on la doctoranda ha participat com a co-autora

1. Mendez R*, Feced L*, **Alcaraz-Serrano V**, González-Jiménez P, Bouzas L, Alonso R, Martínez-Dolz L, Hervás D, Fernández-Barat L, Torres A, Menéndez R. Cardiovascular Events during and after Bronchiectasis exacerbations and long-term mortality. En revisió a Chest. *Co-autors

2. Menéndez R, Méndez R, Amara-Elori I, Reyes S, Montull B, Feced L, Alonso R, Amaro R, **Alcaraz V**, Fernández-Barat L, Torres A. Systemic Inflammation during and after Bronchiectasis Exacerbations. Impact of *Pseudomonas aeruginosa*. J Clin Med 2020, 9, 2631. doi:10.3390/jcm9082631. IF: 3.303 Q1

3. Ielpo A*, Crisafulli E*, **Alcaraz-Serrano V**, Gabarrús A, Oscanoa P, Scioscia G, Fernández-Barat L, Cillóniz C, Amaro R, Torres A. Aetiological diagnosis in new adult outpatients with bronchiectasis: role of predictors derived from real life experience. Respir Med 2020. 172:106090. doi: 10.1016/j.rmed.2020.106090. IF: 3.095 Q2. *Co-autors

4. Herrero-Cortina B, **Alcaraz-Serrano V**, Torres A, Polverino E. Reliability and minimal important difference of sputum weight in people with bronchiectasis. Respir Care 2020. 65(3). doi: 10.4187/respcare.07175. IF: 2.066 Q3

5. Scioscia G*, Amaro R*, **Alcaraz- Serrano V,** Gabarrus A, Oscanoa P, Fernandez L, Menendez R, Mendez R, Foschino Barbaro M, Torres A. Clinical Factors Associated with a Shorter or Longer Course of Antibiotic Treatment in Patients with Exacerbations of Bronchiectasis: A Prospective Cohort Study. J Clin Med 2019. 8, 1950. doi: 10.3390/jcm8111950. IF: 5.688 Q1. *Co-autors

6. Méndez R, Moscardó A, Latorre A, Feced L, González-Jiménez P, Piró A, **Alcaraz-Serrano V**, Scioscia G, Amaro R, Torres A, Menéndez R. Soluble P-Selectin in acute exacerbations and stable bronchiectasis in adults. Ann Am Thorac Soc 2019. 16(12): 1587-91 doi:10.1513/AnnalsATS.201902-140RL. IF: 4.026 Q2

7. Amaro R, Panagiotaraka M, **Alcaraz V**, Torres A. The efficacy of inhaled antibiotics in non-cystic fibrosis bronchiectasis. Expert Rev Respir Med. 2018 Jul 16. doi: 10.1080/17476348.2018.1500179. IF: 2.607 Q2

8. Herrero-Cortina B, **Alcaraz V**, Vilaró J, Torres A, Polverino E. Impact of hypertonic saline solutions on sputum expectoration and their safety profile in patients with bronchiectasis: a randomized crossover trial. J Aerosol Med Pulm Drug Deliv. 2018 Jun 7. doi: 10.1089/jamp.2017.1443. IF: 2.927 Q2

9. Polverino E, Rosales-Mayor E, Benegas M, Menendez R, **Alcaraz-Serrano V**, Ansotegui E, Montull B, Girón RM, Cisneros C, Vendrell M, Muñoz G, Marcos MA, Sanchez M, Torres A. Pneumonic and non-pneumonic exacerbations in bronchiectasis: clinical and microbiological differences. J Infect. 77 (2018): 99-106. doi: 10.1016/j.jinf.2018.04.006. IF: 4.603 Q1

10. Menéndez R, Méndez R, Polverino E, Rosales-Mayor E, Amara-Elori I, Reyes S, Sahuquillo-Arce JM, Fernández-Barat L, **Alcaraz V**, Torres A. Risk factors for multidrug-resistant pathogens in bronchiectasis exacerbations. BMC Infect Dis. 2017 Sep 30;17(1):659 doi: 10.1186/s12879-017-2754-5. IF: 2.768 Q2

11. Rosales-Mayor E, Polverino E, Raguer L, **Alcaraz V**, Gabarrus A, Ranzani O, Menendez R, Torres A. Comparison of two prognostic scores (BSI and FACED) in a Spanish cohort of adult patients with bronchiectasis and improvement of the FACED predictive capacity for exacerbations. PLoS One. 2017 Apr 6; 12(4):e0175171. doi: 10.1371/journal.pone.0175171. IF: 2.806 Q1

12. Herrero-Cortina B, Vilaró J, Martí JD, San Miguel M, **Alcaraz V**, Polverino E. Short-term effects of three slow-expiratory airway clearance techniques in non-cystic fibrosis bronchiectasis: a randomized crossover trial. Physiotherapy. 2015 Dec 1. pii: S0031-9406(15)03852-3. IF: 1.911 Q1

13. Polverino E, Cilloniz C, Menendez R, Gabarrus A, Rosales-Mayor E, **Alcaraz V**, Terraneo S, Puig de la Bella Casa J, Mensa J, Ferrer M, Torres A. Microbiology and outcomes of community acquired pneumonia in non cystic-fibrosis bronchiectasis patients. J Infect. 2015 71(1): 28-36. doi: 10.1016/j.jinf.2015.03.009. IF: 4.441 Q1

APÈNDIX 2. Llistat de projectes de recerca finançats durant el període de doctorat

1.1 "¿Es suficiente una única sesión diaria que combine la nebulización de suero hipertónico y técnicas de drenaje de secreciones para conseguir beneficios clínicos a largo plazo en los pacientes con bronquiectasias? Ensayo clínico aleatorizado de no

inferioridad". Finançat per SEPAR, codi: 891/2019. Figura de la doctoranda: investigadora principal.

1.2 "*Nuevos métodos para diagnosticar los biofilms de Pseudomonas aeruginosa en el esputo de los pacientes con enfermedad pulmonar obstructiva crónica y bronquiectasias no fibrosis quística*". Finançat per l'Institut de Salut Carlos III, codi: FIS PI1800145. Figura de la doctoranda: investigadora col·laboradora.

1.3 "*Importancia de las biopelículas de Pseudomonas aeruginosa en las agudizaciones en pacientes con bronquiectasias con y sin enfermedad pulmonar obstructiva crónica*". Finançat per SEPAR, codi: 628/2018. Figura de la doctoranda: investigadora col·laboradora.

1.4 "*Rehabilitación respiratoria y fisioterapia respiratoria en pacientes con bronquiectasias no derivadas de fibrosis quística*". Finançat per SEPAR, codi: 052/2017. Figura de la doctoranda: investigadora principal.

1.5 "*Epidemiología y caracterización clínica-microbiológica de las agudizaciones en las bronquiectasias no asociadas a fibrosis quística*". Finançat per SEPAR, codi: 106/2012. Figura de la doctoranda: investigadora col·laboradora.

A més, la doctoranda ha estat coordinadora a l'Hospital Clínic de més de 10 assajos clínics en bronquièctasis.

APÈNDIX 3. Llistat de comunicacions acceptades i presentades a congressos nacionals i internacionals

3.1. Congressos Nacionals de la Societat Espanyola de Pneumologia (SEPAR)

3.1.1 53 Congrés SEPAR, virtual 2020

- Pòster discussió: *"Asociación entre actividad física y riesgo a hospitalizar en pacientes con bronquiectasias".* Elena Gimeno, **Victoria Alcaraz**, Giulia Scioscia, Albert Gabarrús, Adrià Navarro, Beatriz Herrero, Rosanel Amaro, Laia Fernández, Antoni Torres.

3.1.2 52 Congrés SEPAR, Santiago de Compostela 2019

- Pòster discussió: "*Pseudomonas aeruginosa, una bacteria que afecta las propiedades viscoelásticas del esputo y a la clínica de los pacientes con bronquiectasias".* **Victoria Alcaraz**, Laia Fernández, Giulia Scioscia, Joan Llorens, Elena Gimeno, Beatriz Herrero, Rosanel Amaro, Antoni Torres.

- Pòster exposició: "*Validación de un modelo diagnóstico etiológico en adultos con bronquiectasias"*. Giulia Scioscia, Antonella Ielpo, Ernesto Crisafulli, **Victoria Alcaraz**, Albert Gabarrús, Patricia Oscanoa, Rosanel Amaro, Antoni Torres.
- Pòster exposició: "*Características del paciente con agudización por bronquiectasias y su influencia en la duración del tratamiento antibiótico"*. Patricia Oscanoa, Rosanel Amaro, Albert Gabarrús, **Victoria Alcaraz**, Giulia Scioscia, Rosario Menéndez, Raúl Méndez, Antoni Torres.
- Pòster exposició: "*Análisis comparativo de la respuesta inflamatoria sistémica en bronquiectasias durante las exacerbaciones y en situación de estabilidad clínica"*. Laura Feced, Paula González, Raúl Méndez, **Victoria Alcaraz**, Rosanel Amaro, Giulia Scioscia, Soledad Reyes, Antoni Torres, Rosario Menéndez.

3.1.3 51 Congrés SEPAR, Mallorca 2018

- Pòster discussió: "*En pacientes con bronquiectasias, ¿la presencia de Pseudomonas aeruginosa en el esputo altera sus propiedades reológicas?"*. **Victoria Alcaraz**, Joan Llorens, Elena Gimeno, Edmundo Rosales, Beatriz Herrero, Laia Fernández, Eva Polverino, Rosanel Amaro, Antoni Torres.
- Pòster discussió: "*Factores relacionados con la exacerbación de bronquiectasias por Pseudomonas aeruginosa multirresistente"*. Paula González, Raúl Méndez, Isabel Amara, Rosanel Amaro, **Victoria Alcaraz**, Soledad Reyes, Antoni Torres, Rosario Menéndez.
- Pòster discussió: "*Inflamación sistémica durante las exacerbaciones de bronquiectasias"*. Isabel Amara, Raúl Méndez, Soledad Reyes, Eva Polverino, Alba Piró, **Victoria Alcaraz**, Rosanel Amaro, Ricardo Alonso, Marta Suescun, Antoni Torres, Rosario Menéndez.

3.1.4 50 Congrés SEPAR, Madrid 2017

- Pòster exposició: "*Evaluación de la actividad física en pacientes con bronquiectasias no derivadas de fibrosis quística"*. **Victoria Alcaraz**, Edmundo Rosales, Eva Polverino, Elena Gimeno, Adrià Navarro, Rosanel Amaro, Antoni Torres.

3.1.5 49 Congrés SEPAR, Granada 2016

- Pòster discussió: "*Efectos del suero hipertónico (7%) sobre el drenaje bronquial en pacientes con bronquiectasias: ensayo aleatorizado, cruzado y doble ciego"*. **Victoria Alcaraz**, Beatriz Herrero, Jordi Vilaró, Edmundo Rosales, Antoni Torres, Eva Polverino.
- Pòster discussió: *"Factores relacionados con la estancia hospitalaria en las bronquiectasias no debidas a fibrosis quística".* Tomás Posadas, Raúl Méndez,

Isabel Amara, Beatriz Montull, Emilio Ansotegui, Edmundo Rosales, **Victoria Alcaraz**, Eva Polverino, Antoni Torres, Rosario Menéndez.

- Pòster discussió: "*Efecto del uso previo de corticoides inhalados en pacientes con bronquiectasias que presentan una agudización".* Edmundo Rosales, **Victoria Alcaraz**, Isabel Amara, Beatriz Montull, Alexandra Gimeno, Eric Rojas, Montserrat Vendrell, Rosa Maria Girón, Rosario Menéndez, Antoni Torres, Eva Polverino.
- Pòster discussió: *"Neumonía en las Bronquiectasias no asociadas a Fibrosis Quística (BQnoFQ): factores predictores".* Edmundo Rosales, **Victoria Alcaraz**, Isabel Amara, Emilio Ansotegui, Alexandra Gimeno, Gerard Muñoz, Montserrat Vendrell, Rosa María Girón, Rosario Menendez, Antoni Torres, Eva Polverino.
- Pòster discussió: *"Caracterización de la agudización de bronquiectasias no fibrosis quística causada por Pseudomonas aeruginosa*". Isabel Amara, Edmundo Rosales, Beatriz Montull, Tomás Posadas, Raúl Menéndez, Alexandra Gimeno, **Victoria Alcaraz**, Emilio Ansotegui, Eva Polverino, Antoni Torres, Rosario Menéndez.

3.1.6 48 Congrés SEPAR, Gran Canària 2015

- Pòster discussió: "*Agudizaciones y neumonías en las Bronquiectasias no asociadas a Fibrosis Quística (BQ-noFQ): Características clínicas y microbiológicas".* **Victoria Alcaraz**, Edmundo Rosales, Rosa Maria Girón, Rosario Menendez, Montserrat Vendrell, Antoni Torres, Eva Polverino.

3.1.7 47 Congrés SEPAR, Bilbao 2014

- Comunicació oral: *"Cuantificación del esputo como variable objetiva en un ensayo clínico cruzado en BQ-noFQ: fiabilidad y sensibilidad al cambio".* Beatriz Herrero, Eva Polverino, Marta San Miguel, **Victoria Alcaraz**, Dani Martí, Jordi Vilaró, Antoni Torres.

3.2 Congressos Internacionals de la European Respiratory Society (ERS)

3.2.1 ERS International Congress, Virtual 2020

- Pòster discussion: *"Association between physical activity and risk of hospitalisation in bronchiectasis".* **Victoria Alcaraz**, Elena Gimeno Giulia Scioscia, Albert Gabarrús, Adrià Navarro, Beatriz Herrero, Rosanel Amaro, Laia Fernández, Antoni Torres.

3.2.2 ERS International Congress, Madrid 2019

- Pòster discussió: "*Mucoid Pseudomonas aeruginosa alters sputum viscoelastic properties in patients with non-cystic fibrosis bronchiectasis*". **Victoria Alcaraz**, Laia Fernandez, Giulia Scioscia, Joan Llorens, Elena Gimeno, Beatriz Herrero, Nil Vazquez, Albert Gabarrus, Rosanel Amaro, Rosario Menendez, Antoni Torres.
- Comunicació oral: "*Longitudinal examination of bronchiectasis sputum allows the early Pseudomonas aeruginosa detection*". Laia Fernández, Nil Vázquez, **Victoria Alcaraz**, Lena Lingren, Leticia Bueno, Daniel Martinez, Elena Gonzalvo, Rosanel Amaro, Adrian Ceccato, Giulia Scioscia, Laura Muñoz, Jorge Puig, Niels Hoiby, Antoni Torres.
- Pòster discussió: "*Platelet activation correlates with the severity of the disease in bronchiectasis*". R Méndez, A Moscardo, A Latorre, A Piro, P Gonzalez, L Feced, L Bouzas, R Amaro, **V Alcaraz**, A Torres, R Menendez.
- Pòster exposició: "*Acute exacerbation of bronchiectasis and the impact on the duration of antibiotic therapy*". Patricia Oscanoa, Rosanel Amaro, Albert Gabarrús, **Victoria Alcaraz**, Giulia Scioscia, Rosario Menéndez, Raúl Méndez, Antoni Torres.
- Pòster exposició: "*Validation of an etiological diagnostic model in adults with a diagnosis of bronchiectasis*". Giulia Scioscia, Antonella Ielpo, Ernesto Crisafulli, **Victoria Alcaraz**, Albert Gabarrús, Patricia Oscanoa, Rosanel Amaro, Antoni Torres.
- Pòster exposició: "*The role of systemic markers of inflammation in bronchiectasis*". Giulia Scioscia, Rosanel Amaro, **Victoria Alcaraz**, Albert Gabarrús, Patricia Oscanoa, Rosario Menéndez, Raúl Méndez, Antoni Torres.
- Pòster exposició: "*Heart rate recovery after 6-min walk test in people with bronchiectasis. A cross-sectional study*". Juanan Saez, Beatriz Herrero, **Victoria Alcaraz**, Marina Francin, Marta San Miguel, Maria Hernández, Elena Gimeno, Antoni Torres, Ane Arbillaga.

3.2.3 ERS International Congress, Paris 2018

- Pòster exposició: "*Does Pseudomonas aeruginosa infection alter sputum viscoelastic properties in bronchiectasis patients?"* **Victoria Alcaraz**, Joan Llorens, Elena Gimeno, Albert Gabarrús, Beatriz Herrero, Edmundo Rosales, Laia Fernández, Eva Polverino, Rosanel Amaro, Antoni Torres.

3.2.4 ERS International Congress, Milà 2017

- Pòster exposició: "*Physical activity assessment in non-cystic fibrosis bronchiectasis*". **Victoria Alcaraz**, Elena Gimeno, Edmundo Rosales, Eva Polverino, Adrià Navarro, Rosanel Amaro, Antoni Torres.

3.2.5 ERS International Congress, Londres 2016

- Comunicació oral: "*Effects of hypertonic saline on sputum clearance in patients with bronchiectasis".* **Victoria Alcaraz**, Beatriz Herrero, Jordi Vilaró, Edmundo Rosales, Antoni Torres, Eva Polverino.
- Comunicació oral: *"Pneumonic vs non-pneumonic exacerbations in bronchiectasis".* Edmundo Rosales, Rosario Menendez, **Victoria Alcaraz**, Emilio Ansotegui, Beatriz Montull, Rosa Maria Girón, Carolina Cisneros, Montserrat Vendrell, Gerard Muñoz, María Ángeles Marcos, Antonio Torres, Eva Polverino.
- Pòster discussió: *"Chronic inhaled corticosteroids in patients with bronchiectasis who suffer an exacerbation".* Edmundo Rosales, **Victoria Alcaraz**, Isabel Amara, Beatriz Montull, Alexandra Gimeno, Gerard Muñoz, Montserrat Vendrell, Rosa Maria Girón, Rosario Menendez, Eva Polverino, Antoni Torres.

3.2.6 ERS International Congress, Àmsterdam 2015

- Pòster discussió: "*Exacerbations and pneumonia in bronchiectasis: clinical and microbiological characterization*". **Victoria Alcaraz**, Edmundo Rosales, Rosa Maria Girón, Rosario Menendez, Montserrat Vendrell, Antoni Torres, Eva Polverino.

3.2.7 ERS International Congress, Múnich 2014

- Pòster exposició: "*Wet sputum as an objective outcome in a randomized crossover train in NCF-BE: Reliability and responsiveness*". Beatriz Herrero, Eva Polverino, Marta San Miguel, **Victoria Alcaraz**, Dani Marti, Jordi Vilaró, Antoni Torres.

3.3 Congrés Mundial de Bronquièctasis

3.3.1 4t World Bronchiectasis Conference, Virtual 2020

- Pòster discussió: *"Association between physical activity and risk of hospitalisation in bronchiectasis".* **Victoria Alcaraz**, Elena Gimeno Giulia Scioscia, Albert Gabarrús, Adrià Navarro, Beatriz Herrero, Rosanel Amaro, Laia Fernández, Antoni Torres.
- Pòster discussió: "*High level of resistance to recomended antimicrobial agents in Pseudomonas aeruginosa from patients with bronchiectasis*". Roberto Cabrera, Laia Fernández, Nil Vázquez, **Victoria Alcaraz**, Leticia Bueno, Rosanel Amaro, Patricia Oscanoa, Rubén López, L Muñoz, Jordi Vila, Antoni Torres.
- Pòster discussió: "*Longitudinal assessment of Health related quality of life in patients with bronchiectasis colonized by Pseudomonas aeruginosa*". Leticia Bueno, **Victoria Alcaraz**, Laia Fernández, Giulia Scioscia, Patricia Oscanoa, Nil

Vázquez, Alexandre López, Albert Gabarrús, Rosanel Amaro, Adrián Ceccato, Rubén López, Antoni Torres.

3.3.2 1r World Bronchiectasis Conference, Hannover 2016

- Comunicació oral: *"Pneumonic vs non-pneumonic exacerbations in bronchiectasis".* Edmundo Rosales, **Victoria Alcaraz**, Rosario Menendez, Emilio Ansotegui, Beatriz Montull, Rosa Maria Girón, Carolina Cisneros, Montserrat Vendrell, Gerard Muñoz, María Angeles Marcos, Eva Polverino, Antoni Torres.
- Pòster exposició: *"Effects of hypertonic saline on sputum clearance in patients with bronchiectasis".* **Victoria Alcaraz**, Beatriz Herrero, Jordi Vilaró, Edmundo Rosales, Antoni Torres, Eva Polverino.
- Pòster exposició: *"Exacerbations by Pseudomonas aeruginosa in patients with bronchiectasis".* Edmundo Rosales, **Victoria Alcaraz**, Laura Raguer, Rosario Menendez, Emilio Ansotegui, Beatriz Montull, Rosa María Girón, Carolina Cisneros, Montserrat Vendrell, Gerard Muñoz, María Ángeles Marcos, Eva Polverino, Antoni Torres.
- Pòster exposició: *"Evaluation of two prognostic scores in adult patients with non-cystic fibrosis bronchiectasis".* Edmundo Rosales, Laura Raguer, **Victoria Alcaraz**, Eva Polverino, Antoni Torres.

3.4 Congressos de la Societat Catalana de Pneumologia (SOCAP)

3.4.1 XXXVII Congrés de la SOCAP, Terrassa 2019

- Comunicació oral: "*La Pseudomonas aeruginosa mucoid altera les propietats viscoelàstiques de l'esput en pacients amb bronquièctasis".* **Victoria Alcaraz**, Laia Fernández, Giulia Scioscia, Joan Llorens, Elena Gimeno, Beatriz Herrero, Nil Vázquez, Jordi Puig, Albert Gabarrús, Rosanel Amaro, Antoni Torres.

3.4.2 XXXVI Congrés de la SOCAP, Lleida 2018

- Pòster discussió: "*Avaluació de l'activitat física en pacients amb bronquièctasis".* **Victoria Alcaraz**, Elena Gimeno, Adrià Navarro, Edmundo Rosales, Eva Polverino, Albert Gabarrús, Rosanel Amaro, Antoni Torres.
- Pòster discussió: "*Efectes del sèrum hipertònic (7%) sobre el drenatge bronquial en pacients amb bronquièctasis*". **Victoria Alcaraz**, Beatriz Herrero, Jordi Vilaró, Edmundo Rosales, Eva Polverino, Antoni Torres.

3.5 Altres congressos

3.5.1 1r Congreso Nacional COVID-19, Virtual 2020.

- Comunicació oral: *"Indicación de Fisioterapia en Covid-19: opinión de los médicos especialistas".* Raúl Escudero, Teresa García-Barredo, **Victoria Alcaraz**, Mireia Pardàs, Antonio Tomás.

3.5.2 XII Jornada de Formación CIBERES, Escuela Nacional de Sanidad, Madrid 2019.

- Comunicació oral: *"Antimicrobial Susceptibility and Molecular Mechanisms of Resistance in Pseudomonas aeruginosa Strains Isolated from Patients with Bronchiectasis"*. Roberto Cabrera, Laia Fernández, Nil Vázquez, **Victoria Alcaraz**, Leticia Bueno, Rosanel Amaro, Patricia Oscanoa, Rubén López, Muñoz L, Jordi Vila, Antoni Torres.

3.5.3 European Society of Clinical Microbiology and Infectious Diseases (ESCMID), Madrid 2018.

- Pòster exposició: *"The biofilm ring test, a rapid method for routine analysis of Pseudomonas aeruginosa in sputum from bronchiectasis patients with and without COPD"*. Laia Fernández, Anna Motos, **Victoria Alcaraz**, Rosanel Amaro, Adrián Ceccato, Leticia Bueno, A Clement, C Provot, Jordi Puig, Nil Vázquez, L Muñoz, Jordi Vila, Antoni Torres.

APÈNDIX 4. Premis, beques i altres fets que la doctoranda vol fer constar durant el període de la Tesi

- Primer premi a la millor comunicació de l'Àrea d'Infermeria i Fisioteràpia del XXXVII Congrés de la Societat Catalana de Pneumologia (Terrassa 2019).
- Guanyadora d'una beca pel projecte Sàhara Salut, a l'any 2017, per realitzar treballs de formació i capacitació dels professionals saharauis. Estància realitzada al març 2018.
- Primer premi a la millor comunicació de l'Àrea d'Infermeria de l'Hospital Clínic a les "Jornades d'Innovació, 2017".
- Guanyadora d'una beca Respira els anys 2016 i 2017 per assistir al congrés Nacional de la SEPAR per l'alta puntuació de la comunicació enviada.
- Vocal de l'Àrea de Fisioteràpia Respiratòria de la SEPAR des del 2018.
- Membre de la "Task Force" de drenatge de secrecions en bronquièctasis de la ERS.