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La bacteriemia como marcador pronóstico de la neumonía neumocócica adquirida en la comunidad en pacientes inmunocompetentes hospitalizados

Tesis Doctoral

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"... stay hungry, stay foolish"

Steve Jobs, Universidad de Stanford, California, 2005

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I. INTRODUCCION

A pesar del avance experimentado en los últimos cien años en el conocimiento, manejo y tratamiento de las enfermedades infecciosas, la neumonía continúa siendo en la actualidad un problema de salud mundial. De entre los múltiples microorganismos responsables de este cuadro, el neumococo es probablemente el más estudiado en la literatura. Sin embargo existen varios aspectos de esta enfermedad que son motivo de controversia. Los estudios que forman esta Tesis Doctoral pertenecen a una misma línea de investigación llevada a cabo con el objetivo de tratar de esclarecer el papel que la presencia de una bacteriemia tiene en la evolución y en el pronóstico de los pacientes diagnosticados de una neumonía neumocócica adquirida en la comunidad. Pensamos que los resultados obtenidos y publicados en revistas de amplia difusión internacional aportan una información relevante y útil en el manejo de esta entidad.

Las infecciones del tracto respiratorio inferior constituyen una de las principales causas de mortalidad en el mundo (1). Entre ellas, la neumonía adquirida en la comunidad (NAC) es la infección respiratoria de mayor gravedad con una incidencia anual de 2-5 casos/1.000 habitantes/año en la población adulta (2-4). Representa en su conjunto, la primera causa de muerte por infección y la tercera de hospitalización en el grupo de pacientes de más de 65 años (5,6). Entre un 20 y un 40% de los pacientes con una neumonía requieren de un ingreso hospitalario y un 5-10% de ellos necesitarán ser admitidos en una unidad de cuidados intensivos (UCI) (7). Pese a las mejoras en los métodos diagnósticos, avances en los cuidados y en los tratamientos antibióticos, la mortalidad de este cuadro sigue siendo elevada y oscila entre el 2-10% de los pacientes hospitalizados en planta convencional al 34-50% de los ingresados en una UCI, especialmente entre aquellos que necesitan ventilación asistida (8,9). Desde un punto de vista económico es responsable de una sobrecarga importante para el sistema sanitario debido fundamentalmente a los costes directos derivados de las hospitalizaciones y de su impacto en la calidad de vida de los pacientes (10,11).

En cuanto a la etiología, a pesar de los avances en las técnicas diagnósticas, el diagnóstico microbiológico de certeza únicamente se consigue en torno al 50% de los casos. Este hecho es debido fundamentalmente a la complejidad para realizar algunas de estas técnicas, lo que dificulta su generalización en la práctica clínica (12-14). Además, la propia NAC en sí misma es una entidad heterogénea causada por diferentes patógenos que van a diferir dependiendo de factores tales como el área geográfica, la presencia de comorbilidades, hábitos tóxicos o la edad (15-18). En los últimos años y coincidiendo con un uso cada vez más extendido de técnicas de diagnóstico molecular basadas en la reacción en cadena de la polimerasa (PCR) para el diagnóstico de las infecciones causadas por virus respiratorios, estamos asistiendo a un incremento en el porcentaje de diagnósticos etiológicos a expensas de un posible y probablemente "ficticio" descenso en el peso que tiene la etiología bacteriana como agente causal de esta entidad. Todo esto hace que sea complicado estimar la prevalencia real de cada patógeno.

Neumonía neumocócica

Streptococcus pneumoniae es el agente etiológico de una NAC identificado con más frecuencia con independencia de la edad y la presencia de enfermedades asociadas en la mayor parte de las series publicadas (18,19). A su vez, el neumococo es el principal responsable de las hospitalizaciones (en planta convencional y/o UCI) y de las muertes por neumonía (10,20). En la era preantibiótica, *S. pneumoniae* era el responsable de más del 75% de los casos de NAC. Sin embargo, en la actualidad es el causante únicamente del 5-15% de los casos en EEUU y del 19% en Europa (Tablas 1 y 2) (13,16,20,21). Entre las causas de este descenso en el número de casos se encuentran el uso universal de la vacuna antineumocócica conjugada 13-valente (PCV-13) en

niños, la vacunación antineumocócica en adultos de grupos de riesgo y la reducción del tabaquismo. Sin embargo, es posible que su incidencia esté realmente infravalorada debido a que, como hemos comentado, el diagnóstico de certeza bacteriológico sólo se consigue, en general, en menos de la mitad de los pacientes con NAC.

Tabla 1. Etiología de la neumonía adquirida en la comunidad según el lugar de tratamiento. Modificada de (20).

Etiología	Lugar de tratamiento		
	Ambulatorio (n = 514) %	Hospital (n = 2521) %	UCI (n = 488) %
Desconocida	68,7	58,7	46,7
Streptococcus pneumoniae	10,9	17,7	22,5
Patógenos intracelulares*	11,3	6,7	7,6
Virus respiratorios	2,9	4,9	2
Haemophilus influenzae	1,6	2,1	1,6
Bacilos entéricos gramnegativos	0,2	0,9	0,6
Staphylococcus aureus	0,2	0,7	1,2
Pseudomonas aeruginosa	0,2	1,5	2,5
Neumonías polimicrobianas	2,9	5,4	11,9
Otros microorganismos	1,2	1,3	3,1

**Legionella pneumophila, Mycoplasma pneumoniae, Clamydophila pneumoniae, Clamydophila psittaci* y *Coxiella burnetii*

La prescripción precoz de un tratamiento antibiótico con la consiguiente reducción en la sensibilidad de las técnicas de diagnóstico bacteriológico clásicas y el uso más restringido de las mismas propuesto actualmente en las guías de práctica clínica, son los factores que podrían favorecer el incremento de los casos de etiología desconocida y en los que el neumococo podría ser el agente causal en una alta proporción de casos (22,23). El empleo de técnicas diagnósticas complejas basadas en

el estudio molecular de patógenos respiratorios y que tienen una mayor rentabilidad diagnóstica parecen sugerir esto (24).

Tabla 2. Etiología de la neumonía adquirida en la comunidad en el Servicio de Neumología del Hospital Universitario Cruces (años 2005-2018).

Etiología	N=3331	%
Desconocida	2156	65,2
Streptococcus pneumoniae	838	25,3
Legionella pneumophila	123	3,7
Otras bacterias atípicas respiratorias	37	1,1
Bacilos entéricos gramnegativos	21	0,6
Otros *Streptococcus*	22	0,6
Haemophilus influenzae	6	0,1
Staphylococcus aureus	9	0,2
Otras bacterias	4	0,1
Virus de la gripe (Influenza) A	105	3,1
Otros virus respiratorios	10	0,3

El desarrollo de la neumonía neumocócica se produce a partir de la colonización de la nasofaringe por *S. pneumoniae* y por lo tanto es más frecuente en edades donde ésta es más elevada, como entre los menores de 2 años y los mayores de 65 años. En los adultos, la incidencia de neumonía neumocócica se incrementa con la edad, el tabaquismo, así como con la presencia de determinadas comorbilidades, principalmente diabetes mellitus, hepatopatía crónica y enfermedades crónicas cardiorrespiratorias (Figura 1 y Tabla 3). Este hecho es especialmente significativo en los pacientes de mayor edad en los que con frecuencia coexisten múltiples de estas enfermedades (25,26).

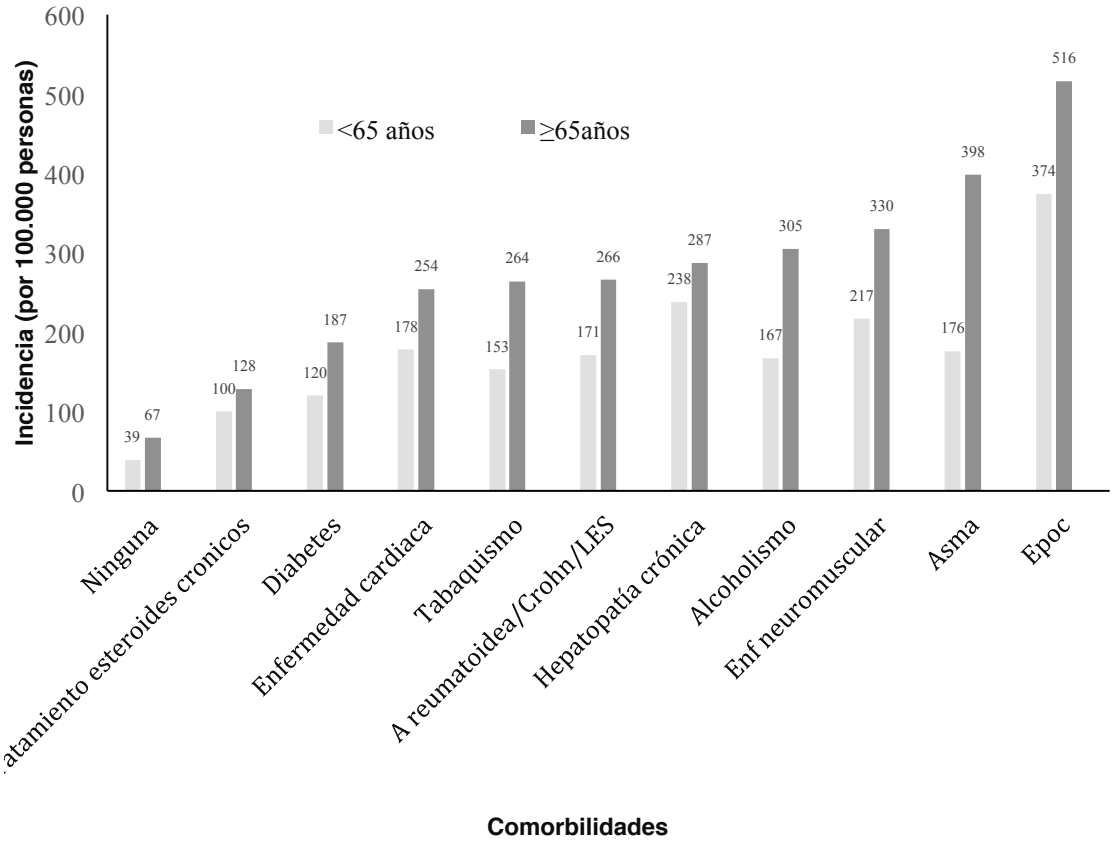

Figura 1. Factores de riesgo asociados a neumonía adquirida en la comunidad por *S. pneumoniae* en función de la edad. Modificado de (26).

El envejecimiento progresivo de la población y el incremento observado en la supervivencia de los pacientes más ancianos debido a la mejora en las condiciones socio-sanitarias en los países desarrollados, ponen de relieve la importancia que este grupo de población tiene desde el punto de vista sanitario. En efecto, conceptos como fragilidad, edad biológica, comorbilidad múltiple o situación funcional aparecen hoy como parámetros para tener en cuenta en la evaluación de los pacientes de más edad con una neumonía (27,28).

Tabla 3. Comorbilidades presentes en 1306 casos de neumonía adquirida en la comunidad por *S. pneumoniae* (Hospital Universitario Cruces y Hospital Universitario Galdakao).

Comorbilidades	Neumonías bacteriémicas N = 561 (%)	Neumonías no bacteriémicas N = 745 (%)
Tabaquismo	184 (32,9)	170 (23)
Alcoholismo	81 (15)	74 (10,3)
EPOC	93 (16,6)	166 (22,3)
Diabetes mellitus	87 (15,5)	139 (18,7)
Insuficiencia cardiaca	77 (13,7)	67 (9)
Enfermedad cerebrovascular	30 (5,3)	47 (6,3)
Enfermedad renal crónica	34 (6,1)	36 (4,8)
Enfermedad hepática crónica	30 (5,3)	24 (3,2)

La cápsula polisacárida que rodea al neumococo constituye uno de los principales elementos responsables de su patogenicidad y sirve como elemento de referencia para su serotipificación. Su presencia evita el aclaramiento del germen por parte del sistema inmunitario pudiendo favorecer la presencia de formas invasivas. Por el contrario, su propia capacidad antigénica constituye la base sobre la que se han desarrollado las actuales vacunas (29). Dependiendo de su estructura polisacárida podemos identificar en esta bacteria hasta 100 serotipos (30). A su vez, dentro de cada serotipo y en función de posibles variaciones en su estructura genética se pueden identificar varias clones que podrían tener diferentes capacidades para producir una bacteriemia (31). Además de la cápsula existen otros elementos presentes tanto en la

superficie bacteriana como en su interior que se podrían liberar tras la lisis bacteriana y que van a influir también en la virulencia y en la capacidad invasora del neumococo (Tabla 4)(29).

Tabla 4. Principales factores de virulencia de *Streptococcus pneumoniae.*

Cápsula polisacárida	Pili
Pneumolisina	Bacteriocina
Autolisina	Neuraminidasa
Proteínas de superficie	Proteasa IgA
Adhesina A	Biofilm

Casi una cuarta parte de los pacientes con una neumonía neumocócica van a presentar una bacteriemia (32). Su existencia va a depender, entre otros factores, del serotipo de *S. pneumoniae* que produce la infección (Tabla 5) (33,34).

Tabla 5. Agrupación de los serotipos de *S. pneumoniae* según su patogenicidad.

	Serotipos
Riesgo de mortalidad	
• Alto	3, 6A, 6B, 9N,19F, 23F
• Medio	9V, 12F, 14, 22F
• Bajo	1, 4, 5, 7F, 8
Riesgo de bacteriemia	
• Alto	1, 5, 7F
• Medio	4, 9V, 14, 18C
• Bajo	3, 6A, 6B, 8, 19F, 23F

Se puede considerar que los serotipos con una mayor capacidad invasora se van a encontrar con menor prevalencia como formas portadoras nasofaríngeas. Debemos de tener en cuenta que el neumococo y el paciente no se comportan como compartimentos

estancos sino que interaccionan. De este modo, el mismo microorganismo se puede comportar de forma distinta dependiendo de la edad del paciente, su situación funcional o la presencia de una o múltiples comorbilidades. Se pueden identificar una serie de serotipos con una alta capacidad invasora (1, 5, 7F) que infectarían fundamentalmente a individuos sanos y se podrían comportar como patógenos primarios. Por el contario otros serotipos con una baja capacidad invasora primaria (3, 6A, 6B, 8, 19F, 23F) cuando encuentran un "medio ambiente adecuado" se comportan como patógenos oportunistas causando una enfermedad invasiva grave y, en muchos casos, mortal. Estos serotipos oportunistas en su mayoría presentan un mayor grosor de la cápsula que podría dificultar su capacidad invasora primaria. Sin embargo, en determinadas circunstancias en las cuales se convierten en invasivos, este tipo de cápsula les podría proteger del sistema inmunitario provocando incluso una mayor activación del mismo con la consiguiente liberación de citoquinas proinflamatorias, contribuyendo de esta forma a una mayor gravedad del cuadro (35-37). De hecho si clasificamos a los diferentes serotipos en función de su letalidad potencial podemos ver que los serotipos 3, 6A, 6B, 19F, 23F (considerados oportunistas), además de los serotipos 9N y 19A, van a estar asociados a un mayor riesgo de muerte, mientras que los serotipos 1, 5, 7F (invasivos primarios) junto con el 4 y 8 se asocian a un menor riesgo (38). Se podría deducir que el pronóstico de estos pacientes no va a depender de la capacidad invasora intrínseca del germen sino de los factores propios del huésped, fundamentalmente la edad y la presencia de determinadas comorbilidades. Es quizás ahí en donde un desequilibrio entre mecanismos inflamatorios intrínsecos ligados al neumococo y al propio paciente, podrían ser los responsables de generar una respuesta inflamatoria exagerada que va a condicionar la gravedad, la aparición de complicaciones y, finalmente, la muerte.

La presencia de complicaciones durante la fase aguda de la enfermedad va a influir en la evolución del paciente con independencia de la gravedad estimada en su ingreso hospitalario (39,40). Su desarrollo va a ser en general una consecuencia de la gravedad del propio cuadro infeccioso y de su repercusión, en algunos casos, sobre una serie de comorbilidades preexistentes (41). La aparición de un fallo respiratorio es probablemente una de las complicaciones más importantes y graves, responsable de una elevada morbimortalidad. Su presencia, en el contexto de una neumonía neumocócica bacteriémica, es el resultado de la interacción entre determinados factores relacionados con el huésped (la edad, la presencia de comorbilidades crónicas cardiorrespiratorias, etc.) que probablemente van a influir en el aislamiento de serotipos de *S. pneumoniae* oportunistas como son el 3, 19A y 19F (42). Otro tipo de complicaciones son las cardiovasculares que han sido objeto de estudio en los últimos años en los pacientes con un diagnóstico de NAC en general y en algún caso de los originados por el neumococo. Su aparición, incluso en pacientes sin antecedentes previos de cardiopatía, se ha asociado a una mayor probabilidad de fallo terapéutico, una estancia hospitalaria más prolongada y una mayor mortalidad (43,44).

En una revisión reciente de 39 estudios que incluyeron en total a 92.188 pacientes con NAC, se comprobó la presencia de complicaciones cardiacas en 13,9%, de ellos: 9,2% presentaron insuficiencia cardiaca, 7,2% arritmias y 4,5% síndrome coronario agudo (45). El motivo de su aparición es con frecuencia multifactorial e incluye el efecto cardiodepresor asociado a la propia sepsis, la hipoxemia, el efecto de determinados fármacos (inotropos, broncodilatadores, etc.) o de los procedimientos empleados (ventilación mecánica), además de las propiedades patogénicas específicas del propio germen responsable del cuadro. Tratar de clarificar el papel individual que tienen estos factores y los que son dependientes del huésped presenta un gran interés de cara a conocer mejor las circunstancias que pudieran favorecer la aparición de este tipo

de complicaciones, su importancia y contribución real al pronóstico global de la enfermedad del paciente.

La mayor parte de los estudios publicados han considerado a la neumonía como un cuadro infecciosos agudo sin repercusion en la evolución posterior del paciente. Sin embargo, existe una evidencia creciente de que los pacientes ingresados por una NAC presentan una mayor tasa de mortalidad a medio y largo plazo en comparación con la población general, siendo ésta del 8% a los 90 días, 21% al año y 36% a los cinco años (46-50). Los datos existentes sobre el papel del neumococo como agente causal de una NAC y la supervivencia a largo plazo de estos pacientes son escasos y los resultados son contradictorios en relación con la importancia que pudiera tener la presencia de una bacteriemia en su pronóstico (51,52). Por todo ello, es interesante clarificar el papel que pudiera tener el neumococo como agente etiológico de una NAC en el pronóstico a medio y largo plazo de estos pacientes, así como poder valorar si esa supervivencia se ve influenciada por haber tenido una forma bacteriémica de infección neumocócica.

2. METODOLOGÍA

En este apartado se va a describir de forma resumida la metodología básica del proyecto, iniciado en el año 2002 y que ha generado esta línea de investigación. La metodología específica para responder a cada uno de los objetivos concretos se puede encontrar en las secciones de material y métodos de cada uno de los artículos que integran la presente Tesis Doctoral.

Diseño y ámbito del estudio

Los trabajos recogidos en esta Tesis Doctoral son el resultado de una serie de estudios observacionales basados en el análisis de un registro prospectivo de pacientes adultos (edad ≥18 años) sin inmunodeficiencias que han requerido un ingreso hospitalario por una neumonía neumocócica en dos hospitales terciarios de la Comunidad Autónoma Vasca (Hospital Universitario de Cruces y Hospital Universitario de Galdakao) desde el año 2002. El diagnóstico bacteriológico se ha basado en los resultados de la determinación de antígeno urinario y/o de los hemocultivos realizados a la llegada del paciente al Servicio de Urgencias.

Se han excluido:

1) Pacientes con inmunodeficiencia congénita, o causada por el VIH o por tratamiento farmacológico.

2) Pacientes con antecedentes de hospitalización en las dos semanas previas o que hayan sido diagnosticados de neumonía en los tres meses previos al diagnóstico actual.

De cara a estimar la gravedad del cuadro infeccioso al ingreso se ha utilizado el *Pneumonia Severity Index* (*PSI*) y/o la escala *CURB-65* (39,40).

Aspectos éticos

El protocolo de estudio utilizado ha sido aprobado por el Comité de Ética de la Investigación con Medicamentos de Euskadi (número de aprobación EPA2019043).

Variables a estudio

En nuestros dos hospitales, desde el año 2002, se viene realizando un registro de todos los pacientes hospitalizados por una NAC. Este registro incluye múltiples variables demográficas, relativas a la presencia de comorbilidades, estado vacunal contra neumococo e influenza, signos vitales al ingreso así como sobre el resultado de diferentes estudios analíticos y radiológicos realizados al ingreso en el servicio de urgencias. Los pacientes durante su ingreso hospitalario recibieron tratamiento empírico con antibióticos en función del criterio de su médico responsable y de acuerdo con las recomendaciones de la Sociedad Española de Patología Respiratoria (SEPAR) (53).

Como variables relacionadas con el tratamiento antibiótico administrado se ha evaluado:

1) Administración de antibióticos previo al ingreso.

2) Clase de antibióticos prescrito al ingreso.

3) Adherencia del tratamiento a la normativa SEPAR.

4) Tiempo trascurrido entre la llegada al Servicio de Urgencias hospitalarias y la administración de la primera dosis de antibióticos.

5) Tiempo en pasar la medicación antibiótica de intravenosa a oral.

Como factores indicadores de la evolución y pronóstico se han evaluado:

1) Necesidad de ingreso en UCI.

2) Necesidad de soporte ventilatorio invasivo.

3) Presencia de shock séptico.

4) Presencia de complicaciones sistémicas al ingreso y/o durante su estancia hospitalaria.

5) Fallo terapéutico.

6) Mortalidad intrahospitalaria.

7) Duración de la estancia hospitalaria.

8) Mortalidad a largo plazo, tras el alta hospitalaria.

Para evaluar la mortalidad a largo plazo hemos utilizado datos obtenidos del Servicio Vasco de Salud (Osakidetza). A la hora de analizar la mortalidad a largo plazo y de cara a evitar la posible existencia de sesgos hemos excluido a los pacientes que fallecieron en los primeros 30 días tras el alta hospitalaria. Para estimar el impacto que el episodio de neumonía tiene en la supervivencia de los pacientes tras el alta hospitalaria hemos comparado la supervivencia de nuestra cohorte con la estimada en función de la edad, sexo y año de hospitalización según tablas obtenidas del Instituto Nacional de Estadística (años 2000-2017) (54).

Estudios microbiológicos

El diagnóstico bacteriológico se ha basado en los resultados de la determinación del antígeno urinario y/o de los hemocultivos realizados a la llegada al Servicio de Urgencias. La determinación de antígeno de neumococo en orina se ha realizado mediante inmunocromatografía (BinaxInc, Scarborough, ME, EEUU) utilizando orina

concentrada. En los casos de neumonía bacteriémica se han identificados los serotipos causantes. Estos serotipos han sido analizados agrupados en función de su mortalidad asociada: alto grado de mortalidad (serotipos 3, 6A, 6B, 9N, 19F, 19A y 23F) y bajo riesgo (serotipos 1, 7F, 8, 4 y 5) (38).

Definiciones

Se ha definido neumonía como la presencia de un infiltrado radiológico pulmonar junto con la presencia de signos y síntomas sugestivos de infección de vías bajas respiratorias. Se ha considerado la existencia de un shock séptico en aquellos pacientes con tensión arterial sistólica inferior a 90 mm de Hg y que han precisado de la administración de fármacos vasopresores durante por lo menos cuatro horas tras la correcta reposición de fluidos (55). El diagnóstico de alteración del estado mental se ha basado en la observación de que el estado mental del paciente no era normal con respecto a su situación basal. En los pacientes con demencia previa al ingreso se consideró este diagnóstico ante la presencia de un deterioro en su estado mental con respecto a la situación basal previa (40). Se definió fallo terapéutico como la persistencia o reaparición de fiebre y/o la presencia de datos de inestabilidad hemodinámica y/o aumento del infiltrado radiológico y/ o agravamiento o aparición de una insuficiencia respiratoria que obligaba a un cambio en el tratamiento antibiótico prescrito (56).

Se han considerado como comorbilidades preexistentes las siguientes entidades clínicas diagnosticadas previamente al ingreso hospitalario: Enfermedad pulmonar crónica, diabetes mellitus, enfermedad cerebrovascular, enfermedad hepática crónica, enfermedad renal crónica, dislipemia, hipertensión arterial sistémica, presencia de arritmias cardiacas auriculares (fibrilación auricular). Se incluyeron sólo a aquellos

pacientes con cáncer definido como tumor sólido que no habían requerido de tratamiento con quimioterapia y/o radioterapia en el año previo al episodio de neumonía, excluyéndose a los pacientes con neoplasia hematológica activa o en seguimiento. La presencia de cualquier de estas condiciones clínicas en pacientes no conocedores de las misma o no registradas en los antecedentes médicos recogidos en la historia clínica se ha considerado como nuevo episodio-complicación aguda.

Análisis estadístico

La descripción detallada de la metodología estadística utilizada se puede encontrar en las secciones de material y métodos de cada uno de los artículos que componen la presente Tesis Doctor

3. HIPÓTESIS Y OBJETIVOS GENERALES

Se han planteado cuatro hipótesis en este trabajo de Tesis Doctoral que se enumeran a continuación:

1.- Los pacientes con una neumonía por *S. pneumoniae* presentan unas características clínicas y un pronóstico diferente en función de la forma en la que se alcanza el diagnóstico de certeza etiológica (antigenuria y/o hemocultivo).

Su conocimiento podría ser de utilidad para tratar de establecer futuras estrategias que garanticen un mejor cuidado de los pacientes así como decisiones relativas al alta hospitalaria.

2.- Los pacientes con una neumonía por *S. pneumoniae* presentan un comportamiento diferente en función del huésped.

La identificación de subgrupos de población en función de factores dependientes del huésped (edad y presencia de comorbilidades acompañantes) puede ayudar a determinar el posible valor de determinados programas de prevención en nuestro medio, tales como la vacunación.

3.- Los pacientes hospitalizados por una neumonía neumocócica presentan un mayor riesgo de sufrir un evento cardiaco durante el episodio agudo.

De entre estas complicaciones, la fibrilación auricular es quizás la más frecuente. Sin embargo no queda claro si la neumonía por sí misma incrementa el riesgo de desarrollar este tipo de complicaciones o, si por el contrario, su aparición podría estar influenciada por una serie de factores exógenos al propio cuadro infeccioso. De confirmarse esta primera circunstancia, el desarrollo de una fibrilación auricular *de novo* durante la fase aguda podría ser un indicador de disfunción orgánica y tener implicaciones pronósticas tanto a corto plazo como, probablemente, tras el alta hospitalaria. Este hecho podría ser de interés de cara a tratar de planificar diferentes estrategias de cuidados y seguimiento de

estos pacientes.

4.- Los pacientes que han sobrevivido a una hospitalización por una neumonía tendrán un mayor riesgo de muerte a largo plazo tras el alta con respecto a la población general.

Este hecho podría ser más acusado en el contexto de aquellos cuadros con una importante afectación sistémica inflamatoria, como es en el caso de una neumonía bacteriémica por *S. pneumoniae*. La confirmación de esta hipótesis junto con el conocimiento de los factores que pueden influir en la misma podría permitir el desarrollo de una estrategia de seguimiento y un proceso de cuidados a largo plazo que modificaran el pronóstico de los pacientes tras el alta hospitalaria.

Para tratar de dar explicación a estas hipótesis nos planteamos en esta Tesis Doctoral el objetivo principal de evaluar el papel que la presencia de una bacteriemia por *S. pneumoniae* tiene en el pronóstico a corto (durante el ingreso) y a largo plazo en una cohorte prospectiva de pacientes con diagnóstico de neumonía neumocócica que han requerido de ingreso hospitalario. Conocer el impacto que los factores relacionados con el huésped y la presencia de complicaciones cardiacas tienen en el pronóstico de estos pacientes tanto durante la fase aguda como tras el alta hospitalaria.

Para alcanzar este objetivo principal se han propuesto dos objetivos secundarios:

1. Conocer la posible existencia de subgrupos clínicos con implicaciones pronósticas en función de la forma de diagnóstico (antigenuria y/o hemocultivo) entre los pacientes diagnosticados de una neumonía por *S. pneumoniae*.

2. Conocer el impacto que la edad y la presencia de comorbilidades tienen en la evolución de los pacientes.

4. HIPÓTESIS Y OBJETIVOS ESPECÍFICOS

Se enumeran a continuación las hipótesis y objetivos específicos de cada uno de los manuscritos que configuran esta Tesis doctoral por compendio de publicaciones.

A) HIPÓTESIS Y OBJETIVOS DE LA PUBLICACIÓN 1

Datos de la publicación:

A Capelastegui, R Zalacain, A Bilbao, M Egurrola, LA Ruiz, JM Quintana, A Gómez, C Esteban, PP España.

Pneumococcal pneumonia: Differences according to blood culture results.

BMC Pulm Med 2014; 14: 128

Hipótesis:

Hasta un 25% de los pacientes diagnosticados de una neumonía neumocócica presentan una bacteriemia por dicho germen. Las implicaciones pronósticas de este hecho han sido objeto de controversia. Se podría especular que estos pacientes podrían presentar una peor evolución durante su hospitalización y estar sujetos a un mayor riesgo de desarrollar un shock séptico debido a un mayor grado de afectación sistémica.

Objetivos:

1.- Evaluar el papel que la presencia de una bacteriemia tiene como marcador pronóstico de gravedad en una cohorte de pacientes con neumonía neumocócica adquirida en la comunidad que han requerido un ingreso hospitalario.

2.- Evaluar si la presencia de bacteriemia se ha asociado con una mayor incidencia de shock séptico al ingreso o durante la hospitalización y con un riesgo de muerte más elevado.

Métrica:

Factor de Impacto 2014: 2.98

Cuartil: Q1

Capelastegui et al. BMC Pulmonary Medicine 2014, 14:128
http://www.biomedcentral.com/1471-2466/14/128

BMC Pulmonary Medicine

RESEARCH ARTICLE Open Access

Pneumococcal pneumonia: differences according to blood culture results

Alberto Capelastegui[1*], Rafael Zalacain[3], Amaia Bilbao[4], Mikel Egurrola[1], Luis Alberto Ruiz Iturriaga[3], Jose M Quintana[2], Ainhoa Gomez[3], Cristobal Esteban[1] and Pedro P España[1]

Abstract

Background: Bacteremia by *Streptococcus pneumoniae* has been traditionally associated with poor outcomes in patients with pneumonia; however, data on its impact on outcomes are limited and are sometimes contradictory.

Methods: We performed a prospective study in two hospitals in northern Spain in which cases diagnosed with pneumococcal pneumonia were selected from a cohort of hospitalized patients with pneumonia between January 2001 and July 2009. We compared patients with pneumococcal bacteremic pneumonia with those with pneumococcal non-bacteremic pneumonia.

Results: We compared 492 patients with negative blood culture and 399 with positive culture results. Host related factors were very similar in both groups. Severity of illness on admission measured by CURB-65 score was similar in both groups. Adjusted analysis showed a greater likelihood of septic shock during in-hospital course among patients with pneumococcal bacteremia (OR, 2.1; 95% CI, 1.2–3.5; P = 0.006). Likewise, patients with positive blood culture had greater in-hospital mortality (OR 2.1; 95% CI, 1.1 – -3.9; P = 0.02), 15-day mortality (OR 3.6; 95% CI, 1.7 – 7.4; P = 0.0006), and 30-day mortality (OR, 2.7; 95% CI, 1.5 – 5; P = 0.002).

Conclusions: Although host related factors and severity on admission were very similar in the two groups, bacteremic patients had worse in-hospital course and outcomes. Bacteraemia in pneumococcal pneumonia is of prognostic significance.

Keywords: Pneumococcal pneumonia, Bacteremia

Background

Despite the introduction of pneumococcal vaccination and advances in antimicrobial agents, case-fatality rates among adults with bacteremic pneumococcal pneumonia vary significantly (ranging from 6% to 30%); they have improved little in the past three decades and, in general, remain high [1-6]. In addition, bacteremic pneumococcal pneumonia continues to evolve, and regular comprehensive analysis of this entity is necessary.

The severity of sepsis can be graded, using the American Collage of Chest Physicians/Society of Critical Care Medicine classification [7], into different progressive stages: bacteremia, systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, septic shock, and multiple organ dysfunctions. Although there is a hierarchical continuum of severity across sepsis, severe sepsis, septic shock, and multiple organ dysfunction [8], the presence of SIRS has no prognostic significance [9,10], and the prognostic significance of bacteremia remains unclear. Among patients with pneumonia, bacteremia due to *Streptococcus pneumoniae* has traditionally been associated with poor outcomes, it being considered an invasive form of infection. To date, however, there has been little research on the impact of *Streptococcus pneumoniae* bacteremia on the outcome of pneumococcal pneumonia: most studies have focused on bacteremic infection [5,11-13], or on the impact of antibiotic resistance on clinical outcome [14-16], few reports having compared the clinical outcomes of pneumonia patients with and without pneumococcal bacteremia. Moreover, among the few existing comparative studies the findings are contradictory and characteristics of some of the

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B) HIPÓTESIS Y OBJETIVOS DE LA PUBLICACIÓN 2

Datos de la publicación:

R Zalacain, A Capelastegui, LA Ruiz, A Bilbao, A Gómez, A Uranga, PP España.

Streptococcus pneumoniae **antigen in urine: Diagnostic usefulness and impact on outcome of bacteraemic pneumococcal pneumonia in a large series of adult patients.**

Respirology 2014; 19: 936-943.

Hipótesis:

La sensibilidad de la detección del antígeno neumocócico en orina en el contexto de una neumonía por esta bacteria podría venir limitada tanto por las características especificas del propio paciente como por las del microorganismo (serotipo). Su positividad en el contexto de una neumonía bacteriémica podría condicionar la existencia de fenotipos clínicos con implicaciones pronósticas.

Objetivos:

1.- Evaluar la utilidad de la técnica de inmunocromatografía en la detección de antígeno de neumococo en orina para detectar la posible existencia de diferencias en su resultado en función de las características tanto del paciente como del propio microorganismo (serotipo).

2.- Evaluar si el resultado de esta prueba diagnóstica tiene también implicaciones pronósticas en una cohorte de pacientes con diagnóstico de neumonía bacteriémica por *S. pneumoniae* que han requerido ingreso hospitalario.

Métrica:

Factor de Impacto 2014: 3.92

Cuartil: Q1

Official Journal of the Asian Pacific Society of Respirology
Respirology

ORIGINAL ARTICLE

Streptococcus pneumoniae antigen in urine: Diagnostic usefulness and impact on outcome of bacteraemic pneumococcal pneumonia in a large series of adult patients

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ABSTRACT

Background and objective: **Urinary pneumococcal antigen detection provides good results in the diagnosis of pneumococcal pneumonia but has rarely been used in bacteraemic pneumococcal pneumonia and it is not known whether it is associated with outcome in this type of pneumonia. Our objectives were to assess the usefulness of an immunochromatographic technique for detecting the pneumococcal antigen in urine in a large prospective study of patients with bacteraemic pneumococcal pneumonia and explore any potential association with outcomes.**

Methods: **This study, carried out over 8 years, included all adult immunocompetent patients admitted for bacteraemic pneumococcal pneumonia. An immunochromatographic test for the *Streptococcus pneumoniae* antigen in urine was performed in the first 24 h. The sensitivity of test was assessed and patients were divided into two groups according to test results to explore differences on admission and during the course of the illness using logistic regression models.**

Results: **Of the 350 patients with bacteraemic pneumococcal pneumonia included, 261 (74.6%) were positive for the antigen. Patient characteristics were very similar on admission and differences in severity (Pneumonia Severity Index) were not statistically significant. In the adjusted analysis, antigen-positive patients had a higher risk of intensive care unit admission, treatment failure and adverse outcome.**

Conclusions: **The sensitivity of the immunochromatographic urinary antigen test was 74.6% and positive results were associated with poorer clinical outcome. We therefore recommend systematic use of this test when pneumonia is diagnosed in the emergency department.**

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Article first published online: 26 June 2014

SUMMARY AT A GLANCE

In bacteraemic pneumococcal pneumonia patients, urinary pneumococcal antigen had good sensitivity. In addition, we present a novel finding, that in these patients, despite a similar severity as assessed by the PSI, those positive for the antigen were associated with poorer clinical outcome.

Key words: bacteraemic pneumococcal pneumonia, community-acquired pneumonia, outcome, sensitivity, urinary pneumococcal antigen.

Abbreviations: BPP, bacteraemic pneumococcal pneumonia; CAP, community-acquired pneumonia; CI, confidence interval; ICT, immunochromatography; ICU, intensive care unit; IMV, invasive mechanical ventilation; OR, odds ratio; PSI, Pneumonia Severity Index; UPA, urinary pneumococcal antigen.

INTRODUCTION

It is well established that *Streptococcus pneumoniae* is the aetiological agent most commonly associated with community-acquired pneumonia (CAP). It can, however, be very difficult to make a definitive microbiological diagnosis. The introduction of a technique based on the detection of the antigen in urine by immunochromatography (ICT) has been effective in increasing the microbiological diagnosis.[1,2] Various authors have demonstrated that this test has good sensitivity (70–80%) and excellent specificity (>90%). Unfortunately, these studies have included few patients (never over 100) of bacteraemic pneumococcal pneumonia (BPP), those considered as having definitive diagnoses.[3–9] This type of pneumonia is characterized by its severity; hence, it is important to identify a method to rapidly obtain the aetiological diagnosis and thence administer a specific antibiotic treatment[10] while in the emergency department.

C) HIPÓTESIS Y OBJETIVOS DE LA PUBLICACIÓN 3

Datos de la publicación:

LA Ruiz, R Zalacain, A Capelastegui, A Bilbao, A Gómez, A Uranga, PP España.

Bacteremic pneumococcal pneumonia in elderly and very elderly patients. Host and pathogen-related factors, process of care and outcome.

J Gerontol A Biol Sci Med 2014; 69: 1018-1024.

Hipótesis:

La edad y la presencia de enfermedades asociadas podrían implicar diferencias en el tipo de serotipo de *S. pneumoniae* identificado y en el proceso de cuidados recibidos e impactar en el pronóstico de un paciente que ha requerido de ingreso hospitalario por una neumonía bacteriémica por neumococo. Esta circunstancia podría ser más acusada en los pacientes ancianos con mayor edad.

Objetivos:

1.- Conocer los factores relacionados con el microorganismo, el huésped y el pronóstico de los pacientes ancianos y muy ancianos que han requerido un ingreso por una neumonía bacteriémica por *S. pneumoniae*.

2.- Evaluar la posible existencia de diferencias en el proceso de cuidados hospitalarios en función de la edad en esta cohorte de pacientes.

3.- Conocer los factores asociados con la mortalidad de los pacientes con 65 años o más ingresados en el hospital con una neumonía bacteriémica por *S. pneumoniae*.

Métrica:

Factor de Impacto 2014: 5.41

Cuartil: Q1

Journals of Gerontology: MEDICAL SCIENCES
Cite journal as: J Gerontol A Biol Sci Med Sci 2014 August;69(8):1018–1024
doi:10.1093/gerona/glt288

Advance Access publication January 27, 2014

Bacteremic Pneumococcal Pneumonia in Elderly and Very Elderly Patients

Host- and Pathogen-Related Factors, Process of Care, and Outcome

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Background. Hospitalizations due to pneumonia increase steadily with age. The purpose of this study is to explore differences in host- and pathogen-related factors, process of care, and outcome as a function of age in elderly patients with bacteremic pneumococcal pneumonia and identify factors related to mortality.

Methods. This was a prospective observational study of a cohort of elderly (65–79 years) and very elderly patients (≥80 years old) diagnosed with bacteremic pneumococcal pneumonia. The serotypes of the strains isolated and their resistance were also analyzed.

Results. During the study period, 399 patients were identified, of whom 225 patients (140 elderly and 85 very elderly patients) were included. Despite the groups having similar characteristics on admission, very elderly patients had higher rates of both hospital (16.47% vs 7.14%, $p = .028$) and 30-day (20% vs 6.43%, $p = .002$) mortality. Factors found to be predictors of mortality were: altered mental status (odds ratio [OR]: 13.18; 95% confidence interval [CI]: 3.68–47.23), respiratory rate more than or equal to 30/min (OR: 5.82; 95% CI: 1.82–18.64), systolic blood pressure less than 90 mmHg (OR: 10.90; 95% CI: 1.45–81.93), blood urea nitrogen more than 30 mg/dL (OR: 5.41; 95% CI: 1.03–28.42), bilateral or multilobar lung involvement (OR: 5.24; 95% CI: 1.55–17.76), and age (OR: 1.19; 95% CI: 1.09–1.30).

Conclusions. Very elderly patients have poorer outcomes with no significant differences in host- and pathogen-related factors or process of care. Mortality rates in these patients are associated with age and the severity of their clinical condition.

Key Words: Pneumonia in elderly persons—Bacteremic pneumococcal pneumonia—Pneumonia and mortality.

Received June 20, 2013; Accepted December 29, 2013

Decision Editor: James Goodwin, PhD

PNEUMONIA caused by *Streptococcus pneumoniae* is one of the leading causes of hospital admission and mortality in patients older than 65 years (1). Approximately 20% of patients diagnosed with pneumococcal pneumonia develop bloodstream infections, this being traditionally associated with poorer and slower recovery (2,3). Recently, some authors have not found this association, although their studies have focused on the general population and not only on elderly patients (4).

The progressive population aging, the increase in the incidence of pneumococcal pneumonia with age (5), and improvement in survival rates in the last decade in elderly patients (6) make it important to explore the characteristics of the disease in various subgroups of the elderly population to improve the planning of care.

To date, little information is available regarding the process of care or host- and pathogen-related factors associated with bacteremic pneumococcal pneumonia (BPP) in elderly and very elderly patients (≥80 years old). For this reason, we assessed the impact of age group (65–79 vs ≥80 years old) on clinical presentation, process of care markers, outcome, and risk factors associated with 30-day mortality in a large cohort of elderly patients.

Materials and Methods

Setting, Patients, and Study Design

The study was conducted between January 2002 and January 2010 in two hospitals (Cruces University Hospital and Galdakao-Usansolo Hospital) in the Basque Country (Spain). We prospectively included all adults admitted for BPP. Patients were divided into two age groups: younger

D) HIPÓTESIS Y OBJETIVOS DE LA PUBLICACIÓN 4

Datos de la publicación:

LA Ruiz, PP España, A Gómez, A Bilbao, C Jaca, A Aramburu, A Capelastegui, M I Restrepo, R Zalacain.

Age-related differences in management and outcomes in hospitalized healthy and well-functioning bacteremic pneumococcal pneumonia patients: A cohort study.

BMC Geriatr 2017; 17:130.

Hipótesis:

El proceso de envejecimiento fisiológico se caracteriza por una alteración en el funcionamiento de los órganos y una progresiva inmunosenescencia, aun en ausencia de enfermedades relevantes concomitantes. Se podría especular que la supervivencia de los pacientes con buena capacidad funcional y buen estado de salud, que han sido diagnosticados de una neumonía bacteriémica por *S. pneumoniae,* podría ser menor que la de los pacientes mas jóvenes de similares características.

Objetivos:

1.- Evaluar las características clínicas de una cohorte de pacientes con 65 años o más y con una buena capacidad funcional que han requerido un ingreso hospitalario por una neumonía bacteriémica por *S. pneumoniae*.

2.- Evaluar el papel especifico que la edad y los factores relacionados con *S. pneumoniae* (serotipo) tienen en la evolución y en el proceso de cuidados de esta cohorte especifica de pacientes.

Métrica:

Factor de Impacto 2017: 3.09

Cuartil: Q1

Ruiz et al. BMC Geriatrics (2017) 17:130
DOI 10.1186/s12877-017-0518-0

BMC Geriatrics

RESEARCH ARTICLE Open Access

Age-related differences in management and outcomes in hospitalized healthy and well-functioning bacteremic pneumococcal pneumonia patients: a cohort study

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Abstract

Background: Limited data are available regarding fit and healthy patients with pneumonia at different ages. We evaluated the association of age with clinical presentation, serotype and outcomes among healthy and well-functioning patients hospitalized for bacteremic pneumococcal community–acquired pneumonia.

Methods: We performed a prospective cohort study of consecutive healthy and well-functioning patients hospitalized for this type of pneumonia. Patients were stratified into younger (18 to 64 years) and older (≥65 years) groups.

Results: During the study period, 399 consecutive patients were hospitalized with bacteremic pneumococcal pneumonia. We included 203 (50.8%) patients who were healthy and well-functioning patients, of whom 71 (35%) were classified as older. No differences were found in antibiotic treatment, treatment failure rate, antibiotic resistance, or serotype, except for serotype 7F that was less common in older patients. In the adjusted multivariate analysis, the older patients had higher 30-day mortality (OR 6.83; 95% CI 1.22–38.22; $P = 0.028$), but were less likely to be admitted to the ICU (OR 0.14; 95% CI 0.05–0.39; $P < 0.001$) and had shorter hospital stays (OR 0.71; 95% CI 0.54–0.94; $P = 0.017$).

Conclusions: Healthy and well-functioning older patients have higher mortality than younger patients, but nevertheless, ICU admission was less likely and hospital stays were shorter. These results suggest that the aging process is a determinant of mortality, beyond the functional status of patients with bacteremic pneumococcal pneumonia.

Keywords: Bacteremic pneumococcal pneumonia, Community-acquired pneumonia, Pneumonia in older people

Background

The incidence of pneumonia and associated mortality are higher in older than younger people. Pneumonia is the third most frequent cause of hospitalization in patients aged 65 years or over [1], streptococcus pneumoniae being the main pathogen isolated. Bacteremic pneumococcal pneumonia constitutes a severe subgroup with its own features.

Many previous studies have found that the mortality risk among older patients with pneumonia depends on the severity of the lung infection, and adequacy of the response to the infection and other host factors including comorbidities and low functional status [2, 3]. Ageing is among the most important known risk factors for most chronic diseases.

Older patients with pneumonia tend to have multiple comorbid chronic conditions leading to loss of functional independence and an inadequate response to the infectious process. The role of age in mortality prediction is controversial due to interactions between age and comorbidities. Further, pneumonia itself can trigger

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E) HIPÓTESIS Y OBJETIVOS DE LA PUBLICACIÓN 5

Datos de la publicación:

LA Ruiz, L Serrano, PP España, L Martinez-Indart, A Gómez, B González, A Artaraz, R Zalacain.

New-onset atrial fibrillation in patients with pneumococcal pneumonia. Impact of timing and duration on short and medium-term mortality.

J Infect 2021; 82: 67-75.

Hipótesis:

La aparición de un episodio de fibrilación auricular "de novo" en el contexto de una neumonía neumocócica podría considerarse como un indicador de disfunción orgánica y por tanto ser considerado como un marcador de gravedad del propio cuadro infeccioso asociándose a un mayor riesgo de muerte. Es posible que la persistencia del cuadro, al contrario que su resolución precoz, podría ser indicativa de una baja reserva funcional y asociarse a un peor pronóstico tras el alta hospitalaria.

Objetivos:

1.- Conocer la incidencia de una arritmia por fibrilación auricular "de novo" en una cohorte de pacientes con diagnóstico de neumonía neumocócica que han requerido de ingreso hospitalario.

2.- Conocer los factores asociados al desarrollo de esta complicación.

3.- Conocer el momento de su aparición, duración e implicación pronóstica, tanto durante el ingreso como en los primeros 6 meses tras el alta hospitalaria.

Métrica:

Factor de impacto 2020: 6.04

Cuartil: Q1

Journal of Infection 82 (2021) 67–75

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New-onset atrial fibrillation in patients with pneumococcal pneumonia. Impact of timing and duration on short- and medium-term mortality

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ARTICLE INFO

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Key words:
Atrial fibrillation
Bacteremia
Pneumococcal pneumonia
Pneumonia

SUMMARY

Objetives: To assess the incidence, related factors, timing and duration of new- onset atrial fibrillation in a cohort of consecutive patients diagnosed with pneumococcal pneumonia.
Methods: Observational study including all immunocompetent adults hospitalized for pneumococcal pneumonia. Patients were classified by time (atrial fibrillation recognized on emergency room arrival or developed during hospitalization) and duration (paroxysmal or persistent). Patients were followed-up for 6 months after discharge.
Results: We included 1092 patients, of whom 109 (9.9%) had new-onset atrial fibrillation. An early event was documented in 87 (79.8%) cases. Arrhythmia was classified as paroxysmal in 78 patients. Older age, heavy drinking, respiratory rate $\geq$ 30/minute, leukopenia, severe inflammation and bacteremia were independent risk factors for developing new-onset atrial fibrillation on admission. Overall, 48 (4.4%) patients died during hospitalization, the rate being higher in those patients who developed new-onset arrhythmia (17.9% vs 2.9% $p<0.001$). Among patients with events recognized at admission, in-hospital mortality was higher in those with persistent arrhythmia (34.8% vs 6.3%, $p=0.002$) and 6-month survival was better among those who developed paroxysmal event.
Conclusions: The development of new-onset atrial fibrillation was associated with pneumonia severity, and higher in-hospital mortality. Bacteremia and severe systemic inflammation were factors associated with its development.

Introduction

Community-acquired pneumonia is the leading cause of mortality in patients with infection[1]. Overall, *Streptococcus pneumoniae* is the most commonly identified pathogen in pneumonia, being responsible for the highest rates of bacteremia, hospital admission and mortality[2]. The prognosis of patients with pneumococcal pneumonia has not changed in the last decade in spite of improvements in the quality of the process of care during hospitalization[3]. Moreover, it has been recognized that pneumonia is associated with poor long-term outcomes after hospital admission[4–6].

The development of cardiac complications in general and new-onset atrial fibrillation (AF) in particular has been documented in a substantial number of patients hospitalized for pneumonia[7–10]. Mechanisms responsible for these conditions have yet to be clearly elucidated and probably reflect the impact of inflammation and potential "cardiotoxicity" of a specific pathogen on host condition[11,12]. The host-pathogen interaction might be especially relevant in patients with bacteremia due to their elevated inflammatory response[13]. If so, we could speculate that the development of a new-onset AF itself could be considered a surrogate marker

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Factors influencing long-term survival after hospitalization with pneumococcal pneumonia.

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Hipótesis:

El hallazgo de una bacteriemia en el contexto de una neumonía por neumococo se ha asociado a una mayor liberación de citoquinas e inflamación sistémica. Es posible que este hecho podría impactar negativamente en la evolución a largo plazo de algunas enfermedades concomitantes. Se podría hipotetizar que la presencia de una bacteriemia en el contexto de una neumonía neumocócica podría ser, entre otros, un marcador de mala evolución futura.

Objetivos:

1.- Conocer la supervivencia a largo plazo de una cohorte de pacientes con diagnóstico de neumonía por neumococo que han requerido de ingreso en el hospital.

2.- Evaluar la posible existencia de diferencias entre la supervivencia observada y la estimada en función de la edad, sexo y año de ingreso hospitalario.

3.- Conocer los factores de riesgo asociados con un peor pronóstico a largo plazo en esta cohorte de pacientes.

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Factors influencing long-term survival after hospitalization with pneumococcal pneumonia

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SUMMARY

Objective: To assess survival and identify predictors of survival more than 30-days after discharge in a cohort of consecutive patients diagnosed with pneumococcal pneumonia.

Methods: Observational study including all consecutive immunocompetent adult patients surviving more than 30-days after hospitalization. The bacteriological diagnosis was based on the results of urinary antigen testing and/or blood culture. Life expectancy was calculated for each patient considering their sex, age and date of discharge.

Results: We included 1114 patients that survived more than 30- days after discharge. Of them, 431 (38.6%) died during follow-up (median follow-up of 6.7 years). Age, history of cancer, liver disease, chronic renal disease, chronic obstructive pulmonary disease, cerebrovascular disease, atrial arrhythmia and coronary disease, red cell distribution width (RDW) > 15%, positive blood culture, hematocrit < 30% and living in a nursing home were independent risk factors for reduced long-term survival after hospital discharge. Cumulative 1-, 3- and 5-year survival rates were 93.9%, 85.3% and 76%, respectively. Among non-survivors, 361 (83.8%) died earlier than expected given their life expectancy.

Conclusions: Survival after hospital discharge is mainly associated with age and comorbidities. The findings of bacteremia and elevated RDW on admission could help identify patients at high risk of long-term mortality.

Introduction

Pneumonia remains a common cause of morbidity and mortality around the world. In fact, this entity represents the leading cause of infection-related death.[1] Traditionally, pneumonia has been considered an acute process that, once resolved, has no impact on patient survival. There is growing evidence, however, of a higher risk of death after recovery from the acute episode than that the general population.[2–4] The excess mortality observed in these patients may be as high as 50% within 5 years after hospital discharge.[5]

Streptococcus pneumoniae is the most commonly identified pathogen in pneumonia, being responsible for the highest rates of hospital admission and mortality. Approximately 20% of patients diagnosed with pneumococcal pneumonia develop bloodstream infections, and this type of pneumonia has traditionally been associated with poorer outcomes during hospitalization.[6,7] By contrast, for both bacteremic and non-bacteremic pneumococcal pneumonia, there is limited information in the literature on mortality after hospitalization.[8,9] At this point, it could be speculated that the acute infectious episode acts as a trigger to create a persistent inflammatory state which, in turn, has a negative effect on host-related factors such as age or comorbidities.[2] This could be even more relevant in patients with bacteremia due to their elevated cytokine production.[10] Considering the higher incidence of invasive pneumococcal disease in older people and those with underlying conditions, together with the results of recent animal studies reporting a possible association between "cardiotoxicity" and invasive pneumococcal infection, we hypothesized that invasive pneumococcal disease, among other factors, is a marker of impaired long-term survival in these patients.[11,12]

Given this, the objectives of our study were to assess the survival rate after hospitalization in a prospective cohort of patients with pneumococcal pneumonia requiring hospital admission as well as to identify risk factors associated with outcome, to guide

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5. RESUMEN Y DISCUSIÓN DE LOS RESULTADOS OBTENIDOS

Entre un 15 y 25% de las neumonías por neumococo van a presentar una forma bacteriémica, con aislamiento del microorganismo causal en hemocultivos (32). Su significado, desde un punto de vista pronóstico ha sido objeto de múltiples controversias. En el **primero de los estudios,** que recopila este proyecto de Tesis de Doctorado, se realizó un estudio con el objetivo de tratar de clarificar el papel que la presencia de una bacteriemia por neumococo pudiera tener en el grado de gravedad (medido por la escala *CURB-65*) y en la posibilidad de presentar un curso clínico complicado durante el ingreso. Con este propósito, evaluamos una cohorte prospectiva de 891 pacientes con un diagnóstico de neumonía neumocócica adquirida en la comunidad, a los que se les realizó un hemocultivo de la sangre extraída en las primeras 24 horas tras su admisión en urgencias. Se observó una bacteriemia por neumococo en 399 pacientes (44,8%). No se observaron diferencias ni en el tipo y número de comorbilidades (salvo mayor presencia de cardiopatía en el grupo objeto de estudio), ni en la gravedad del cuadro en el momento del ingreso cuando comparamos las dos cohortes (pacientes con y sin bacteriemia). Es posible que las escalas de gravedad utilizadas habitualmente en la práctica clínica no sean capaces de identificar todas las características inherentes a este subgrupo concreto de pacientes con bacteriemia, especialmente cuando se aplican de forma precoz (en la evaluación inicial en urgencias) y sea necesario aplicarlas de forma dinámica en los primeros días tras el ingreso hospitalario. Sin embargo, el hallazgo en los pacientes bacteriémicos de un mayor grado de deterioro en la función renal y de una mayor afectación radiológica fueron factores que orientaron en la gravedad del cuadro clínico (39). Al igual que otros autores, sí que observamos diferencias significativas en la incidencia de bacteriemia en función del sexo (57,58). Las mujeres presentaron una predisposición menor para desarrollar una sepsis, probablemente de causa multifactorial (59).

En nuestra serie pudimos observar que los pacientes con un diagnóstico de neumonía neumocócica bacteriémica presentaron con mayor probabilidad un curso clínico complicado, con una mayor incidencia de shock séptico al ingreso o durante la hospitalización con independencia del proceso de cuidados aplicado. Estos pacientes tuvieron además una mayor mortalidad intrahospitalaria tanto a los 15 como a los 30 días. A pesar de que no evaluamos el papel de los marcadores de inflamación, es posible que la mayor liberación de citoquinas y la consecuente respuesta inflamatoria descrita por otros autores en este tipo de cuadros bacteriémicos, sean responsables de la mala evolución observada (60). Se puede concluir que la presencia de una bacteriemia es un indicador de gravedad con implicaciones pronósticas en el contexto de un paciente con NAC neumocócica. Otros autores han encontrado resultados contradictorios, aunque con diferencias relevantes tanto en el diseño de los estudios como en el tipo de población estudiada (61,62).

A pesar de que casi en la mitad de los casos se desconoce el agente etiológico causante de la neumonía, *S. pneumoniae* es el patógeno más frecuente (18,19). Desde el año 2002 disponemos de la posibilidad de realizar una determinación de antígeno de neumococo en orina en aquellos pacientes que son evaluados por sospecha de neumonía. Es un método fácil, rápido y fiable, que permite obtener un diagnóstico microbiológico de certeza (63,64). Analizar la sensibilidad de esta técnica requiere de un *gold standard* adecuado, en este caso la identificación de neumococo en sangre. Con este objetivo realizamos **un segundo estudio** en una cohorte de 350 pacientes inmunocompetentes con diagnóstico de neumonía bacteriémica por neumococo adquirida en la comunidad a los que se les había realizado una determinación del antígeno de neumococo en orina en las primeras 24 horas tras su llegada al hospital. Además, nos planteamos evaluar la existencia de posibles diferencias en la forma de presentación y en la evolución posterior con el objeto de tratar de diferenciar un

fenotipo clínico en estos pacientes en función de la positividad de la antigenuria de neumococo. La sensibilidad de la técnica en nuestro medio fue del 74,6%, valor que es concordante con lo publicado por otros autores en otras series con tamaños de muestra más pequeños (65-70).

Tratar de explicar la causa de obtener un resultado negativo falso es controvertido. Se ha especulado con que la formación de inmunocomplejos (anticuerpo-antígeno polisacárido bacteriano) pudiera provocar una disminución en su excreción urinaria (71). Otros factores como la prescripción precoz de un tratamiento antibiótico extrahospitalario, el tiempo de evolución de los síntomas hasta el ingreso o la propia gravedad del cuadro, no parecen ser los responsables, dada la ausencia de diferencias significativas entre los grupos en nuestro estudio (69). Desde un punto de vista técnico el uso de orina concentrada para mejorar la sensibilidad de la técnica ha sido motivo de controversia (66,67). En nuestros hospitales esta práctica se lleva a cabo de forma rutinaria. Es fácil de realizar y no provoca un retraso significativo en el diagnóstico.

En este trabajo pudimos observar que cuando los pacientes se estratificaban en función del resultado de la antigenuria no se observaban diferencias significativas en las características demográficas, en la gravedad (estimada en función del *PSI*) o en el proceso de cuidados aplicados en cada grupo. Por el contrario, aquellos pacientes con antigenuria neumocócica, sí que tuvieron en el ingreso datos sugestivos de presentar un mayor grado de alteración pulmonar (frecuencia respiratoria elevada y/o hipoxemia y/o mayor afectación radiológica). Además, observamos que una antigenuria positiva era un factor de mal pronóstico, que se asoció con un mayor riesgo de requerir un ingreso en la UCI, de presentar un fallo terapéutico y un curso clínico complicado durante su estancia hospitalaria. La causa de esta peor evolución podría ir unida a una probable mayor carga bacteriana en este subgrupo de pacientes. A este respecto, Rello et al. publicaron una

asociación entre carga bacteriana en sangre, gravedad y riesgo de muerte en paciente con neumonía (72). En nuestro trabajo, aunque no realizamos este tipo de determinaciones, se podría especular que con una mayor carga bacteriana se produce una mayor excreción de antígeno en orina. A pesar de que en este estudio no pudimos observar diferencias significativas en el grado de inflamación, medido en función del valor de la proteína C reactiva al ingreso, podríamos hipotetizar que esta mayor carga bacteriana sería la responsable de generar una mayor respuesta inflamatoria y ser la causa de la gravedad del cuadro (73).

En este estudio se pudo identificar un serotipo en 288/350 (82,3%) pacientes. Los pacientes que tuvieron una antigenuria positiva fueron infectados con mayor frecuencia por serotipos asociados con un mayor riesgo de muerte (36,9% versus 18,5%, p= 0,005) aunque no se observaron diferencias en los diferentes factores asociados al huésped. A pesar de que en este estudio no pudimos observar diferencias significativas en el grado de inflamación sistémica, se podría hipotetizar que la infección provocada por estos serotipos se asocia con una mayor carga inflamatoria y una mayor posibilidad de complicación del curso clínico.

El pronóstico de los pacientes con una neumonía depende de tres factores: el paciente y sus circunstancias específicas, el microorganismo responsable del cuadro y su virulencia intrínseca, y la administración precoz de un tratamiento antibiótico adecuado.

Con el objetivo de tratar de evaluar la contribución que los factores relacionados con el microorganismo (serotipo) y el huésped (edad, presencia y número de comorbilidades, estado de fragilidad, etc.) tienen en la evolución de una neumonía neumocócica, nuestro grupo evaluó en dos estudios (artículos **tercero y cuarto)** una

cohorte prospectiva de 399 pacientes con neumonía bacteriémica por neumococo adquirida en la comunidad.

En el **tercer artículo** los pacientes se estratificaron en función de la edad (<65 años versus ≥65 años, 65-79 años versus ≥80 años). Centrándonos en el subgrupo de los pacientes con edad ≥ 65 años, pudimos observar que los pacientes más ancianos (edad ≥80 años) tuvieron un peor pronóstico, a pesar de recibir un tratamiento antibiótico de forma más precoz y no observarse diferencias significativas en los diferentes serotipos identificados agrupados en función del riesgo de muerte. Aunque algunas enfermedades concomitantes, como la hepatopatía crónica y la enfermedad pulmonar obstructiva crónica, fueron más prevalentes en los pacientes con edad de 65- 79 años, en general no se encontraron diferencias ni en el resto de comorbilidades ni en el número de las mismas. En este estudio hemos observado que la edad, la alteración del estado mental al ingreso, la frecuencia respiratoria elevada (igual o mayor a 30 respiraciones por minuto), la hipotensión arterial sistólica (menor de 90 mm de Hg), el BUN > 30 mg/dL y la afectación radiológica bilateral o multilobar al ingreso, fueron factores consistentes como predictores de muerte. Nuestros resultados muestran, por tanto, que la mortalidad en esta cohorte de pacientes se asoció fundamentalmente a la gravedad del propio cuadro infeccioso. La falta de diferencias tanto en el proceso de cuidados como en la tasa de fallo terapéutico con respecto a los pacientes que sobrevivieron, junto al elevado porcentaje de mortalidad precoz (en los primeros tres días tras el ingreso) son factores que podrían justificar estos resultados.

El papel de la edad como factor pronóstico en las neumonías es controvertido debido a la interacción existente entre edad, la presencia de comorbilidades asociadas y la pérdida de independencia funcional. A pesar de su importancia en las escalas pronósticas más habitualmente utilizadas (*PSI, CURB-65*), diversos autores no han

encontrado un impacto negativo de la misma en la supervivencia por neumonía (28, 74-77). Esta discrepancia se podría explicar por el hecho de que la edad tuviera menos peso como factor pronóstico comparado con otros factores dependientes del huésped en series exclusivamente basadas en pacientes ancianos. A diferencia de otros autores, en nuestra cohorte la presencia de comorbilidades no se asoció de forma significativa con un peor pronóstico (78,79). Es posible que las características específicas de la población estudiada con un pequeño porcentaje de pacientes institucionalizados y/o con comorbilidades múltiples haya influido en este hecho. En nuestros resultados hemos observado una relación directa entre la edad (al estratificar la cohorte en edad <65 años versus ≥65 años) y la presencia de enfermedades concomitantes.

Si nos centramos en el microorganismo, observamos que los pacientes más jóvenes fueron infectados por serotipos "más benignos" asociados a un menor riesgo de muerte. Por el contrario, observamos que los pacientes con una edad ≥65 años presentaron una tendencia a ser infectados por serotipos más agresivos, sin que las diferencias fueran significativas probablemente debido al tamaño de la muestra analizada. A la vista de esto podría ser interesante conocer la contribución de estos factores dependientes del huesped en el pronóstico final de la enfermedad.

Desde un punto de vista teórico, un paciente previamente sano, con buen estado funcional y sin comorbilidades relevantes podría representar un modelo adecuado para evaluar el impacto que la edad pudiera tener sobre una determinada enfermedad. Por esto, nos planteamos un **cuarto estudio** con una cohorte de 203 pacientes diagnosticados de NAC bacteriémica por neumococo con estas características. En nuestra cohorte observamos que los pacientes con edad ≥65 años, sin comorbilidades, con buen estado de salud y que requirieron un ingreso hospitalario presentaron, a diferencia de los más jóvenes, una tasa mayor de mortalidad a los 30 días (OR 6,82) sin

objetivarse diferencias significativas ni en el tipo de tratamiento antibiótico prescrito ni en la distribución de los diferentes serotipos identificados agrupados en función de riesgo asociado de mortalidad. Desde un punto de vista individual sólo el serotipo 7F fue identificado con más frecuencia entre los pacientes menores de 65 años, no observándose diferencias en los pacientes de mayor edad. A este respecto se ha especulado con que los factores relacionados con el huésped (edad, comorbilidad, estado funcional, etc.) podrían actuar favoreciendo la infección por serotipos con baja capacidad invasora primaria y que en un "medio ambiente" adecuado se podrían comportar como invasores oportunistas y asociarse con una mayor mortalidad (35-37). Estos resultados podrían sugerir que ha sido la presencia de una comorbilidad subyacente el factor probablemente más importante a la hora de seleccionar el serotipo infectante en nuestra cohorte de pacientes.

En su conjunto, los resultados obtenidos en estos dos estudios resaltan el papel que tiene la edad en el pronóstico de estos pacientes. Por el contrario, otros autores no han encontrado que la edad por sí mismo influya en la mortalidad de un paciente previamente sano con neumonía, salvo en el grupo de más de 80 años (80). El posible papel de la inmunosenescencia o envejecimiento fisiológico del sistema inmunitario y la consiguiente respuesta peor del mismo contra las infecciones podría ser determinante a la hora de tratar de explicar estos resultados (81-83). Unido a esto, se podría especular con que la propia neumonía se muestre en sí misma como un marcador del estado de salud, de tal forma que su presencia podría revelar la existencia de una baja reserva fisiológica (27). Este hecho unido al deterioro en el funcionamiento de los diferentes órganos relacionado con el envejecimiento podría afectar a la capacidad para responder de forma adecuada a un evento agudo. Además, hemos observado, al igual que otros autores, que la edad se ha comportado como un factor limitante a la hora de indicar el ingreso en la UCI independiente al grado de gravedad de la neumonía al ingreso. (84-

86). Esta circunstancia es especialmente importante en una época como la actual en la que las prestaciones sociales y los avances en salud están favoreciendo un incremento en la población anciana con buen estado general de salud. Es ahí precisamente donde una valoración integral en la que se tenga en cuenta, entre otros factores, la edad biológica más que la edad cronológica pueda ser interesante de cara a una mejor adecuación de los servicios sanitarios de cuidados del paciente (87,88).

Otra consecuencia importante derivada de la interacción entre paciente y microorganismo es el desarrollo de complicaciones durante la fase aguda de la enfermedad. Su presencia va a condicionar en parte, el pronóstico del paciente. Beatty et al. evaluaron una cohorte prospectiva de 1636 pacientes con diagnóstico de neumonía neumocócica bacteriémica, de ellos un 29% presentaron una o varias complicaciones importantes durante el ingreso. Su presencia, y especialmente la coexistencia de varias, se asoció de forma significativa con una mayor probabilidad de muerte durante el ingreso (41).

En los últimos años ha cobrado especial interés el desarrollo de complicaciones cardiovasculares en los pacientes con diagnóstico de neumonía. Corrales-Medina et al. evaluaron una serie de 1343 pacientes, de ellos un 26,7% desarrollaron alguna complicación, como la exacerbación de una patología cardiaca preexistente o la presencia de una de nueva aparición (43). Viasus et al. estudiaron a 3921 pacientes encontrando alguna complicación cardiaca de "novo" hasta en el 8% de los mismos. En su análisis observaron que la identificación de *S. pneumoniae* como agente etiológico de la neumonía se comportó como un factor independiente a la hora de desarrollar este tipo de complicaciones (44). En ambos estudios, la aparición de este tipo de complicaciones se ha asociado con un curso clínico complicado y un mayor riesgo de muerte. Desde un

punto de vista etiológico, varios estudios han encontrado una relación entre neumococo y el desarrollo de las mismas, principalmente de arritmias auriculares (43,44,89,90).

Con el objetivo de conocer la incidencia que la fibrilación auricular de nueva aparición tiene en los pacientes con neumonía neumocócica y tratar de identificar los factores que pudieran estar implicados en su aparición nos planteamos un **quinto estudio.** Se evaluó una cohorte de 1092 pacientes, una vez excluidos aquellos con antecedentes de arritmia auricular crónica persistente (estable o exacerbada durante el cuadro de neumonía) o paroxística, de los que 460 presentaron un cuadro bacteriémico. Del total de los pacientes, 109 (9,9%) presentaron una fibrilación auricular "de novo", de los que en 87 (79,8% -87 de 109-) se objetivó en el momento de su llegada a urgencias. Diferenciar el momento en el que se produce esta complicación es importante al permitirnos eliminar situaciones clínicas o tratamientos intercurrentes que pudieran predisponer a su aparición.

En nuestra cohorte, el hallazgo de una fibrilación auricular de nueva aparición fue independiente de la presencia de los factores de riesgo cardiovascular tradicionales. Podríamos especular con que su aparición precoz (a la llegada a urgencias) podría ser interpretada como un marcador de disfunción orgánica.

El mecanismo responsable de la génesis de este tipo de complicación no está claramente definido. Varios factores, la mayor parte dependientes del propio cuadro infeccioso, como son la liberación de citoquinas, la presencia de una respuesta inflamatoria desproporcionada y la depresión miocárdica que acompaña a un cuadro séptico, podrían estar involucrados en su posible aparición (91-93). En este estudio observamos que la edad, la ingesta excesiva de bebidas alcohólicas, la leucopenia, la taquipnea grave al ingreso (frecuencia respiratoria $\geq$ 30 respiraciones por minuto), la presencia de datos sugestivos de una respuesta inflamatoria excesiva y el hallazgo de

una bacteriemia fueron factores independientemente asociados con la aparición de esta complicación. Otros estudios han descrito la relación entre ingesta de bebidas alcohólicas y la génesis de un episodio de fibrilación auricular incluso en pacientes sin alteraciones estructurales cardiacas (94). A este respecto, el alcohol podría tener un efecto favorecedor de la liberación de catecolaminas, algo semejante a lo que podría ocurrir en una situación de alto estrés, como sucede durante un episodio séptico grave, y de esta forma inducir a la aparición de este tipo de arritmias (95,96).

La relación existente entre inflamación y complicaciones cardiovasculares es conocida (97). En este sentido nuestro estudio pone de manifiesto la interrelación que existe entre inflamación sistémica, la presencia de bacteriemia y la gravedad del cuadro infeccioso. En efecto, algunos factores de virulencia relacionados con el patógeno, incluida la presencia de una bacteriemia y la respuesta inflamatoria secundaria, podrían ser elementos claves en el desarrollo de este tipo de arritmias. Este hecho podría incluso ser más relevante en el caso del neumococo (98-101). El hallazgo de pequeñas lesiones en el miocardio durante la fase aguda, la liberación de neumolisinas y su papel en la dinámica de los iones intracelulares unido al efecto de un producción aumentada de citoquinas podrían ser, entre otros, los responsables de su aparición (99, 102).

Al igual que otros autores (43,100), hemos observado que la presencia de esta complicación se ha asociado a una mayor mortalidad intrahospitalaria (17,9% versus 2,9%). Esta peor evolución se relacionó con la duracion de la arritmia. A diferencia de los pacientes que presentaron un episodio paroxístico, los que tuvieron un cuadro persistente tuvieron una mayor probabiliad de morir (34,8% versus 6,3%). Este hecho que también se pudo observar en los primeros meses tras el alta probablemente nos esté indicando un cierto grado de alteración estructural cardiaca subclínico y una baja reserva funcional. Los resultados de este estudio ponen de manifiesto la importancia

que, entre otros factores, tiene la presencia de una bacteriemia por neumococo a la hora de explicar la gravedad de este cuadro infeccioso. Reconocer este tipo de complicaciones y la relativa frecuencia con la que pueden aparecer e identificarlas como un posible marcador de disfunción orgánica podría ser importante a la hora de estratificar la gravedad de una neumonía por neumococo.

Tradicionalmente se ha considerado a la neumonía como un evento agudo que, una vez resuelto no debería de tener repercusión en la supervivencia posterior del paciente. Sin embargo, diversos estudios han puesto de manifiesto un mayor riesgo de muerte entre los enfermos que han superado este cuadro neumónico en comparación al de la población general (46,47,103,104). Se podría especular que el padecer una neumonía generaría un estado inflamatorio persistente que podría influir a largo plazo en la historia natural de algunas comorbilidades preexistentes (104). Este estado podría incluso ser más evidente en los pacientes con cuadros bacteriémicos debido a la mayor producción de citoquinas descrita (105). Por otro lado, la neumonía en si misma podría comportarse como un marcador de mal estado de salud (clínico o subclínico).

Con el objetivo de confirmar estos hallazgos nos planteamos **un sexto estudio** en el que evaluamos a 1190 pacientes consecutivos que requirieron un ingreso hospitalario por una neumonía neumocócica. De los 1114 que permanecían vivos al mes del alta, 431 (38,6%) fallecieron durante una mediana de seguimiento de siete años. De ellos (83,4% -381 de 431-) lo hicieron antes que lo esperado, calculado según las Tablas de Mortalidad del Instituto Nacional de Estadística-INE en función de su edad, sexo y año de ingreso (54). En nuestro estudio observamos que los factores relacionados con el huésped (edad y presencia de comorbilidades asociadas) y el hecho de vivir en una residencia de ancianos (circunstancia que probablemente esté reflejando un mayor grado de fragilidad y una baja reserva funcional) fueron factores independientes

asociados a una mayor probabilidad de muerte a largo plazo. La relación entre presencia de comorbilidades y supervivencia a largo plazo podría ser una consecuencia simple de la historia natural de las mismas. Es posible que el desarrollo secundario de un estado inflamatorio persistente de bajo grado podría empeorar o acelerar su evolución natural o incluso desenmascarar algún proceso subclínico (103,106,107). Además, la propia neumonía, por si misma, podría comportarse como un epifenómeno y que su presencia nos estaría indicando un mal estado de salud subyacente y un mayor riesgo de muerte añadido. A diferencia de otros, no hemos observado que el ingreso en UCI y, en especial, la necesidad de requerir de soporte ventilatorio invasivo se haya asociado con un peor pronóstico a largo plazo. Este hecho podría estar influenciado por la posible diferencia en los criterios de admisión en UCI incluido la edad, como ya demostramos en el artículo número 4 de la presente Tesis Doctoral y que ha sido observado también por otros autores (84-86).

Un aspecto novedoso de este trabajo ha sido lograr identificar, entre otros, la presencia de una bacteriemia y el hallazgo de hematíes con un ancho de banda (RDW, *Red blood cell Distribution Width*) >15% en el hemograma realizado al ingreso como factores asociados a un peor pronóstico a largo plazo. El papel deletéreo de la bacteriemia por neumococo podría estar en relación con un doble motivo. Su presencia se ha asociado a una mayor carga inflamatoria que podría influir en la historia natural de otras patologías clínicas o subclínicas preexistentes. Por otro lado, el hecho de desarrollar una bacteriemia podría ser una consecuencia de la interacción bacteria-huésped y reflejar, como ya hemos comentado previamente, una alteración en el estado previo de salud del paciente (35-37). El hallazgo en el hemograma de hematíes con un RDW >15% y su papel como marcador pronóstico durante el episodio agudo ha sido descrito previamente en otras entidades incluyendo sepsis y neumonía adquirida en la comunidad (108-110). Es posible que este parámetro se pueda comportar como un

marcador de estrés oxidativo y bajo grado de inflamación (110). En nuestro estudio observamos un efecto sumatorio de ambos parámetros presente incluso en los pacientes más jóvenes y más acusado en los de edad ≥ 65 años y con comorbilidades asociadas.

En resumen, los resultados obtenidos en estos seis artículos, que componen el cuerpo de esta Tesis Doctoral, resaltan el papel que la presencia de una bacteriemia tiene como elemento clave en la mortalidad, en la aparición de ciertas complicaciones durante la fase aguda de la enfermedad y en la supervivencia a largo plazo tras el alta hospitalaria de los pacientes con una neumonía por neumococo adquirida en la comunidad. Estos resultados apoyan la importancia que tiene la prevención de la neumonía neumocócica en general y de las formas bacteriémicas en particular, subrayando el papel fundamental que tiene la vacunación antineumocócica como estrategia de salud pública.

6. CONCLUSIONES

Esta Tesis Doctoral es una recopilación de seis artículos con un objetivo común cuyos resultados nos permiten concluir que:

1.- La presencia de bacteriemia en el contexto de una neumonía neumocócica adquirida en la comunidad se asocia a una mayor probabilidad de presentar un curso clínico complicado con una mayor incidencia de shock séptico y muerte.

2.- La antigenuria en orina para neumococo es una técnica sencilla con una sensibilidad del 74.6% en nuestro medio y que permite obtener un diagnostico bacteriológico de certeza de forma rápida y fiable. Además, su positividad va a tener implicaciones pronósticas y nos va a permitir diferenciar a un subgrupo de pacientes con neumonía neumocócica bacteriémica con riesgo de presentar un curso clínico complicado.

3.- La edad y la presencia de comorbilidades acompañantes va a condicionar tanto el serotipo identificado como el pronóstico de los pacientes con un diagnóstico de neumonía neumocócica bacteriémica.

4.- En los pacientes con una neumonía bacteriémica por neumococo, de entre los factores relacionados con el huésped, la edad juega un papel primordial en el pronóstico tanto desde un punto de vista fisiológico como en la limitación de ciertos cuidados.

5.- La existencia de complicaciones cardiacas como la fibrilación auricular “de novo” en los pacientes con diagnóstico de neumonía por neumococo adquirida en la comunidad es relativamente frecuente estando presente en el 9.9% de los pacientes. Su desarrollo va a tener implicaciones pronósticas y se va a asociar a una mayor probabilidad de muerte tanto durante el ingreso como en los primeros meses tras el alta hospitalaria. El hallazgo de una bacteriemia y la existencia de parámetros de inflamación grave al ingreso van a ser, entre otros, factores implicados en su desarrollo.

6.- La supervivencia a largo plazo de los pacientes que han sido dados de alta por una neumonía neumocócica es menor que la estimada en la población general en función de la edad, sexo y año de ingreso. La presentación al diagnóstico como neumonía bacteriémica y el hallazgo de un ancho de banda eritrocitario mayor a 15 en el hemograma realizada al ingreso son factores, entre otros, que nos van a permitir identificar a un subgrupo de pacientes con una reducción en la supervivencia a largo plazo.

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8. ANEXO

Trabajos publicados

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Pneumococcal pneumonia: differences according to blood culture results

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Abstract

Background: Bacteremia by *Streptococcus pneumoniae* has been traditionally associated with poor outcomes in patients with pneumonia; however, data on its impact on outcomes are limited and are sometimes contradictory.

Methods: We performed a prospective study in two hospitals in northern Spain in which cases diagnosed with pneumococcal pneumonia were selected from a cohort of hospitalized patients with pneumonia between January 2001 and July 2009. We compared patients with pneumococcal bacteremic pneumonia with those with pneumococcal non-bacteremic pneumonia.

Results: We compared 492 patients with negative blood culture and 399 with positive culture results. Host related factors were very similar in both groups. Severity of illness on admission measured by CURB-65 score was similar in both groups. Adjusted analysis showed a greater likelihood of septic shock during in-hospital course among patients with pneumococcal bacteremia (OR, 2.1; 95% CI, 1.2–3.5; P = 0.006). Likewise, patients with positive blood culture had greater in-hospital mortality (OR 2.1; 95% CI, 1.1 – -3.9; P = 0.02), 15-day mortality (OR 3.6; 95% CI, 1.7 – 7.4; P = 0.0006), and 30-day mortality (OR, 2.7; 95% CI, 1.5 – 5; P = 0.002).

Conclusions: Although host related factors and severity on admission were very similar in the two groups, bacteremic patients had worse in-hospital course and outcomes. Bacteraemia in pneumococcal pneumonia is of prognostic significance.

Keywords: Pneumococcal pneumonia, Bacteremia

Background

Despite the introduction of pneumococcal vaccination and advances in antimicrobial agents, case-fatality rates among adults with bacteremic pneumococcal pneumonia vary significantly (ranging from 6% to 30%); they have improved little in the past three decades and, in general, remain high [1-6]. In addition, bacteremic pneumococcal pneumonia continues to evolve, and regular comprehensive analysis of this entity is necessary.

The severity of sepsis can be graded, using the American Collage of Chest Physicians/Society of Critical Care Medicine classification [7], into different progressive stages: bacteremia, systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, septic shock, and multiple organ dysfunctions. Although there is a hierarchical continuum of severity across sepsis, severe sepsis, septic shock, and multiple organ dysfunction [8], the presence of SIRS has no prognostic significance [9,10], and the prognostic significance of bacteremia remains unclear. Among patients with pneumonia, bacteremia due to *Streptococcus pneumoniae* has traditionally been associated with poor outcomes, it being considered an invasive form of infection. To date, however, there has been little research on the impact of *Streptococcus pneumoniae* bacteremia on the outcome of pneumococcal pneumonia: most studies have focused on bacteremic infection [5,11-13], or on the impact of antibiotic resistance on clinical outcome [14-16], few reports having compared the clinical outcomes of pneumonia patients with and without pneumococcal bacteremia. Moreover, among the few existing comparative studies the findings are contradictory and characteristics of some of the

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studies have limited their generalizability: the enrolment of relatively small numbers of patients [17-20]; collection of information from a single institution [21,22]; and no adjusted analysis [17,23,24].

Our main objective was to assess whether bacteremia in patients with pneumonia was related to severity on admission, septic shock at admission or during hospitalization, and mortality in a large pneumococcal pneumonia study. We hypothesized that the presence of bacteremia would be associated with higher severity on admission, and also higher rates of shock and mortality due to a greater degree of systemic invasion.

Methods

Study population, design and setting

We analysed 4389 adult (18 years or older) patients hospitalized with pneumonia between January 2001 and July 2009. For this study, we selected patients diagnosed with pneumococcal pneumonia and compared the subgroups in this sample with bacteremic and non-bacteremic pneumonia. All patients with a diagnosis of pneumonia and at least one positive blood culture for *Streptococcus pneumoniae* taken within 48 hours of presentation to the hospital were included in the "pneumococcal bacteremic" group. The "pneumococcal non-bacteremic" group included patients with positive *Streptococcus pneumoniae* antigen in urine and negative blood cultures . Any individuals with concurrent meningitis and/or endocarditis were excluded from the analysis.

Data were collected prospectively from two hospitals (Galdakao-Usansolo Hospital and Cruces University Hospital) in the Basque Country (northern Spain). Galdakao-Usansolo Hospital is a 400-bed general teaching hospital serving a population of 300,000, while Cruces University Hospital is a nearby large teaching hospital with a catchment population of 400,000.

Patients were treated empirically with antibiotics according to local practice guidelines: betalactam in combination with macrolides, levofloxacin or betalactamics. Medical care following discharge was determined by patient's health-care providers. No interventions were instigated as part of this study.

Study variables

All patients' clinical and demographic characteristics were recorded, as well as their vaccination status and any previous antibiotic treatment for the current episode. To measure the severity of pneumonia upon admission to the emergency department, we used the CURB-65 (Confusion, Urea nitrogen, Respiratory rate, Blood pressure, age ≥65 years) score [25].

Process-of-care variables included: 1) whether appropriate antibiotics were given (defined as an initial antibiotic treatment consistent with the recommendations of Spanish Thoracic Society [SEPAR] [26]: third generation cephalosporins or amoxicillin-clavulanic acid plus a macrolide, or levofloxacin in monotherapy for patients admitted to a hospital ward; non-antipseudomonal cephalosporin plus a macrolide, or levofloxacin instead of macrolide for patients admitted to an intensive care unit)); and 2) and 3) whether antibiotics were administered within 4 or within 8 hours of arrival at the emergency department, respectively; as well as 4) length of antibiotic therapy; 5) length of intravenous antibiotic therapy; and 6) the type of antibiotics given.

Clinical in-hospital measures included: whether the patient 1) was admitted to the intensive care unit (ICU); 2) received mechanical ventilation; or 3) developed septic shock; as well as whether there was 4) treatment failure; or 5) severe sepsis.

Outcome measures included: 1) in-hospital mortality; 2) and 3) mortality at 15 and 30 days after admission; 4) hospital readmission within 30 days; and 5) length of hospital stay (calculated as the date of discharge minus the date of admission).

This study was approved by Galdakao Ethics Committee and Cruces University Hospital Ethics Committee.

The formal consent to participate was verbal because this study was not interventional.

Definitions

Pneumonia was defined as pulmonary infiltrate on a chest X-ray not known to have pre-existed and symptoms consistent with pneumonia, including cough, dyspnoea, fever, and/or pleuritic chest pain. Patients with pneumonia were excluded if they were known to be positive for human immunodeficiency virus, were chronically immunosuppressed (defined as immunosuppression for solid organ transplantation, postsplenectomy, receiving ≥10 mg/day of prednisone or the equivalent for more than 30 days, treatment with other immunosuppressive agents, or neutropenia, i.e., $<1.0 \times 10^9$/L neutrophils), had been hospitalized for the previous 14 days before the diagnosis of pneumonia, or had hospital-acquired pneumonia.

Septic shock was defined as systolic blood pressure <90 mmHg and the need for vasopressors for 4 hours or more, while severe sepsis was defined as sepsis associated with organ dysfunction and perfusion abnormalities [27]. Treatment failure was defined as clinical deterioration during hospitalization with hemodynamic instability, confirmation of respiratory failure or the onset thereof, the institution of mechanical ventilation, demonstrated radiological progression of pneumonia or the appearance of a new focus of infection, or persistent fever or the reappearance of fever if a change in treatment was needed [28].

Bacteriological studies

The strategy for pneumococcal diagnosis included blood cultures and a urinary antigen test during the first 24 hours after arrival at hospital. The detection of *Streptococcus pneumoniae* was performed by analysing concentrated urine samples with an immunochromatographic membrane assay (Binax Inc; Scarborough, ME). An etiologic diagnosis of pneumococcal pneumonia was considered to be definitive if one or both of the following criteria were met: 1) isolation of *Streptococcus pneumoniae* in a sterile specimen (blood and pleural fluid); and/or 2) positive urinary antigen test for *Streptococcus pneumoniae*.

Statistical analysis

Descriptive statistics included frequency tables and mean and standard deviation (SD). Patient characteristics, process of care, in-hospital course and outcomes were compared stratifying by blood culture result (positive vs. negative). Chi-square and Fisher's exact tests were performed for the comparison of categorical variables, and the Student's *t*-test or nonparametric Wilcoxon tests were performed for continuous variables.

Univariate logistic regression models were also used to compare in-hospital course and outcomes between the two groups of patients (unadjusted results). Then, multivariate logistic regression models were built for the comparison, adjusting for severity of illness at admission, measured by CURB-65, as well as for patient characteristics and variables related to the process of care found to be significantly different in the groups stratified by blood culture results. In the final multivariate models, only adjusting variables found to be statistically significant were kept. We determined odds ratios (ORs) and 95% confidence intervals (95% CIs). For comparing lengths of hospital stay, a general linear model was built, and due to the skewed distribution of length of stay, the logarithmic transformation was used.

Finally, Kaplan-Meier curves were constructed for 15- and 30-day mortality for each group of patients, and comparisons were performed with the log-rank test. Further, Cox proportional hazards model was used to compare survival between the two groups of patients adjusting for the same variables as stated previously. We determined the hazard ratios (HRs) and 95% CIs.

All effects were considered significant at $P < 0.05$. All statistical analysis was performed using SAS for Windows, version 9.2 (SAS Institute, Cary, NC) and S-Plus 2000 (MathSoft Inc., 1999).

Results

A total of 891 patients were identified in the study period with a diagnosis of pneumococcal pneumonia and with blood culture results. Pneumococcal bacteremia was identified in 399 (44.8%) cases. The group of pneumococcal non-bacteremic pneumonia included 492 (55.2%) cases, all of them with positive antigen in urine and negative blood culture. The patient characteristics are summarized in Table 1 by the blood culture result. Host-related factors were very similar in the two groups, although statistically significant differences were found in sex, alcoholism, pneumococcal vaccine, congestive heart failure, blood urea nitrogen and the radiological findings on admission. Patients with positive blood cultures had higher rates of bilateral or multilobe radiological involvement and pleural effusion and were less likely to have had the pneumococcal vaccine in the last 5 years. Severity of illness on admission measured by the CURB-65 score was similar in the two groups. A total of 395 (99.9%) of 399 blood isolates were available for in vitro susceptibility testing. In nine (2.3%) cases, pneumococci was highly resistant to penicillin (minimum inhibitory concentration ≥ 4 μg/ml).

Process of care indicators in both groups are shown in Table 2. Statistically significant differences were observed in antibiotic management between the two groups. In particular, the use of antibiotics was appropriate according to SEPAR guidelines in 85.3% of patients with negative cultures and just 68.6% of those with positive cultures. In both groups, however, over 90% of patients received antibiotics within 8 hours and the length of antibiotic therapy was similar.

In-hospital course and outcome indicators in the two groups are shown in Table 3 (unadjusted analysis). Patients with pneumococcal bacteremia had significantly higher rates of mechanical ventilation use, septic shock and treatment failure during the hospitalization, and higher in-hospital, 15-day and 30-day mortality, as well as longer hospital stays.

Table 4 shows the comparison of in-hospital course and outcomes in the two groups adjusting for severity of illness at admission, measured by CURB-65, as well as for patient characteristics and variables related to the process of care found to be significantly different in the two groups of patients, such as sex, congestive heart failure, alcoholism, pneumococcal vaccine in last 5 years, pleural effusion, appropriate antibiotic, antibiotics within 4 hours, dual antibiotic therapy including a macrolide, and antibiotic administration prior to hospital admission. A higher likelihood of septic shock (OR, 2.1; 95% CI, 1.2 – 3.5; P = 0.006) during the hospital stay was found among patients with pneumococcal bacteremia. Likewise, patients with positive blood cultures had higher in-hospital mortality (OR 2.1; 95% CI, 1.1 – 3.9; P = 0.02), 15-day mortality (OR, 3.6; 95%CI, 1.7 – 7.4; P = 0.0006), and 30-day mortality (OR, 2.7; 95% CI, 1.5 – 5; P = 0.002). Kaplan-Meier survival curves for each of the groups demonstrate markedly different survival trajectories in 15- and 30-day mortality (Figure 1). Adjusted cox proportional hazards models

Table 1 Characteristics of patients hospitalized with pneumonia by *Streptococcus pneumoniae* by blood culture result

Characteristics	Blood culture positive (N = 399)	Blood culture negative (N = 492)	*P* value
Age, years, mean (SD)	63.6 (18.5)	65.2 (17)	0.2
Age ≥65 years	225 (56.4)	290 (58.9)	0.4
Age >75 years	130 (32.6)	167 (33.9)	0.7
Women	131 (32.8)	210 (42.7)	0.003
Underlying diseases			
Cancer	27 (6.8)	17 (3.5)	0.2
Liver disease	18 (4.5)	12 (2.4)	0.1
Congestive heart failure	54 (13.5)	43 (8.7)	0.02
Cerebrovascular disease	22 (5.5)	32 (6.5)	0.5
Renal disease	27 (6.8)	24 (4.9)	0.2
Chronic obstructive pulmonary disease	74 (18.6)	116 (23.6)	0.07
Diabetes mellitus	60 (15.1)	97 (19.8)	0.07
Number of comorbid conditions			0.96
0	203 (50.9)	253 (51.4)	
1	130 (32.6)	156 (31.7)	
≥2	66 (16.5)	83 (16.9)	
Nursing home resident	13 (3.3)	20 (4.1)	0.5
Smoking			0.06
No	130 (43.5)	225 (47.8)	
Yes	86 (28.8)	100 (21.2)	
Ex-smoker	83 (27.8)	146 (31)	
Alcoholism	58 (15.3)	44 (9.4)	0.008
Influenza vaccine in the last year	93 (26.4)	149 (30.9)	0.2
Pneumococcal vaccine in the last 5 years	14 (3.8)	121 (25.5)	<0.0001
Findings on physical examination on admission			
Altered mental status	39 (9.8)	49 (10)	0.9
Pulse ≥ 125/min	62 (15.6)	62 (12.6)	0.2
Respiratory rate ≥ 30/min	98 (24.8)	96 (19.5)	0.06
Systolic blood pressure < 90 mmHg	30 (7.5)	42 (8.5)	0.6
Temperature < 35°C or ≥ 40°C	7 (1.8)	4 (0.8)	0.2
Laboratory findings on admission			
Blood urea nitrogen > 30 mg/dL	192 (48.1)	163 (33.1)	<0.0001
Glucose ≥ 250 mg/dL	39 (9.8)	38 (7.7)	0.3
Hematocrit < 30%	10 (2.5)	23 (4.7)	0.1
Sodium < 130 mmol/L	33 (8.3)	22 (4.5)	0.02
PaO_2 < 60 mmHg	188 (47.1)	209 (42.5)	0.2
Arterial pH < 7.35	31 (7.8)	24 (4.9)	0.07
Radiological findings on admission			
Bilateral or multilobe radiological involvement	142 (35.7)	122 (24.8)	0.0004
Pleural effusion	65 (16.3)	43 (8.7)	0.0006
Severity of illness on admission			
CURB65 score*			0.07
0,1	145 (36.3)	215 (43.7)	
2	159 (39.9)	167 (33.9)	
>2	95 (23.8)	110 (22.4)	

SD, standard deviation.
Data are expressed as numbers (percentage) unless otherwise stated.
Percentages exclude patients with missing data.
*Severity of illness on admission assessed with CURB-65 (Confusion, Urea nitrogen, Respiratory rate, Blood pressure, age ≥65 years) score.

Table 2 Process-of-care of patients hospitalized with pneumonia by *Streptococcus pneumoniae* by blood culture result

Process-of-care	Blood culture positive (N = 399)	Blood culture negative (N = 492)	*P* value
Previous antibiotic treatment	26 (6.5)	56 (11.4)	0.013
Appropriate antibiotic*	273 (68.6)	419 (85.3)	<0.0001
Antibiotics within 4 hours	257 (73)	389 (79.7)	0.019
Antibiotics within 8 hours	330 (93.8)	471 (96.5)	0.06
Length of antibiotic therapy, days, mean (SD)†	14.7 (7.2)	13.9 (4.6)	0.9
Length of intravenous antibiotic therapy, days, mean (SD)†	7 (7.2)	5.9 (4.8)	0.4
Antibiotic treatment			<0.0001
Beta-lactam monotherapy	93 (23.4)	113 (23)	
Beta-lactam/macrolide	13 (3.3)	30 (6.1)	
Fluoroquinolones	257 (64.6)	346 (70.5)	
Macrolide monotherapy	1 (0.3)	0 (0)	
Others	34 (8.5)	2 (0.4)	
Dual antibiotic therapy including a macrolide	13 (3.3)	31 (6.3)	0.037

SD, standard deviation.
Data are given as number (percentage) unless otherwise indicated.
The percentage excluded patients with missing data.
*Appropriate antibiotic defined as usage of antibiotics recommended in the guidelines of the SEPAR.
†Deaths are excluded.

Table 3 In-hospital course and outcomes of patients hospitalized with pneumonia by *Streptococcus pneumoniae* by blood culture result

In-hospital evolution and outcomes	Positive blood culture (N = 399)	Negative blood culture (N = 492)	*P* value	Odds ratio (95% CI)
In-hospital course				
Admission to intensive care unit	92 (23.1)	101 (20.5)	0.4	1.2 (0.8 – 1.6)
Need for mechanical ventilation	42 (10.5)	27 (5.5)	0.005	2 (1.2 – 3.4)
Septic shock*	53 (14.9)	33 (6.7)	0.0001	2.4 (1.5 – 3.8)
Treatment failure	72 (18.2)	59 (12.1)	0.01	1.6 (1.1 – 2.3)
Severe sepsis	185 (46.4)	203 (41.3)	0.1	1.2 (0.9 – 1.6)
Outcomes				
In-hospital mortality	35 (8.8)	22 (4.5)	0.009	2.1 (1.2 – 3.6)
15-day mortality	33 (8.3)	14 (2.9)	0.0003	3.1 (1.6 – 5.8)
30-day mortality	37 (9.3)	18 (3.7)	0.0005	2.7 (1.5 – 4.8)
30-day readmission	10 (3.3)	27 (5.6)	0.1	0.6 (0.3 – 1.2)
Length of hospital stay (days)†				
Mean (SD)	10 (13.7)	7 (5.5)	0.02	1.2 (1.04 – 1.3)‖
Median (IRQ)	6 (4 – 10)	6 (4 – 8)	0.02	
>3 days	295 (81)	373 (79.4)	0.5	1.1 (0.8 – 1.6)

SD, standard deviation; CI, Confidence interval; IRQ, Interquartile range.
Data are given as number (percentage) unless otherwise indicated. Percentages exclude patients with missing data. Treatment failure is defined in the text.
*Septic shock is defined as arterial systolic blood pressure <90 mm Hg and the need for vasopressors for a minimum of 4 hours.
†Deaths are excluded.
‖For the comparison of length of hospital stay as a continuous variable, the general linear model was used, and due to the skewed distribution of length of stay, the logarithmic transformation was applied. Hence, data are given as the exponential of the estimated beta parameter, indicating how many times longer the length of stay was among blood culture-positive than culture-negative patients with *Streptococcus pneumoniae*.

confirmed the previous comparison of survival between the two groups of patients: for 15-day mortality, the HR was 3.3 (95% CI, 1.7 – 6.5, P = 0.0005); and for 30-day mortality, the HR was 2.8 (95% CI, 1.6 – 5.1, P = 0.0006).

Discussion

Our findings confirm that there are substantial differences in in-hospital course and outcomes among patients hospitalized with pneumonia due to *Streptococcus pneumoniae* as a function of their blood culture results. We found that patients with pneumococcal bacteremia have a poorer in-hospital course – in terms of septic shock – and poorer outcomes – in terms of in-hospital, 15- and 30-day mortality. Notably, we also identified that the illness severity on admission assessed by CURB-65 score was similar in the two groups.

Our study is important as comparing bacteremic with non-bacteremic pneumoccocal pneumonia we have identified that both course and outcomes are poorer for bacteremic patients while they show a similar severity of illness on admission. There is one previous study with the same design and similar results; the differences observed in the mortality were not, however, adjusted for host-related factors or antibiotic treatment [18]. Others strengths of this study are its prospective design, identification of cases based on clinical diagnosis, relatively large sample of non-selected patients, comprehensive assessment of outcomes, detailed collection of clinical data, and use of a robust risk-adjustment model.

When comparing characteristics of two groups of patients, the similarities rather than the differences are initially what are most important. In our study, patients were similar in age, level of comorbidity, and severity of illness on admission. Observed gender differences are consistent with the results of other studies [29,30], suggesting that women are less likely to develop sepsis, maybe related to the sex hormones or anatomic, lifestyle and behavioural differences [31]. Blood urea nitrogen, higher in bacteremic patients group, is an independent variable associated with the severity of pneumonia [25]. The dehydration, which is common in older patients hospitalized for pneumonia [32], may also contribute to a higher urea level. Besides, the rate of bilateral or multilobe radiological involvement and pleural effusion were significantly higher in bacteremic patients. Our findings indicate that the bacteremic patients had a poorer prognosis and higher case-fatality rate, while the illness severity on admission was similar in the two groups as assessed by the CURB-65 score. It is possible that bacteremic pneumococcal pneumonia adds some features that are not captured by this severity score.

The fact that clinical outcomes of pneumonia patients are different depending on whether or not they have

Table 4 Comparison between in-hospital course and outcomes of patients hospitalized with pneumonia by *Streptococcus pneumoniae* according the blood culture results: adjusted analysis

	Odds ratio (95% CI)*	*P* Value
In-hospital course		
Admission to intensive care unit	1 (0.7 – 1.4)	0.8
Use of mechanical ventilation	1.7 (1 – 3.1)	0.06
Septic shock†	2.1 (1.2 – 3.5)	0.006
Treatment failure	1.4 (1 – 2.1)	0.06
Severe sepsis	1.1 (0.8 – 1.5)	0.4
Outcomes		
In-hospital mortality	2.1 (1.1 – 3.9)	0.02
15-day mortality	3.6 (1.7 – 7.4)	0.0006
30-day mortality	2.7 (1.5 – 5)	0.002
30-day readmission	0.5 (0.2 – 1.1)	0.08
Length of hospital stay (days)‡		
Continuous	1.1 (1 – 1.2)‖	0.1
>3 days	1 (0.7 – 1.4)	0.8

CI, confidence interval.
*Odds ratio adjusted by severity of illness on admission measured by CURB-65, and those characteristics of patients and variables related to process-of-care which were found statistically significant according to blood culture results, such as sex, congestive heart failure, alcoholism, pneumococcal vaccine in last 5 years, pleural effusion, appropriate antibiotic, antibiotics within 4 hours, dual antibiotic therapy including a macrolide, and antibiotic administration prior to hospital admission. Only significant adjusting variables were kept in each model.
†Septic shock defined as arterial systolic blood pressure <90 mm Hg and need for vasopressors ≥ 4 hours.
‡Deaths are excluded.
‖For the comparison of length of hospital stay as a continuous variable, the general linear model was used, and due to the skewed distribution of length of stay, the logarithmic transformation was applied. Hence, data are given as the exponential of the estimated beta parameter, indicating how many times longer the length of stay was among blood culture-positive than culture-negative patients with *Streptococcus pneumoniae*.

pneumococcal bacteremia is an important long-standing issue that has yet to be fully understood. Our study adds new data on this issue in that it shows that the bacteremia is associated with poorer in-hospital course and outcomes. There are previous studies [17-20] with contradictory findings, although all of these have a small sample size without the adequate power to detect outcome differences between bacteremic and non-bacteremic groups of patients.

In agreement with our findings, several studies [14, 21,22,24] have found that bacteremia is a risk factor for death in patients with pneumonia. A meta-analysis [24] identified 11 factors, including bacteremia, with statistically significant associations with mortality in patients with pneumonia; however, the authors were unable to determine whether these factors are independently associated with mortality due to the nature of the primary data. Garcia-Vidal et al. [21], in a study carried out in a single hospital, identified pneumoccocal bacteremia as an independent factor associated with early death in patients with pneumonia. Further, a recent study [22] performed in one hospital in Taiwan found that the presence of *Streptococcus pneumoniae* bacteremia predicted mortality in pneumococcal pneumonia, although these authors included immunosuppressed patients and children. In contrast to our study, however, a Canadian multicentre study [23] showed similar outcomes in bacteremic pneumococcal pneumonia and non-bacteremic pneumonia, though using non-adjusted analysis. The low mortality rate (of 5.3%) among patients with pneumococcal bacteremia in that study is attributable to the fact that the most severely ill patients were often not enrolled. An international, retrospective study [33] concluded that pneumococcal bacteremia does not increase the risk of poor outcomes in patients with pneumonia; ICU admission rate and the non-adjusted pneumonia-mortality were, however, significantly higher in the pneumococcal bacteremic pneumonia

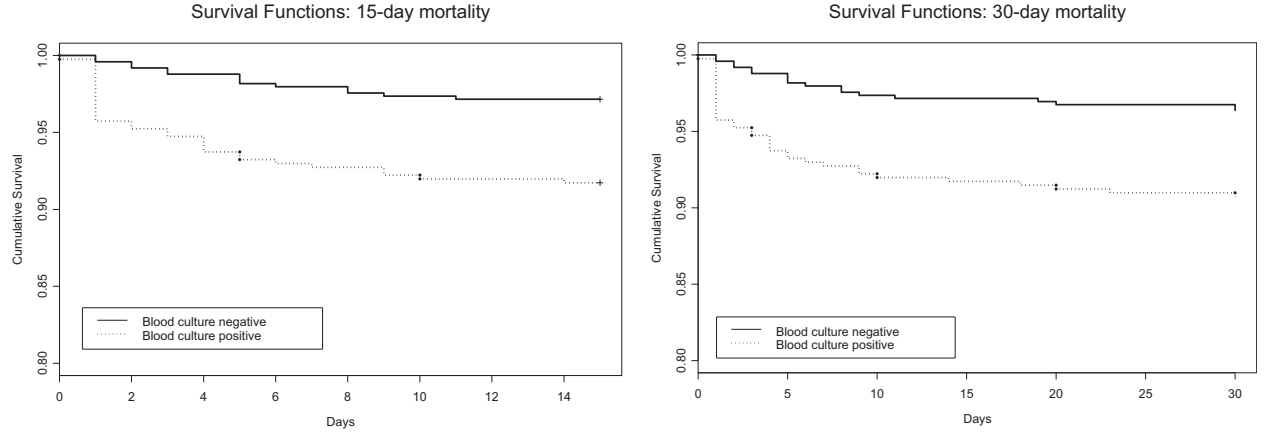

Figure 1 Kaplan-Meier survival curves for the blood culture positive and negative patients.

group. In a Spanish multicentre study [34] conducted in patients with pneumonia admitted to the ICU, bacteremia was not found to affect outcomes: in this case, the results may be due in part to enrolment bias, because the requirements for ICU admission in Spain have a selective approach for patients with advanced age and chronic risk factors.

Although we have assessed the differences in mortality between bacteremic and non-bacteremic groups adjusting for the antibiotic treatment used, the prescription of an antibiotic was appropriate according SEPAR guidelines in less than 70% of cases in the bacteremic group, because of the use of beta-lactam antibiotics alone. This treatment may be considered suboptimal because previous research [35,36] suggests a benefit of combination therapies, including a macrolide, applied to pneumonia associated with *Streptococcus pneumoniae* bacteremia. On the other hand, these studies are hampered by design limitations, and their conclusions should be interpreted with caution [37].

A potential weakness should be noted. In the current study, the ratio of bacteremic to non-bacteremic episodes was 81.1% (399/492 patients) when the percentage of patients with pneumococcal pneumonia and positive blood culture does not usually exceed 30%. In this study, only cases with blood culture results were included. The number of diagnosed cases of pneumococcal pneumonia was higher during the study period. This was due to the fact that requests for blood cultures in pneumonia are optional and depend on the judgment of the attending physician. In fact, it is accepted clinical practice not to request a blood culture once an immediate diagnosis has been obtained by the urinary antigen test. An another question to take into account. Inclusion criteria for "pneumococcal non-bacteremic" group were stringent in order to achieve an unquestionable diagnosis. Only the patients with positive antigen in urine and negative blood culture were included in this group. For this study we excluded patients whose diagnosis was just based on sputum culture, because a diagnosis method of pneumococcal pneumonia that does not depend on sputum culture is desirable.

Conclusions

We have examined the differences in pneumococcal pneumonia as a function of blood culture results. Although the host-related factors and severity on admission were very similar in the two groups, bacteremic patients had a poorer in-hospital course and outcomes. Bacteremia in pneumococcal pneumonia has prognostic significance given that is associated with poorer outcomes.

Abbreviations

CI: Confidence interval; CURB 65: Confusion, Urea nitrogen, Respiratory rate, Blood pressure, age ≥65 years; HR: Hazard ratio; ICU: Intensive care unit; OR: Odds ratio; SIRS: Systemic inflammatory response syndrome; SEPAR: Spanish Thoracic Society.

Competing interest

The authors have no competing interest to declare and sponsors had no role in this study.

Authors' contributions

AC, RZ, AB, LARI, JMQ, and PPE conceived and designed the study. RZ, ME, LARI, AG, and CE enrolled patients and collected and compiled data. AB performed the statistical analysis. AC, RZ, AB, ME AG, JMQ, and PPE analyzed and interpreted the data. AC, RZ, and AB wrote the manuscript. ME, LARI, AG CE, JMQ, and PPE commented and revised the report. All authors read and approved the final manuscript.

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ORIGINAL ARTICLE

Streptococcus pneumoniae antigen in urine: Diagnostic usefulness and impact on outcome of bacteraemic pneumococcal pneumonia in a large series of adult patients

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ABSTRACT

Background and objective: **Urinary pneumococcal antigen detection provides good results in the diagnosis of pneumococcal pneumonia but has rarely been used in bacteraemic pneumococcal pneumonia and it is not known whether it is associated with outcome in this type of pneumonia. Our objectives were to assess the usefulness of an immunochromatographic technique for detecting the pneumococcal antigen in urine in a large prospective study of patients with bacteraemic pneumococcal pneumonia and explore any potential association with outcomes.**

Methods: **This study, carried out over 8 years, included all adult immunocompetent patients admitted for bacteraemic pneumococcal pneumonia. An immunochromatographic test for the *Streptococcus pneumoniae* antigen in urine was performed in the first 24 h. The sensitivity of test was assessed and patients were divided into two groups according to test results to explore differences on admission and during the course of the illness using logistic regression models.**

Results: **Of the 350 patients with bacteraemic pneumococcal pneumonia included, 261 (74.6%) were positive for the antigen. Patient characteristics were very similar on admission and differences in severity (Pneumonia Severity Index) were not statistically significant. In the adjusted analysis, antigen-positive patients had a higher risk of intensive care unit admission, treatment failure and adverse outcome.**

Conclusions: **The sensitivity of the immunochromatographic urinary antigen test was 74.6% and positive results were associated with poorer clinical outcome. We therefore recommend systematic use of this test when pneumonia is diagnosed in the emergency department.**

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SUMMARY AT A GLANCE

In bacteraemic pneumococcal pneumonia patients, urinary pneumococcal antigen had good sensitivity. In addition, we present a novel finding, that in these patients, despite a similar severity as assessed by the PSI, those positive for the antigen were associated with poorer clinical outcome.

Key words: bacteraemic pneumococcal pneumonia, community-acquired pneumonia, outcome, sensitivity, urinary pneumococcal antigen.

Abbreviations: BPP, bacteraemic pneumococcal pneumonia; CAP, community-acquired pneumonia; CI, confidence interval; ICT, immunochromatography; ICU, intensive care unit; IMV, invasive mechanical ventilation; OR, odds ratio; PSI, Pneumonia Severity Index; UPA, urinary pneumococcal antigen.

INTRODUCTION

It is well established that *Streptococcus pneumoniae* is the aetiological agent most commonly associated with community-acquired pneumonia (CAP). It can, however, be very difficult to make a definitive microbiological diagnosis. The introduction of a technique based on the detection of the antigen in urine by immunochromatography (ICT) has been effective in increasing the microbiological diagnosis.[1,2] Various authors have demonstrated that this test has good sensitivity (70–80%) and excellent specificity (>90%). Unfortunately, these studies have included few patients (never over 100) of bacteraemic pneumococcal pneumonia (BPP), those considered as having definitive diagnoses.[3–9] This type of pneumonia is characterized by its severity; hence, it is important to identify a method to rapidly obtain the aetiological diagnosis and thence administer a specific antibiotic treatment[10] while in the emergency department.

In the studies focusing on BPP, the sensitivity of the urinary pneumococcal antigen (UPA) has ranged between 40% and 100%, and there is a lack of consensus over which factors influence this rate.[3–9] We considered that it would be interesting to study a large series of consecutive patients with this type of pneumonia to investigate the sensitivity of the technique and potentially associated factors, as well as the implications of having a positive result on patient outcome.

Our study had two objectives: to assess the usefulness of the ICT technique for detecting the UPA in a large prospective study of patients with BPP and to explore whether the results of the test are associated with outcomes in this type of pneumonia.

METHODS

Patients and study design

The study was conducted between 2002 and 2010 in two hospitals (Cruces Hospital and Galdakao-Usansolo Hospital) in the Basque Country (Spain). Routine UPA testing was carried out on all CAP patients within 24 h.

We prospectively included all adult patients (≥18 years of age) admitted for BPP. Patients were divided into two groups according to their UPA test results (positive or negative). Individuals with pneumonia were excluded if they were known to be positive for human immunodeficiency virus or chronically immunosuppressed, as were any who had had an episode of pneumonia in the previous 3 months and those with hospital-acquired pneumonia.

At the initial visit, a medical history was taken and tests were requested. Patients were treated empirically, in accordance with the local guidelines, with a beta-lactam antibiotic with or without a macrolide or fluoroquinolone. They were monitored daily while in hospital, and when discharged, all the corresponding data were recorded using a computer-assisted protocol. The ethics committees of Cruces and Galdakao hospitals approved the study.

Study variables

Data were collected on patient clinical and demographic characteristics, including the number of days since onset of the clinical symptoms, vaccination status, previous antibiotic treatment, blood test results and X-ray findings. To assess the severity of the pneumonia on admission, we used the Pneumonia Severity Index (PSI).[11]

In terms of the microbiological variables, susceptibility testing of *S.pneumoniae* according to new break points was performed for penicillin, ceftriaxone, erythromycin and levofloxacin.[12] We assessed the various serotypes found, grouping them into those associated with higher (3, 6A, 6B, 9N, 19F, 19A and 23F) and lower (1, 7F, 8, 4 and 5) mortality.[13]

Treatment was characterized using the following variables: (i) appropriate antibiotics (empirical selection in accordance with the recommendations of the Spanish Thoracic Society);[14] (ii) and (iii) antibiotic treatments within the first 4 or first 8 hours after arrival at the emergency department, respectively; (iv) duration of antibiotic treatment; (v) duration of intravenous antibiotic treatment; and (vi) type of antibiotics.

The course of the illness and patient outcome were described using the following variables: (i) admission to the intensive care unit (ICU); (ii) use of invasive mechanical ventilation (IMV); (iii) septic shock; (iv) treatment failure; (v) in-hospital mortality; (vi) adverse outcome; (vii) 30-day mortality; and (viii) length of hospital stay.

Definitions

BPP was defined as the presence of new pulmonary infiltrate on chest X-ray together with acute signs and symptoms suggestive of lower respiratory tract infection in addition to one positive blood culture for *S. pneumoniae* taken within 24 h of presentation to the hospital.

Septic shock was defined as a systolic blood pressure < 90 mm Hg and the need for a vasopressor agent for at least 4 h, after fluid therapy.[15] Treatment was considered to have failed when there was clinical deterioration with haemodynamic instability during hospitalization, appearance or worsening of respiratory failure, a need for mechanical ventilation, progression of the pneumonia as indicated by radiographic findings or the appearance of a new infectious focus, or persistence or reappearance of fever, if a change in treatment was required.[16] Adverse outcome of the illness was defined as in-hospital death and/or the development of shock and/or need for mechanical ventilation.[17]

Microbiological tests

Two blood cultures and a UPA test were performed for each patient within 24 h of their arrival at hospital. We used the BinaxNOW *S. pneumoniae* Antigen Card (Binax, Portland, ME, USA) for testing for the UPA.[3,4] This test detects the C-polysaccharide present on the cell wall of all pneumococcal strains. Urine was concentrated 25-fold by selective ultrafiltration (PM 15000, Minicon Urifil-10 Concentrator; Millipore, Bedford, MA, USA).[5,6] The results were considered qualitatively, positive or negative.

Given that all the patients had a definitive aetiological diagnosis, we did not assess the specificity but rather only the sensitivity of the UPA test using the standard formula.

Statistical analysis

For the descriptive analysis, frequencies and percentages, means and standard deviations or medians and interquartile ranges were calculated, as appropriate. Patient characteristics, the variables related to treatment, course of the illness and outcome were compared in the two groups (positive or negative UPA test results). Qualitative variables were compared with chi-square or Fisher exact tests, and quantitative variables with Student's *t*-tests or non-parametric Wilcoxon tests.

Univariate logistic regression models were used for comparing the variables related to course and outcome in the two groups. Then, multivariate logistic regression models were built, adjusting for severity (PSI score), multilobar involvement and for other variables known to have an impact on these results including previous antibiotic treatment, use of appropriate antibiotics and administration of antibiotics within 8 h.[18–22] The results are reported as odds ratios (ORs) and 95% confidence intervals (CIs). The lengths of hospital stay were compared using a generalized linear model and logarithmic transformation given the skewed distribution of the data. Finally, Kaplan–Meier survival curves were constructed for in-hospital and 30-day mortality for each group of patients, and these were compared using the log-rank test.

Differences were considered statistically significant if $P < 0.05$. All the statistical analysis was performed using SAS for Windows version 9.2 (SAS Institute, Cary, NC, USA) and S-Plus 2000 (MathSoft Inc., Cambridge, MA, USA).

RESULTS

We included 350 patients; UPA test was positive in 261 (74.6%). Patient characteristics, clinical data and test results are summarized in Table 1.

There were no significant differences in patient characteristics or the number of days since onset of the illness. Among antigen-positive patients, there were higher respiratory rates, lower arterial oxygen pressure and pH levels, and a higher rate of multilobar involvement, but the severity measured using the PSI was similar in the two groups ($P = 0.193$). No differences were found regarding other clinical, laboratory or radiological parameters studied, or in the rates of resistance to antibiotics.

Serotypes were identified in 288 (82.3%) and we found between-group differences, serotypes 1 and 3 being those most commonly associated with negative and positive results respectively ($P = 0.006$ and $P = 0.014$). Overall, serotypes 3, 6A, 6B, 9N, 19F, 19A and 23F were more common in antigen-positive (36.9% vs 18.5%, $P = 0.005$), and serotypes 1, 7F, 8, 4 and 5 in antigen-negative (49.2% vs 29.4%; $P = 0.003$) patients.

Treatments used are summarized in Table 2. There were no significant differences in the percentage of patients previously treated with antibiotics, or for whom drugs were selected appropriately or given within the first 4 h, though a higher percentage of antigen-positive patients were started on antibiotics within the first 8 h ($P = 0.024$). Most patients were treated with fluoroquinolones and the type of antibiotics ($P = 0.279$) and duration of the antibiotic treatments did not vary significantly.

In-hospital course and 30-day outcomes are described in Table 3. Among antigen-positive patients, there were higher rates of ICU admission, use of IMV, treatment failure, adverse outcome and 30-day mortality. The mean length of hospital stay was similar in the two groups.

In the adjusted analysis controlling for the variables listed in Table 4, antigen-positive patients had a higher risk of ICU admission (OR, 2.6; 95% CI: 1.1–6; $P = 0.025$), treatment failure (OR, 3.2; 95% CI: 1.2–9.2; $P = 0.023$) and adverse outcome (OR, 3.3; 95% CI: 1.2–9.2; $P = 0.023$). The Kaplan–Meier survival curves for the groups (Fig. 1) revealed differences in 30-day mortality ($P = 0.036$), but the differences in in-hospital mortality were not significant ($P = 0.062$).

DISCUSSION

On the basis of our results, we can confirm that the UPA test has good sensitivity among individuals with BPP. In addition, we present a more novel finding, namely that in patients with this type of pneumonia and with a similar severity as assessed by the PSI, those positive for the antigen tend to have a poorer clinical outcome.

To assess the sensitivity of a technique, it is essential to focus on patients with a definitive diagnosis such as those with BPP. Previously, various studies based on small samples of this type of patient have obtained sensitivities ranging from 40% to 100%.[3–9] Based on the largest sample of subjects reported to date, we found a sensitivity of 74.6%.

The reason why the UPA test is negative in some patients remains unknown, though various factors have been proposed, such as low levels of C-polysaccharide antigen and sequestration of the antigen by binding to serum antibodies in immune complexes, reducing urinary excretion of the antigen.[23] Other possible factors include the number of days from the onset of symptoms to diagnosis,[6] previous antibiotic treatment[4] and even severity.[7] In our sample, in which the test was performed within the first 24 h of arrival to the emergency department in all subjects, we found no associations with these last three factors. A controversial issue with regards to the sensitivity of this technique is the concentration of urine, a procedure that allows the rate of diagnoses to be increased, although the results are variable.[4,5] In our hospitals, urine concentration is used routinely; it is easy to perform and causes only a relatively small delay in diagnosis.

For the first time, we report evidence that positive UPA test results in BPP are associated with an adverse clinical outcome in hospital. We have conducted a prospective study with a large number of patients, collecting a wide range of data and adjusting the statistical analysis for factors known to have an impact on the progression of this type of pneumonia.[18–22] Previously, just one study had found an association between positive UPA test results and BPP,[24] but no association with an adverse outcome had been reported. Our two groups had a similar severity as assessed by the PSI. Further, the serotypes associated with greater mortality[13] were more common among the antigen-positive group, and those associated with a lower mortality more common in antigen-negative individuals.

The question that arises is why, in patients with similar severity, those positive for UPA have a poorer

Table 1 Characteristics of patients hospitalized with community-acquired pneumonia due to *Streptococcus pneumoniae* diagnosed by positive blood culture according to urinary antigen test results

Characteristics	Urinary antigen negative (n = 89)	Urinary antigen positive (n = 261)	P value
Age, years, mean (SD)	61.6 (18.7)	63.4 (18.7)	0.427
Age ≥ 65 years	46 (51.7)	147 (56.3)	0.448
Women	25 (28.1)	88 (33.7)	0.327
Underlying conditions			
Neoplastic disease	8 (9)	19 (7.3)	0.602
Liver disease	4 (4.5)	10 (3.8)	0.759
Congestive heart failure	14 (15.7)	32 (12.3)	0.403
Cerebrovascular disease	6 (6.7)	16 (6.1)	0.837
Renal disease	7 (7.9)	13 (5)	0.311
Chronic obstructive pulmonary disease	15 (17.1)	45 (17.3)	0.955
Diabetes mellitus	15 (17.1)	35 (13.4)	0.400
Number of comorbid conditions			0.306
0	45 (50.6)	138 (52.9)	
1	25 (28.1)	85 (32.6)	
≥ 2	19 (21.4)	38 (14.6)	
Nursing home resident	3 (3.4)	8 (3.1)	1
Smoking habit			0.507
No	33 (37.9)	87 (45.3)	
Yes	28 (32.2)	53 (27.6)	
Ex-smoker	26 (29.9)	52 (27.1)	
Heavy alcohol drinker	14 (16.9)	40 (16.1)	0.875
Influenza vaccine in previous year	21 (27.3)	59 (25.5)	0.764
Pneumococcal vaccine in the last 5 years	6 (6.9)	7 (2.9)	0.115
Findings on physical examination on admission			
Altered mental status	8 (9)	27 (10.3)	0.713
Pulse ≥ 125/min	12 (13.5)	44 (16.9)	0.453
Respiratory rate ≥ 30/min	15 (17.1)	76 (29.3)	0.024
Systolic blood pressure < 90 mm Hg	8 (9)	22 (8.4)	0.871
Temperature < 35°C or ≥ 40°C	1 (1.1)	6 (2.3)	0.683
Laboratory findings on admission			
Blood urea nitrogen > 30 mg/dl	35 (39.3)	133 (51)	0.057
Glucose ≥ 250 mg/dl	6 (6.7)	28 (10.7)	0.273
Haematocrit < 30%	4 (4.5)	5 (1.9)	0.240
Sodium < 130 mmol/L	6 (6.7)	27 (10.3)	0.315
PaO_2 < 60 mm Hg	34 (38.2)	137 (52.5)	0.020
Arterial pH < 7.35	2 (2.3)	22 (8.4)	0.046
CRP (mg/dl), mean (SD)	31.7 (15)	34.4 (17)	0.338
Leucocytes, mean (SD)	16452.8 (7146.4)	14870.3 (8142.8)	0.116
Creatinine (mg/dl), mean (SD)	1.43 (0.87)	1.42 (0.78)	0.720
Radiological findings on admission			
Multilobar involvement on chest X-ray	20 (22.7)	106 (40.6)	0.003
Pleural effusion	11 (12.4)	47 (18)	0.216
Days with symptoms prior to admission, mean (SD)	3.3 (2.2)	3.8 (2.6)	0.077
Severity of illness on admission			
PSI risk class[†]			0.193
I–III	47 (52.8)	114 (43.7)	
IV	33 (37.1)	103 (39.5)	
V	9 (10.1)	44 (16.9)	
Resistance			
Penicillin/amoxicillin	2 (2.3)	7 (2.7)	1
Ceftriaxone	0 (0)	0 (0)	NA
Erythromycin	10 (11.2)	31 (12)	0.853
Levofloxacin	0 (0)	0 (0)	NA
Serotypes			
1	11 (16.9)	13 (6.1)	0.006
14	4 (6.2)	16 (7.5)	1
19A	3 (4.6)	21 (9.8)	0.191
3	7 (10.8)	54 (25.2)	0.014
4	3 (4.6)	20 (9.4)	0.225
7	3 (4.6)	14 (6.5)	0.770
7F	6 (9.2)	14 (6.5)	0.424
8	7 (10.8)	16 (7.5)	0.398

Data are presented as numbers (percentage) unless otherwise stated. Percentages exclude patients with missing data.
[†] Severity of illness on admission assessed with the Pneumonia Severity Index (PSI).
CRP, C-reactive protein; IQR, interquartile range; NA, not applicable; SD, standard deviation.

Table 2 Process-of-care of patients hospitalized with bacteraemic community-acquired pneumonia due to *Streptococcus pneumoniae* according to urinary antigen test results

Process-of-care	Urinary antigen negative (n = 89)	Urinary antigen positive (n = 261)	P value
Previous antibiotic treatment	6 (6.7)	15 (5.8)	0.733
Appropriate antibiotic[†]	66 (75)	178 (68.2)	0.229
Antibiotics within 4 h	53 (65.4)	179 (76.2)	0.059
Antibiotics within 8 h	72 (88.9)	226 (96.2)	0.024
Length of antibiotic therapy, days, mean (SD)[‡]	14.4 (5.7)	15.5 (7.9)	0.589
Length of intravenous antibiotic therapy, days, mean (SD)[‡]	6.4 (6.2)	7.9 (7.9)	0.207
Antibiotic treatment			0.279
B-lactam monotherapy	15 (17.1)	60 (23)	
B-lactam/macrolide	0 (0)	7 (2.7)	
Fluoroquinolones	66 (75)	168 (64.4)	
Macrolide monotherapy	0 (0)	1 (0.3)	
Others	7 (8)	25 (9.6)	

Data are given as number (percentage) unless otherwise indicated. The percentage excluded patients with missing data.
[†] Appropriate antibiotic defined as usage of antibiotics recommended in the guidelines of the Spanish Thoracic Society (SEPAR).
[‡] Deaths are excluded.
SD, standard deviation.

Table 3 In-hospital course and outcomes of patients hospitalized with bacteraemic community-acquired pneumonia due to *Streptococcus pneumoniae* according to urinary antigen test results

	Urinary antigen negative (n = 89)	Urinary antigen positive (n = 261)	P value	Odds ratio[†] (95% CI)
In-hospital course				
Admission to intensive care unit	12 (13.5)	75 (28.7)	0.004	2.6 (1.3–5)
Use of mechanical ventilation	5 (5.6)	35 (13.4)	0.046	2.6 (1–6.9)
Septic shock[‡]	7 (8.6)	41 (17.5)	0.057	2.2 (0.9–5.2)
Treatment failure	8 (9)	56 (21.5)	0.008	2.8 (1.3–6.1)
Outcomes				
In-hospital mortality	3 (3.4)	26 (10)	0.051	3.2 (0.9–10.8)
30-day mortality	3 (3.4)	28 (10.7)	0.035	3.5 (1–11.6)
Adverse outcome[§]	8 (9)	59 (22.6)	0.005	3 (1.4–6.5)
Length of hospital stay (days)[¶]				
Mean (SD)	7.7 (7.7)	11.3 (15.0)	0.053	1.2 (1–1.5)[††]
Median (IQR)	5 (4–9)	7 (4–12)		
>3 days	72 (83.7)	194 (82.6)	0.806	0.9 (0.5–1.8)

Data are given as number (percentage) unless otherwise indicated. Percentages exclude patients with missing data. Treatment failure is defined in the text.
[†] Odds ratios represent the likelihood of a particular in-hospital course or outcome in urinary antigen-positive compared with urinary antigen-negative patients.
[‡] Septic shock is defined as arterial systolic blood pressure < 90 mm Hg and the need for vasopressors for a minimum of 4 h.
[§] Adverse outcome: In-hospital mortality and/or mechanical ventilation and/or septic shock.
[¶] Deaths are excluded.
[††] For the comparison of length of hospital stay as a continuous variable, a general linear model was used, and due to the skewed distribution of these data, a logarithmic transformation was applied. Hence, data are given as the exponential of the beta coefficient estimates, indicating how many times longer the hospital stay was among urinary antigen-positive than urinary antigen-negative patients with *Streptococcus pneumoniae* diagnosed by positive blood culture.
CI, confidence interval; IQR, interquartile range; SD, standard deviation.

clinical outcome. The most likely explanation, although we have not demonstrated this, lies in these patients having higher bacterial burdens. It is, however, difficult to assess this burden. The ICT technique in urine is qualitative. Attempts have been made to obtain a quantitative measure of the antigen indirectly by serial dilutions of urine samples from patients with pneumococcal pneumonia, and it was shown that the maximum dilution factor was higher for the more severe patients.[25] It can be supposed that the intensity of antigen expression in urine is associated with the intravascular burden of the bacteria and, more importantly, the severity of the illness. Nevertheless, the authors did not find any association

Table 4 Comparison between in-hospital course and outcomes of patients hospitalized with community-acquired pneumonia due to *Streptococcus pneumoniae* diagnosed by positive blood culture according to urinary antigen results: Adjusted analysis

	Odds ratio (95% CI)[†]	*P* value
In-hospital course		
Admission to intensive care unit	2.6 (1.1–6)	0.025
Use of mechanical ventilation	3.8 (0.8–17)	0.085
Septic shock[‡]	1.9 (0.7–5.5)	0.223
Treatment failure	3.2 (1.2–9.2)	0.023
Outcomes		
In-hospital mortality	2.2 (0.6–8.6)	0.248
30-day mortality	2.6 (0.7–9.8)	0.159
Adverse outcome[§]	3.3 (1.2–9.2)	0.023
Length of hospital stay (days)[¶]		
Continuous[††]	1 (0.9–1.3)	0.652
>3 days	0.7 (0.3–1.4)	0.285

[†] Odds ratios represent the likelihood of a particular in-hospital course or outcome in urinary antigen-positive compared with urinary antigen-negative patients, adjusted for PSI, multilobar involvement on chest X ray, use of appropriate antibiotics, antibiotic administration prior to hospital admission and antibiotics within 8 h, except for mortality because there was no case without antibiotic within 8 h who died.

[‡] Septic shock defined as arterial systolic blood pressure < 90 mm Hg and need for vasopressors ≥ 4 h.

[§] Adverse outcome: In-hospital mortality and/or mechanical ventilation and/or septic shock.

[¶] Deaths are excluded.

[††] For the comparison of length of hospital stay as a continuous variable, a general linear model was used, and due to the skewed distribution of these data, a logarithmic transformation was applied. Hence, data are given as the exponential of the beta coefficient estimates, indicating how many times longer the hospital stay was among urinary antigen-positive than urinary antigen-negative patients with *Streptococcus pneumoniae* diagnosed by positive blood culture.

CI, confidence interval.

with the course of the illness.[25] For blood, the best approach to determining bacterial burden seems to be a polymerase chain reaction-based technique for detecting genes of *S. pneumoniae*.[26] Rello *et al*., using the autolysin gene in 93 cases of pneumococcal pneumonia, found an association between high bacterial burden and higher mortality, a greater risk of septic shock and need for mechanical ventilation.[27] It seems therefore plausible that a higher bacterial burden would be associated with greater urinary excretion of the antigen and a higher rate of positive test results.

Secondly, it could also be supposed that antigen-positive patients would correspond to those in which there was a stronger inflammatory response that has been associated with greater severity.[28] In our study, the only indicator of inflammation considered was C-reactive protein and the levels were similar regardless of antigen test results.

Thirdly, impairment of renal function could influence the results. A study of patients with BPP found that those with impaired renal function were more likely to be antigen positive; however, as in most cases, the cause was reversible, above all dehydration, thus the high rate of positive results could be due to the urine being more concentrated.[29] No differences were found regarding these renal parameters between our two groups.

Lastly, we should consider the presence of certain serotypes. We observed that the serotypes that have been associated with higher mortality were more commonly found in the antigen-positive patients, while those associated with lower mortality were more prevalent among patients with negative results.[13,20] Although what the ICT technique detects is the C polysaccharide, which is present in all the serotypes, it could be that some have lower levels of this polysaccharide and hence it is not detected in urine.

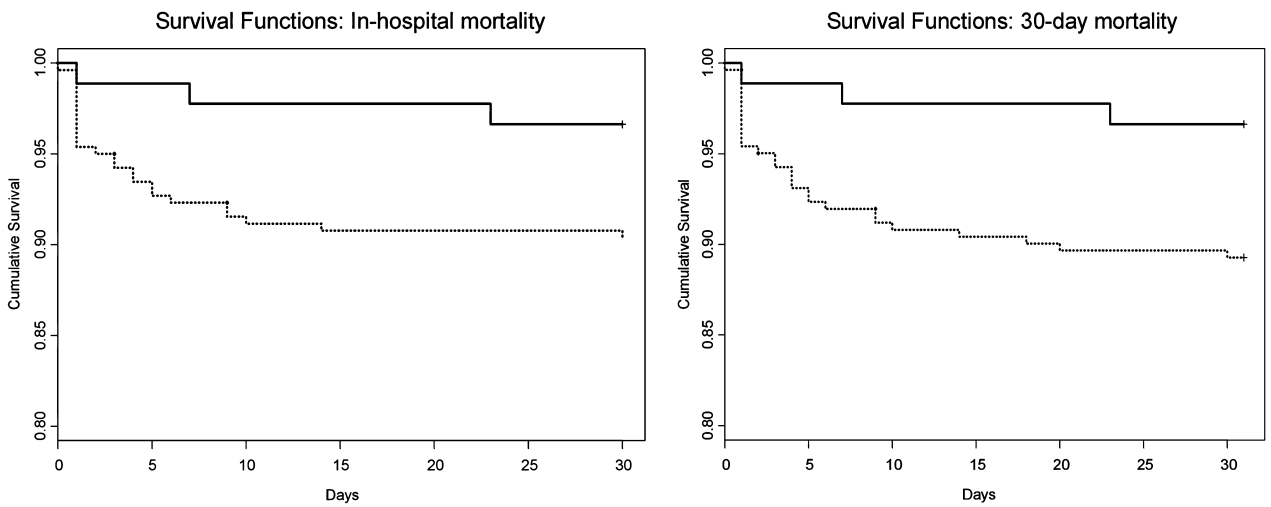

Figure 1 Kaplan–Meier survival curves for in-hospital and 30-day mortality for urinary antigen positive and negative patients. The log-rank test detected statistically significant differences between the two curves for 30-mortality ($P = 0.036$), but not for in-hospital mortality ($P = 0.062$). ———, urinary antigen negative; ·····, urinary antigen positive.

The study has some limitations. Our results exclusively show the patients with BPP. The role of UPA as an adverse outcome marker in non-bacteraemic patients should be explored in future studies. As bacterial burden was not assessed, we are not able explore its relationship with test results or its potential usefulness as a marker of severity.[27] There were few negative UPA with poor evolution which conditioned the statistical analysis. Further, in the multivariate analysis, we would like to have considered use of antibiotic therapy including a macrolide,[30] but were not able to since only seven patients (2%) were given this treatment. It would have also been interesting to adjust for serotypes,[13,20] but this was not possible given the high dispersion of the data.

We conclude that the ICT technique has a sensitivity of nearly 75% in cases of BPP, and is not clearly affected by any of the factors considered, although the role of serotypes should be explored in further studies. In addition, positive UPA test patients tended to have a poorer outcome of the illness. Given this, and consistent with recent recommendations,[1,31] we advocate the routine use of this technique in emergency departments, to guide the decision to start specific antibiotic treatments.

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Bacteremic Pneumococcal Pneumonia in Elderly and Very Elderly Patients

Host- and Pathogen-Related Factors, Process of Care, and Outcome

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Background. Hospitalizations due to pneumonia increase steadily with age. The purpose of this study is to explore differences in host- and pathogen-related factors, process of care, and outcome as a function of age in elderly patients with bacteremic pneumococcal pneumonia and identify factors related to mortality.

Methods. This was a prospective observational study of a cohort of elderly (65–79 years) and very elderly patients (≥80 years old) diagnosed with bacteremic pneumococcal pneumonia. The serotypes of the strains isolated and their resistance were also analyzed.

Results. During the study period, 399 patients were identified, of whom 225 patients (140 elderly and 85 very elderly patients) were included. Despite the groups having similar characteristics on admission, very elderly patients had higher rates of both hospital (16.47% vs 7.14%, $p = .028$) and 30-day (20% vs 6.43%, $p = .002$) mortality. Factors found to be predictors of mortality were: altered mental status (odds ratio [OR]: 13.18; 95% confidence interval [CI]: 3.68–47.23), respiratory rate more than or equal to 30/min (OR: 5.82; 95% CI: 1.82–18.64), systolic blood pressure less than 90 mmHg (OR: 10.90; 95% CI: 1.45–81.93), blood urea nitrogen more than 30 mg/dL (OR: 5.41; 95% CI: 1.03–28.42), bilateral or multilobar lung involvement (OR: 5.24; 95% CI: 1.55–17.76), and age (OR: 1.19; 95% CI: 1.09–1.30).

Conclusions. Very elderly patients have poorer outcomes with no significant differences in host- and pathogen-related factors or process of care. Mortality rates in these patients are associated with age and the severity of their clinical condition.

Key Words: Pneumonia in elderly persons—Bacteremic pneumococcal pneumonia—Pneumonia and mortality.

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PNEUMONIA caused by *Streptococcus pneumoniae* is one of the leading causes of hospital admission and mortality in patients older than 65 years (1). Approximately 20% of patients diagnosed with pneumococcal pneumonia develop bloodstream infections, this being traditionally associated with poorer and slower recovery (2,3). Recently, some authors have not found this association, although their studies have focused on the general population and not only on elderly patients (4).

The progressive population aging, the increase in the incidence of pneumococcal pneumonia with age (5), and improvement in survival rates in the last decade in elderly patients (6) make it important to explore the characteristics of the disease in various subgroups of the elderly population to improve the planning of care.

To date, little information is available regarding the process of care or host- and pathogen-related factors associated with bacteremic pneumococcal pneumonia (BPP) in elderly and very elderly patients (≥80 years old). For this reason, we assessed the impact of age group (65–79 vs ≥80 years old) on clinical presentation, process of care markers, outcome, and risk factors associated with 30-day mortality in a large cohort of elderly patients.

Materials and Methods

Setting, Patients, and Study Design

The study was conducted between January 2002 and January 2010 in two hospitals (Cruces University Hospital and Galdakao-Usansolo Hospital) in the Basque Country (Spain). We prospectively included all adults admitted for BPP. Patients were divided into two age groups: younger

than 65 and aged 65 and older. For the purpose of the analysis, patients aged 65 and older were classified as: (i) elderly patients, aged between 65 and 79 years and (ii) very elderly patients, aged 80 and older. We excluded patients with neutropenia or HIV infection and other immunosuppressed patients including transplant recipients.

A local ethics committee approved the study.

Clinical Assessment and Follow-up

During the initial visit, a thorough medical history, physical examination, and appropriate blood tests were performed. Patients were empirically treated in accordance with current Spanish guidelines. The severity of patients' clinical condition was assessed on admission using the Pneumonia Severity Index (PSI) (7). The following data were collected: (i) demographic data, (ii) epidemiological data, (iii) influenza and pneumococcal vaccination status, (iv) comorbidities, (v) clinical and examination data, (vi) blood test results and radiological findings on admission, (vii) clinical course, and (viii) antibiotic treatment administered.

Two consecutive blood cultures were taken for all patients within 24 hours after admission. Tests were conducted to assess the susceptibility of *S pneumoniae* to different antibiotics. Serotypes were assessed and grouped according to their associated mortality (8) (high mortality: serotypes 3, 6A, 6B, 9N, 19F, 19A, and 23F and lower mortality: serotypes 1, 7F, 8, 4, and 5).

To assess the treatment, the following variables were studied: (i) whether antibiotics were appropriate in accordance with the recommendations of the Spanish Society of Pulmonology (SEPAR) (9), (ii) and (iii) whether antibiotic treatments were started within 4 or 8 hours after arrival at the emergency unit, respectively, and (iv) the type of antibiotics administered.

Regarding inhospital course and outcome, the following variables were studied: (i) admission to the intensive care unit, (ii) use of invasive mechanical ventilation, (iii) septic shock, (iv) treatment failure, (v) early and late inhospital mortality, (vi) 30-day mortality, and (vii) length of hospital stay.

Definitions

Pneumonia was defined as the presence of new pulmonary infiltrate on the chest x-ray together with signs and symptoms suggestive of lower respiratory tract infection.

Septic shock was defined as a systolic blood pressure less than 90 mmHg and a need for vasopressor drugs for at least 4 hours, after fluid therapy (10). Treatment was considered to have failed when patients' clinical condition worsened during their hospital stay with: hemodynamic instability; appearance or worsening of respiratory failure; a need for mechanical ventilation; progression of the pneumonia, as indicted by radiological evidence or the appearance of new foci of infection; and persistence or reappearance of fever, if a change of treatment was required (11). Deaths within less than or equal to 72 hours after hospital admission were used to calculate early mortality. The diagnosis of altered mental status was based on observation that the mental state of the patient was not normal and that this was a new phenomenon, except if an individual was known to have had dementia prior to admission, when deterioration with respect to baseline was required (7).

Statistical Analysis

Descriptive analysis was undertaken, using frequencies and percentages, means and *SD*s, or medians and interquartile ranges. Characteristics of all the patients included were compared with two different groupings (patients aged <65 years vs ≥65 years and patients aged 65–79 years [elderly] vs ≥80 years [very elderly]), as were variables related to treatment, course of the disease, and outcomes. Comparisons were performed with chi-square or Fisher's exact tests for qualitative variables and with *t*-tests or nonparametric Wilcoxon tests for quantitative variables. Univariate logistic regression models were used to identify factors associated with 30-day mortality among patients aged 65 years and older. A multivariate logistic regression model was then constructed to assess the statistical significance of each independent factor. The dependent variable was 30-day mortality, and independent variables were factors found to have p value less than .15 in the univariate analysis. The interactions between independent variables were also considered. In the final multivariate model, only variables with p value less than .05 were included. Results were expressed as odds ratios (ORs) and 95% confidence intervals (CIs). The predictive ability of the final multivariate model was assessed by area under the receiver operating characteristic curve analysis, and the model calibration by comparing the observed with the predicted 30-day mortality using the Hosmer–Lemeshow goodness-of-fit test.

A p value less than .05 was considered statistically significant. Data analysis was performed using the SAS software for Windows version 9.2 (SAS Institute, Cary, NC).

Results

During the study period, 399 patients with BPP were identified, of whom 225 (56.39%) were aged 65 and older. Table 1 shows the baseline characteristics of all patients and differences as a function of their age (<65 vs ≥65 years and 65–79 vs ≥80 years).

Focusing on patients aged 65 and older, comorbidities such as chronic obstructive pulmonary disease and liver disease were more common in elderly patients. No statistically significant differences were observed in other clinical characteristics, blood test results or radiological findings.

Table 1. Comparison of Baseline Characteristics of Patients on Admission by Age

Characteristics	Age < 65 (*N* = 174)	Age ≥ 65 (*N* = 225)	*p* Value	65 ≤ Age < 80 (*N* = 140)	Age ≥ 80 (*N* = 85)	*p* Value
Women	48 (27.59)	83 (36.89)	.050	41 (29.29)	42 (49.41)	.002
Underlying diseases						
Neoplastic disease	7 (4.02)	20 (8.89)	.055	13 (9.29)	7 (8.24)	.788
Liver disease	6 (3.45)	12 (5.33)	.368	11 (7.86)	1 (1.18)	.033
Congestive heart failure	2 (1.15)	52 (23.11)	<.0001	30 (21.43)	22 (25.88)	.442
Cerebrovascular disease	3 (1.72)	19 (8.44)	.004	11 (7.86)	8 (9.41)	.684
Renal disease	3 (1.72)	24 (10.67)	.0004	12 (8.57)	12 (14.12)	.191
Obstructive pulmonary disease	22 (12.72)	52 (23.21)	.008	45 (32.14)	7 (8.33)	<.0001
Diabetes mellitus	15 (8.62)	45 (20.09)	.002	23 (16.43)	22 (26.19)	.078
Number of comorbid conditions			<.0001			.837
0	132 (75.86)	71 (31.36)		43 (30.71)	28 (32.94)	
1	29 (16.67)	101 (44.89)		65 (46.43)	36 (42.35)	
≥2	13 (7.47)	53 (23.56)		32 (22.86)	21 (24.71)	
Nursing home resident	4 (2.30)	9 (4.00)	.343	2 (1.43)	7 (8.24)	.029
Smoking			<.0001			.468
No	43 (29.86)	87 (56.13)		52 (52.5)	35 (62.50)	
Yes	75 (52.08)	11 (7.10)		8 (8.08)	3 (5.36)	
Ex-smoker	26 (18.06)	57 (36.77)		39 (39.39)	18 (32.14)	
Alcoholism	41 (24.40)	17 (8.10)	<.0001	15 (11.36)	2 (2.56)	.024
Influenza vaccine in the last year	10 (5.95)	83 (44.86)	<.0001	46 (38.33)	37 (56.92)	.015
Pneumococcal vaccine in the last 5 y	3 (1.81)	11 (5.37)	.074	6 (4.69)	5 (6.49)	.750
Findings on physical examination						
Altered mental status	9 (5.17)	30 (13.33)	.007	15 (10.71)	15 (17.65)	.138
Pulse ≥125/min	36 (20.69)	26 (11.61)	.013	20 (14.29)	6 (7.14)	.106
Respiratory rate ≥30/min	39 (22.54)	59 (26.58)	.357	37 (26.62)	22 (26.51)	.985
Systolic blood pressure <90 mmHg	21 (12.07)	9 (4.02)	.003	6 (4.29)	3 (3.57)	1
Temperature <35°C or ≥40°C	5 (2.87)	2 (0.90)	.248	2 (1.44)	0 (0)	.528
Laboratory findings						
Blood urea nitrogen >30 mg/dL	53 (30.46)	139 (61.78)	<.0001	80 (57.14)	59 (69.41)	<.0001
Glucose ≥250 mg/dL	8 (4.60)	31 (13.78)	.002	21 (15)	10 (11.76)	.0067
Hematocrit <30%	3 (1.72)	7 (3.11)	.524	4 (2.86)	3 (3.53)	.6472
Sodium <130 mmol/L	16 (9.20)	17 (7.56)	.555	10 (7.14)	7 (8.24)	.8061
PaO_2 <60 mmHg	54 (31.03)	134 (59.56)	<.0001	79 (56.43)	55 (64.71)	<.0001
Arterial pH <7.35	10 (5.75)	21 (9.33)	.185	14 (10)	7 (8.24)	.3696
Radiological findings						
Bilateral or multilobar involvement	67 (38.51)	75 (33.48)	.299	48 (34.29)	27 (32.14)	.5538
Pleural effusion	39 (22.41)	26 (11.56)	.004	15 (10.71)	11 (12.94)	.0131
Severity of illness						
PSI risk class			<.0001			<.0001
I–III	130 (74.71)	53 (23.56)		47 (33.57)	6 (7.06)	
IV	36 (20.69)	119 (52.89)		67 (47.86)	52 (61.18)	
V	8 (4.60)	53 (23.56)		26 (18.57)	27 (31.76)	
Antibiotic resistance						
Penicillin/amoxicillin	2 (1.15)	7 (3.11)	.125	6 (4.38)	1 (1.19)	.257
Ceftriaxone	0 (0)	0 (0)	—	0 (0)	0 (0)	—
Erythromycin	17 (9.77)	26 (11.55)	.723	15 (10.95)	11 (13.10)	.631
Levofloxacin	0 (0)	0 (0)	—	0 (0)	0 (0)	—
Urinary antigen			.553			.753
Negative	43 (24.71)	46 (20.44)		29 (20.71)	17 (20)	
Positive	114 (65.52)	147 (65.33)		93 (66.43)	54 (63.53)	
Not measured	17 (9.77)	32 (14.22)		18 (12.9)	14 (16.5)	
Serotype						
3 + 6A + 6B + 9N + 19F + 19A + 23F	38 (27.34)	69 (37.50)	.055	42 (35.90)	27 (40.30)	.553
1 + 7F + 8 + 4 + 5	56 (40.29)	52 (28.26)	.023	36 (30.77)	16 (23.88)	.318
Others	45 (32.37)	63 (34.24)	.725	39 (33.33)	24 (35.82)	.732

Notes: PSI = Pneumonia Severity Index. Data are presented as numbers (percentage) unless otherwise stated. Percentages exclude patients with missing data.

The very elderly patients were more frequently classified in the higher risk classes of the PSI (IV–V) ($p < .0001$). No significant differences were found in the rates of resistance to antibiotics tested. In 184 (81.77%) patients, the pneumococcal serotypes were identified, the most frequent serotypes being 3 (27.19%), 14 (9.23%), and 8 (8.70%), but differences in risk of death by serotype group were not significant.

The antibiotic treatments used are reported in Table 2. Very elderly patients received antibiotics earlier, but the duration of the treatment was shorter than that in the elderly group (12.49 vs 15.02 days, $p = .010$).

Table 3 shows the inhospital course and outcome indicators. Very elderly patients were less likely than elderly patients to be admitted to the intensive care unit or require mechanical ventilation, but there were no statistically significant differences in rates of septic shock or treatment failure during the hospital stay. Overall, 37 out of 399 (9.27%) patients died within 30 days, of whom 26 out of 225 (11.55%) were aged 65 and older. Very elderly patients had a higher rate of both inhospital (16.47% vs 7.14%, $p = .028$) and 30-day (20% vs 6.43%, $p = .002$) mortality, but a significantly shorter mean hospital stay than the elderly patients (6.89 ± 5.37 vs 10.54 ± 12.02, $p = .014$).

Table 4 summarizes the results of the univariate analysis of factors potentially associated with 30-day all-cause mortality in patients aged 65 and older. In the multivariate analysis, the independent factors that were significantly associated with 30-day mortality (Table 5) were: altered mental status (OR: 13.18; 95% CI: 3.68–47.23; $p < .0001$), respiratory rate more than or equal to 30 breaths/min (OR: 5.82; 95% CI: 1.82–18.64; $p = .003$), systolic blood pressure less than 90 mmHg (OR: 10.90; 95% CI: 1.45–81.93; $p = .020$), blood urea nitrogen more than 30 mg/dL (OR: 5.41; 95% CI: 1.03–28.42; $p = .046$), bilateral or multilobar involvement on chest x-ray (OR: 5.24; 95% CI: 1.55–17.76; $p = .008$), and age (OR: 1.19; 95% CI: 1.09–1.30; $p < .0001$). The area under the receiver operating characteristic

Table 2. Antibiotic Treatment and Time to Initial Administration

Process of Care	Age < 65 (*N* = 174)	Age ≥ 65 (*N* = 225)	*p* Value	65 ≤ Age < 80 (*N* = 140)	Age ≥ 80 (*N* = 85)	*p* Value
Previous antibiotic treatment	11 (6.32)	15 (6.67)	.890	9 (6.43)	6 (7.06)	.854
Appropriate antibiotic	124 (71.26)	149 (66.52)	.312	93 (66.91)	56 (65.88)	.875
Antibiotics within 4 h	116 (73.89)	141 (71.94)	.683	78 (65.55)	63 (81.82)	.013
Antibiotics within 8 h	147 (93.63)	184 (93.88)	.924	110 (92.44)	74 (96.10)	.372
Length of antibiotic therapy, days, mean (*SD*)*	15.45 (7.21)	14.13 (7.10)	.023	15.02 (8.10)	12.49 (4.36)	.010
Antibiotic treatment			.002			.861
β-lactam monotherapy	32 (18.39)	61 (27.23)		37 (26.62)	24 (28.24)	
β-lactam/macrolide	0 (0)	13 (5.80)		7 (5.04)	6 (7.06)	
Fluoroquinolones	123 (70.69)	134 (59.82)		84 (60.43)	50 (58.82)	
Others	18 (10.34)	16 (7.14)		11 (7.91)	5 (5.88)	

Notes: Data are given as number (percentage) unless otherwise indicated. The percentage excluded patients with missing data.
*Deaths are excluded.

Table 3. Inhospital Evolution and Outcomes of Patients by Age Group

	Age < 65 (*N* = 174)	Age ≥ 65 (*N* = 225)	*p* Value	65 ≤ Age < 80 (*N* = 140)	Age ≥ 80 (*N* = 85)	*p* Value
Inhospital evolution						
Admission to intensive care unit	55 (31.61)	37 (16.44)	.001	32 (22.86)	5 (5.88)	.001
Use of mechanical ventilation	25 (14.37)	17 (7.56)	.027	15 (10.71)	2 (2.35)	.021
Septic shock	26 (16.67)	27 (13.43)	.394	19 (14.96)	8 (10.81)	.405
Treatment failure	28 (16.28)	44 (19.64)	.389	24 (17.14)	20 (23.81)	.224
Outcomes						
Inhospital mortality	11 (6.32)	24 (10.67)	.128	10 (7.14)	14 (16.47)	.028
30-d mortality	11 (6.32)	23 (10.22)	.107	9 (6.43)	17 (20)	.002
Early mortality				6 (4.29)	9 (10.59)	.066
Length of hospital stay (d)*						
Mean (*SD*)	10.85 (17.02)	9.25 (10.31)	.810	10.54 (12.02)	6.89 (5.37)	.014
Median (IQR)	7 (4–11)	6 (4–9)	.810	7 (4–11)	5 (3–8)	.014

Notes: IQR = interquartile range. Data are given as number (percentage) unless otherwise indicated. Percentages exclude patients with missing data.
*Deaths are excluded.

Table 4. Odds Ratios (ORs) and 95% Confidence Intervals (CIs) for 30-d Mortality in Patients ≥65 y by Means of Univariate Logistic Regression Analysis

Characteristics*	30-d Mortality		OR (95% CI)	*p* Value
	Yes (*n* = 26)	No (*n* = 199)		
Age, mean (*SD*)	83.42 (8.25)	76.86 (6.78)	1.13 (1.07–1.20)	<.0001
Underlying conditions				
Diabetes mellitus	2 (7.69)	43 (21.72)	0.30 (0.07–1.32)	.112
Nursing home resident	3 (11.54)	6 (3.02)	4.20 (0.98–17.92)	.053
Influenza vaccine in the last year	4 (23.5)	79 (47)	0.35 (0.11–1.11)	.074
Findings on physical examination				
Altered mental status	12 (46.15)	18 (9.05)	8.62 (3.47–21.43)	<.0001
Respiratory rate ≥30/min	15 (60)	44 (22.34)	5.22 (2.19–12.42)	<.001
Systolic blood pressure <90 mmHg	3 (12)	6 (3.02)	4.39 (1.02–18.78)	.046
Laboratory findings				
Blood urea nitrogen >30 mg/dL	23 (88.46)	116 (58.29)	5.49 (1.59–18.87)	.007
PaO_2 <60 mmHg	20 (76.92)	114 (57.29)	2.49 (0.96–6.49)	.062
Arterial pH <7.35	6 (23.08)	15 (7.54)	3.68 (1.28–10.55)	.015
Radiological findings				
Bilateral or multilobar involvement	17 (65.38)	58 (29.29)	4.56 (1.92–10.82)	.001
Severity of illness on admission				
PSI risk class, mean (*SD*)	4.73 (0.45)	3.84 (0.79)	9.87 (4.03–24.16)	<.0001
Process of care				
Antibiotics within 4 h	19 (86.36)	122 (70.11)	2.70 (0.77– 9.52)	.123

Notes: PSI = Pneumonia Severity Index.
*Only variables with a $p < .15$ are shown.

Table 5. Association Between Selected Parameters and 30-d Mortality in Patients ≥65 y Analyzed by Multivariate Logistic Regression Adjusted for All Variables Listed in Table 4

Characteristics	OR (95% CI)	*p* Value
Age (continuous)	1.19 (1.09–1.30)	<.0001
Altered mental status	13.18 (3.68–47.23)	<.0001
Respiratory rate ≥30/min	5.82 (1.82–18.64)	.003
Systolic blood pressure <90 mmHg	10.90 (1.45–81.93)	.020
Blood urea nitrogen >30 mg/dL	5.41 (1.03–28.42)	.046
Bilateral or multilobar involvement on chest x-ray	5.24 (1.55–17.76)	.008
AUC	0.933	
Hosmer–Lemeshow *p* value*	0.9332	

Notes: AUC = area under the receiver operating characteristic curve; CI = confidence interval; OR = odds ratio.
*A significant value for the Hosmer–Lemeshow statistic indicates a significant deviation between predicted and observed outcomes.

curve for this model for predicting mortality was 0.9332. The model was a good fit to the data (Hosmer–Lemeshow, $p = .933$).

Discussion

This study provides a comprehensive evaluation of host-related factors, process of care, and mortality risk factors in a consecutive series of patients (age: ≥65 years) diagnosed with BPP. We found that age, altered mental status on admission, respiratory rate more than or equal to 30 breaths/min, low systolic blood pressure, blood urea nitrogen more than 30 mg/dL, and bilateral multilobar involvement are independent predictors of mortality. The very elderly patients had poorer outcomes—inhospital and 30-day mortality—despite a lack of differences between groups in the presentation of the disease.

The differences observed in clinical presentation and outcome as a function of age confirm that pneumonia in patients aged 65 years and older is a different entity. In this context, our sample is particularly interesting for three reasons: (i) the type of population studied, elderly and very elderly patients; (ii) the characteristics of the disease itself, all the cases being patients with bacteremic pneumonia; and (iii) the design of the study, both the sample size and that the data were prospectively collected on consecutive patients. To our knowledge, this is among the largest series reported focusing on this topic.

Overall, 16% of patients in this series, mostly from the elderly group, were to the intensive care unit. This indicates the negative impact of advanced age and the type of disease on indication for to the intensive care unit (12,13).

In this study, the mortality rate of patients aged 65 years and older was relatively low (11.55%) compared with that reported in other studies (10%–30%) (14). The early use of empirical antibiotic treatment in more than 90% of cases (15, 16) may have a positive influence on these outcomes. This treatment was appropriate according to the SEPAR guidelines (9) in less than 70% of cases, however, mainly due to the use of beta-lactams alone. Although some authors consider such treatment to be suboptimal, there is ongoing debate as to whether the addition of macrolides is beneficial in this type of pneumonia (17).

In this study, the combination of the six factors identified robustly predicts mortality as reflected in an area under the receiver operating characteristic curve of over 0.90. Previous studies have produced various different rules for predicting mortality in elderly patients diagnosed with pneumonia (18–21), but few studies have focused on the subgroup with pneumococcal bacteremia.

The role of age as a prognostic factor for pneumonia is controversial. Despite being the most important risk factor related to mortality in the PSI, its usefulness has been questioned, for overestimating the risk in some patients (22,23). Indeed, other authors have not found that age has a negative effect on survival (20,22,24,25). These findings may be explained by age having less weight as a prognostic factor than other host-dependent factors in series that only include elderly patients. In contrast, in our study, after adjusting for other factors and excluding any interactions between independent variables, we observed a positive correlation between age and inhospital and 30-day mortality. These differences may be mainly attributable to the characteristics of the patients included (invasive pneumococcal disease in all cases), the lower number of comorbid conditions, and pneumococcal vaccination. On the other hand, our findings are consistent with those from previous studies in patients with community-acquired pneumococcal bacteremia (26–28) and justify the routine use of the pneumococcal vaccination in this age group.

Altered mental status, respiratory rate more than or equal to 30 breaths/min, low systolic blood pressure, blood urea nitrogen more than 30 mg/dL, and bilateral or multilobar involvement on chest x-ray are classical predictive factors of mortality included in various prognostic scales validated both for the general (7,29) and elderly populations (24). Our results show that mortality is mainly associated with the severity of the infectious condition itself. The lack of statistically significant differences in the process of care between patients who died and those who survived and the early mortality rate of more than 60% may explain these results. In contrast, the presence of comorbidities was not related to a poorer prognosis, despite previous reports of an association with both the number (28) and severity of comorbidities in the short (30) and long term (15).

Our study has some limitations:

1. The most important limitation was the lack of functional assessment. Functional status, in addition to PSI, could provide information about mortality without overestimating the risk related to chronological age (21,22).
2. The analysis of the mortality risk factors was performed for all patients aged 65 years and older and not separately in the subgroups by age, given that the small number of patients who died would weaken the statistical power of the tests used.
3. In the multivariate analysis, we did not adjust for the use of antibiotic therapy including macrolides, given that this was prescribed in only 13 patients.
4. Only a small number of institutionalized patients were included; therefore, it is not possible to draw conclusions for this subgroup of the population.

To summarize, this study demonstrates that in a large population of patients (age: ≥65 years) diagnosed with BPP, the very elderly group have poorer outcomes despite a lack of statistically significant differences in host-related factors or the process of care compared with the younger elderly group. We also found that mortality is mainly associated with age and the severity of the infectious condition itself. Adequate early empirical antibiotic treatment has a very important role in the design of strategies for improving the process of care in these patients.

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Age-related differences in management and outcomes in hospitalized healthy and well-functioning bacteremic pneumococcal pneumonia patients: a cohort study

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Abstract

Background: Limited data are available regarding fit and healthy patients with pneumonia at different ages. We evaluated the association of age with clinical presentation, serotype and outcomes among healthy and well-functioning patients hospitalized for bacteremic pneumococcal community–acquired pneumonia.

Methods: We performed a prospective cohort study of consecutive healthy and well-functioning patients hospitalized for this type of pneumonia. Patients were stratified into younger (18 to 64 years) and older (≥65 years) groups.

Results: During the study period, 399 consecutive patients were hospitalized with bacteremic pneumococcal pneumonia. We included 203 (50.8%) patients who were healthy and well-functioning patients, of whom 71 (35%) were classified as older. No differences were found in antibiotic treatment, treatment failure rate, antibiotic resistance, or serotype, except for serotype 7F that was less common in older patients. In the adjusted multivariate analysis, the older patients had higher 30-day mortality (OR 6.83; 95% CI 1.22–38.22; $P = 0.028$), but were less likely to be admitted to the ICU (OR 0.14; 95% CI 0.05–0.39; $P < 0.001$) and had shorter hospital stays (OR 0.71; 95% CI 0.54–0.94; $P = 0.017$).

Conclusions: Healthy and well-functioning older patients have higher mortality than younger patients, but nevertheless, ICU admission was less likely and hospital stays were shorter. These results suggest that the aging process is a determinant of mortality, beyond the functional status of patients with bacteremic pneumococcal pneumonia.

Keywords: Bacteremic pneumococcal pneumonia, Community-acquired pneumonia, Pneumonia in older people

Background

The incidence of pneumonia and associated mortality are higher in older than younger people. Pneumonia is the third most frequent cause of hospitalization in patients aged 65 years or over [1], streptococcus pneumoniae being the main pathogen isolated. Bacteremic pneumococcal pneumonia constitutes a severe subgroup with its own features.

Many previous studies have found that the mortality risk among older patients with pneumonia depends on the severity of the lung infection, and adequacy of the response to the infection and other host factors including comorbidities and low functional status [2, 3]. Ageing is among the most important known risk factors for most chronic diseases.

Older patients with pneumonia tend to have multiple comorbid chronic conditions leading to loss of functional independence and an inadequate response to the infectious process. The role of age in mortality prediction is controversial due to interactions between age and comorbidities. Further, pneumonia itself can trigger

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acute mobility impairment and delirium in this population. All of these factors are markers of frailty and increase the likelihood of poor outcomes [4–6]. Frailty refers to an individual's increased susceptibility towards adverse clinical events, and it is becoming recognized that frailty represents a dynamic geriatric syndrome distinct from, but overlapping with, comorbidities and disability [7–9]. On the other hand, improvements in social and health conditions together with a rise in life expectancy have resulted in an increase in the number of "healthy" and well-functioning older people. There is limited information, however, regarding process of care and outcomes of common medical conditions requiring hospital admission in this subgroup of fit and healthy older patients.

Aging is characterized by progressive tissue degeneration leading to a negative effect on the structure and function of vital organs even in the absence of comorbid illness [10]. For this reason, we hypothesized that the survival of healthy older patients would be poorer than that in younger patients. To test this hypothesis, our aim was to assess the association of age with clinical presentation, serotype, process of care and outcomes among healthy and well-fitted older patients hospitalized for bacteremic pneumococcal community–acquired pneumonia.

Methods

Study design and population

This was a prospective observational study of consecutive patients hospitalized for bacteremic pneumococcal pneumonia (positive blood culture taken within 24 h after admission) in two tertiary medical centers. The study was conducted between January 2002 and January 2010. The ethics committees of Cruces and Galdakao Hospitals approved the study.

The healthy and well-functioning patients´ state condition was assessed using the Clinical Frailty Scale (CFS) [11]. This tool provides a quick and easy estimation based on clinical judgment and quantifies frailty on a scale ranging from 1 (very fit) to 9 (terminally ill). Each patient was assigned a score on the CFS by two seniors researchers using data extracted from Cruces/Galdakao prospective pneumonia registry. For the purpose of the study, we only included patients who were considered independent in activities of daily living and had no medical comorbidities (categories 1, "very fit", and 2, "well", of the CFS). These patients were stratified into two groups according to their age: 1) younger adults (18–64 years); and 2) older adults (≥ 65 years).

Study variables

Since 2000, there has been an ongoing prospective and standardized registry of all patients hospitalized for pneumonia in our two hospitals. This registry includes multiple variables characterizing patients and their pneumonia. For eligible patients, we assessed data on socio-demographic characteristics (including ability to carry out basic activities of daily living, self-care activities and regular physical activity), medical comorbidities, influenza and pneumococcal vaccination status, vital signs, results of routine laboratory tests, including the pneumococcal urinary antigen test, and radiological findings on admission. Patients were empirically treated in accordance with the National Guidelines of the Spanish Society of Pulmonology [SEPAR] [12] at the discretion of the attending doctor. The severity of patients' clinical condition was assessed on admission using the *CURB-65 score* [13]. All survivors were followed up to 30 days after discharge or until complete radiological resolution.

Two consecutive blood cultures were taken for all patients within 24 h after hospital admission. Tests were conducted to assess the susceptibility of *Streptococcus pneumoniae* to the following antibiotics: penicillin, ceftriaxone, erythromycin and levofloxacin. Pneumococcal serotypes were assessed and grouped according to the associated risk of mortality into the following categories: 1) high risk, serotypes 3, 6A, 6B, 9 N, 19F, 19A, and 23F; 2) intermediate risk, serotypes 9 V, 12F, 14, and 22F; and 3) low risk, serotypes 1, 7F, 8, 4 and 5 [14].

Clinical outcomes

To assess the treatment, the following variables were studied: 1) appropriateness of the empirical antibiotic used (according to the recommendations of the Spanish Society of Pulmonology [SEPAR]) [12]; 2) and 3) whether antibiotic treatments were started within 4 or 8 h after arrival at the emergency department, respectively; and 4) the class of antibiotics administered.

Clinical in-hospital course and outcome measures included: 1) admission to the intensive care unit (ICU); 2) use of invasive mechanical ventilation; 3) septic shock; 4) in-hospital, early (≤ 48 h) [15] and 30-day mortality; 5) treatment failure; 6) length of hospital stay; and 7) 30-day readmission.

Definitions

Pneumonia was defined as the presence of new pulmonary infiltrate on the chest X-ray together with signs and symptoms suggestive of lower respiratory tract infection. Septic shock was defined as a systolic blood pressure of less than 90 mmHg and a need for vasopressor drugs for at least 4 h, after fluid therapy [16]. Treatment was considered to have failed when patients' clinical condition worsened during their hospital stay with: hemodynamic instability; appearance or worsening of respiratory failure; a need for mechanical ventilation; progression of the pneumonia, as indicated by radiological findings or the appearance of a new focus of infection; or persistence or

reappearance of fever, if a change of treatment was required [17]. The diagnosis of altered mental status was based on observation that the patient's mental state was not normal and that this was a new phenomenon. Comorbidities including the follow conditions: chronic respiratory disease, diabetes mellitus, chronic cardiovascular disease, neurologic disease, liver disease and chronic renal disease.

Statistical analysis

Descriptive analysis was undertaken, using frequencies and percentages, means and standard deviations (SDs) or medians and interquartile ranges (IQRs). Patient characteristics were compared between the groups (younger vs older patients), as were variables related to treatment, serotypes, in-hospital course and outcomes. Comparisons were performed with chi-square or Fisher's exact tests for qualitative variables, and with t tests or non-parametric Wilcoxon tests for quantitative variables.

Univariate logistic regression models were used to compare in-hospital course and clinical outcomes between the groups. Then, multivariate logistic regression models were built adjusting for CURB score (as a continuous variable), variables with $p < 0.05$ and other variables considered clinically relevant in the univariate analysis as potential independent variables. The results are reported as odds ratios (ORs) and 95% confidence intervals (CIs), considering the younger patients (age < 65 years) as the reference group. For comparing length of stay, a general linear model was used, and due to their skewed distribution, these data were log-transformed. Hence, the results are given as the exponential of the estimated beta parameter, indicating how many times longer the mean stay of older patients was than that of younger patients.

A *P* value <0.05 was considered statistically significant. All the statistical analysis was performed using the SAS software for Windows version 9.2 (SAS Institute, Cary, NC).

Results

During the study period, a total of 4978 consecutive patients diagnosed with pneumonia were hospitalized in our two hospitals, including 399 with bacteremic pneumococcal pneumonia. Of these, 203 (50.8%) were healthy and well-functioning, 132 patients being <65 years and 71 being 65 years old or older.

Table 1 summarizes the baseline characteristics of all patients stratified by age. Younger patients were more often smokers and heavy drinkers, and were more likely to have higher heart rate and hypotension, while more of the older patients had altered mental status at admission. In addition, the older patients were more likely to have severe hypoxemia and elevated blood urea nitrogen levels. No statistically significant differences were observed in urinary antigen test or radiological imaging results. The older patients were more frequently classified in the higher risk classes of the *CURB-65 score* (3 to 5) ($P < 0.001$). None of the eligible population for this study had previously been in long-term care facilities.

The antibiotic treatments used are reported in Table 2. Treatment duration was shorter in the older group (13.6 vs 15.7 days, $P = 0.022$). The most common single antibiotic class administered was fluoroquinolones in both groups and differences in antibiotic class and treatment failure rate were not significant. Further, no significant

Table 1 Demographic and clinical characteristics at admission

Characteristics	Age < 65 years (*N* = 132)	Age ≥ 65 years (*N* = 71)	*P* value
Demographics			
Male sex	92 (69.7)	36 (50.7)	0.007
Age (years), mean (SD)	43.67 (11.7)	78.27 (8)	<0.001
Vaccination status			
Influenza vaccine	3 (2.3)	23 (41)	<0.001
Pneumococcal vaccination	0 (0)	1 (1.6)	0.322
Current tobacco use	63 (56.2)	2 (4.8)	<0.001
Heavy drinker (> 80 mg alcohol/day)	29 (22.3)	6 (8.7)	0.016
Clinical characteristics at admission			
Body temperature (°C), mean (SD)	38.05 (1.1)	37.82 (1.1)	0.239
Respiratory rate, mean (SD)	22.50 (6.8)	25.06 (6.7)	0.004
Heart rate, mean (SD)	108.43 (21)	97.70 (17.6)	<0.001
Altered mental status	3 (2.2)	12 (16.9)	<0.001
Systolic blood pressure < 90 mmHg	17 (12.8)	1 (1.4)	0.006
Laboratory and radiological findings			
BUN >30 mg/dL	36 (27.2)	38 (53.5)	<0.001
PaO_2 < 60 mmHg	39 (29.5)	47 (66.2)	<0.001
CRP (mg/dL), mean (SD)	35.23 (18.3)	28.53 (18.4)	0.191
Multilobar pneumonia	53 (40.1)	22 (31.4)	0.222
Pleural effusion	29 (21.9)	8 (11.2)	0.059
Urinary antigen positive	87 (71.3)	51 (83.6)	0.068
Antibiotic resistance			
Penicillin/amoxicillin	1 (0.7)	2 (2.9)	0.267
Ceftriaxone	0 (0)	0 (0)	—
Erythromycin	12 (9.1)	7 (10.2)	0.783
Levofloxacin	0 (0)	0 (0)	—
CURB-65 score			<0.001
0-I	96 (72.7)	4 (5.6)	
2	31 (23.4)	38 (53.5)	
3–5	5 (3.7)	29 (40.8)	

Data are given as frequency (percentage) unless otherwise stated. Percentages exclude patients with missing data
SD Standard deviation, *CRP* C-reactive protein, *BUN* Blood urea nitrogen

Table 2 Indicators for healthy and well-functioning hospitalized patients with pneumococcal pneumonia

Process of care	Age < 65 years (*N* = 132)	Age ≥ 65 years (*N* = 71)	*P* value
Prior antibiotic treatment	8 (6.1)	9 (12.6)	0.104
Antibiotic within 4 h	88 (71.5)	46 (69.7)	0.789
Antibiotic within 8 h	115 (93.5)	59 (89.3)	0.320
Appropriate antibiotic	96 (72.7)	51 (71.8)	0.891
Length of antimicrobial treatment, days, mean (SD)	15.71 (7.3)	13.61 (9.12)	0.022
Antibiotic treatment			0.364
Beta-lactam	21 (15.9)	17 (23.9)	
Fluorquinolones	95 (71.9)	47 (66.2)	
Others	16 (12.1)	7 (9.8)	
Combination therapy including a macrolide	0 (0)	4 (5.6)	0.017
Treatment failure	16 (12.3)	12 (17.1)	0.347

Data are given as frequency (percentage) unless otherwise stated. Percentages exclude patients with missing data
SD Standard deviation

differences were found in the rates of resistance to antibiotics tested. Beta-lactam in combination with a macrolide was only prescribed in four patients, all of them elderly.

Serotype analysis was performed in 165 out of the 203 patients (81.2%), and the serotype distribution was found to vary widely. The most frequent serotypes are listed in Table 3. Of them, serotype 7F was more frequently identified in younger patients. No significant differences were observed in the rest of serotypes studied, either separately or clustered by the associated risk of death.

Table 4 presents the in-hospital course and clinical outcome indicators. The older patients were less likely to be admitted to the ICU. Overall, 13 out of 203 (6.4%) patients died within 30 days. Five of these (two ≥65 years old) had been admitted to the ICU. The older patients had higher in-hospital (12.6% vs 2.2%, $P = 0.004$), early (8.4% vs 0.7%, $P = 0.008$) and 30-day (14.1% vs 2.2%, $P = 0.001$) mortality. There were no significant differences in 30-day readmission rate between groups. In the adjusted multivariate analysis, the older patients had higher 30-day mortality (OR 6.83; 95% CI 1.22–38.22; $P = 0.028$), but were less likely to be admitted to the ICU (OR 0.14; 95% CI 0.05–0.39; $P < 0.001$) and had shorter hospital stays (OR 0.71; 95% CI 0.54–0.94; $P = 0.017$) than the younger patients.

Discussion

The results of this study show that the mortality of healthy older people hospitalized for bacteremic pneumococcal pneumonia is higher than that of younger adult patients (<65 years old) with the same characteristics, independent of the serotype, severity and the type of care provided. Despite their good baseline health and functional status, ICU admission rates are lower in patients ≥65 years old.

Table 3 Serotype distribution by age group

Serotype	Age < 65 years (*N* = 132)	Age ≥ 65 years (*N* = 71)	*P* value
3	17 (16)	15 (25.4)	0.143
4	11 (10.3)	2 (3.3)	0.138
8	9 (8.4)	4 (6.7)	0.772
1	15 (14.1)	7 (11.8)	0.678
19A	9 (8.4)	5 (8.4)	0.997
14	5 (4.7)	3 (5.1)	1
7F	19 (17.9)	4 (6.7)	0.033
22	4 (3.7)	3 (5.1)	0.701
Clusters			
High risk (3 + 6A+ 6B + 9 N + 19F + 19A + 23F)	28 (26.4)	22 (37.2)	0.145
Intermediate risk (9 V + 12F + 14 + 22F)	8 (7.5)	5 (8.4)	1
Low risk (1 + 7F + 8 + 4 + 5)	44 (41.5)	17 (28.8)	0.105

Data are given as frequency (percentage). Percentages exclude patients with missing data

Table 4 In- hospital and 30-day outcomes by age group

Outcome Measures				Non-adjusted analysis		Adjusted analysis[a]
	Age < 65 years (*N* = 132)	Age ≥ 65 years (*N* = 71)	*P* value	Odds ratio (95% CI)		*P* value
In-hospital mortality	3 (2.2)	9 (12.6)	0.004	6.24 (1.63–23.87)	4.22 (0.75–23.69)	0.101
Early mortality	1 (0.7)	6 (8.4)	0.008	12.09 (1.43–102.51)	4.34 (0.36–52.36)	0.248
30-day mortality	3 (2.2)	10 (14.1)	0.001	7.05 (1.87–26.54)	6.83 (1.22–38.22)	0.028
Intensive care unit	38 (28.7)	12 (16.9)	0.060	0.50 (0.24–1.04)	0.14 (0.05–0.39)	<0.001
Invasive mechanical ventilation	13 (9.8)	4 (5.6)	0.301	0.55 (0.17–1.74)	0.32 (0.08–1.32)	0.114
Septic shock	16 (13.4)	8 (12.7)	0.887	0.94 (0.38–2.33)	0.59 (0.19–1.90)	0.377
Length of hospital stay, days[b]						
Mean (SD)[c]	11.02 (17.7)	7.50 (8.2)	0.809	0.85 (0.64–1.13)	0.71 (0.54–0.94)	0.017
Median (IQR)	6 (4–10)	5 (3–8)	0.809			
30-day readmission	2 (2.1)	1 (1.7)	1	0.83 (0.07–9.40)		

Odds ratios are calculated considering the group of patients with age < 65 years old as the reference group
[a]Adjusted analysis: Odds ratio adjusted for CURB (as a continuous variable), sex, heavy drinking, PaO_2 < 60 mmHg, appropriate antibiotic and antibiotic within 4 h
[b]Deaths are excluded
[c]For the comparison of length of hospital stay as a continuous variable, a general linear model was used, and due to the skewed distribution of length of stay, these data were log-transformed. Hence, data is given as the exponential of the estimated beta parameter, indicating how many times longer the mean stay of patients ≥65 years was than that of those <65 years old. CI, confidence interval; IQR interquartile range; SD, standard deviation

The interest of our study lies in the type of population studied. To our knowledge, this is the first study specifically focused on the subgroup of healthy and well-functioning young and older adults with bacteremic pneumococcal pneumonia.

In developed countries, the prognosis of pneumonia in older people has changed in the last decade, mainly due to improvements in healthcare and social conditions. As a consequence, it has recently been proposed that diagnostic and therapeutic decisions should be based more on the patients' degree of frailty than their age [18, 19]. This concept may be a better reflection of biological than chronological age. Nevertheless, frail is not synonym for having comorbidities or functional limitations; rather it is recognized as a distinct clinical syndrome characterized by a decrease in physiological reserve and resistance to stressful situations, making individuals more vulnerable to health problems [9]. There is no consensus, however, as to how frailty should be assessed. There are many definitions, the majority of which are based on complex scales and which have not gained acceptance among practicing clinicians [20]. The CSHA Clinical Frailty Scale is a simple and reproducible tool that provides a realistic and simple way to assess the reality of these patients in different medical conditions [21, 22].

The prevalence rates of chronic disease and functional impairment in adults increase proportionally with age [23]. Nonetheless, the contribution of underlying diseases to outcomes in patients with pneumonia remains somewhat controversial [24–26]. Further, a recent study has shown that serotype rather than the presence of comorbidities is the most important risk factor for the development of respiratory failure in patients with pneumococcal pneumonia [27]. Conversely, evidence on the role of functional status seems to be one of the most consistent predictors of poor clinical outcomes [28, 29].

Several studies have investigated the association between frailty and outcomes in hospital and after discharge but none of them to our knowledge have been designed to compare healthy and well-functioning patients stratified by age [21, 30, 31]. Although there are no specific studies on this population, it is generally assumed that there are no significant differences between the management of older and younger patients with the same characteristics [18]. In this study, however, we found that older patients have higher 30-day mortality. Other authors have reported a poorer prognosis for pneumonia in elderly patients without comorbidities but none of these studies have been adjusted for severity [32, 33].

The reason for this poorer outcome is not clear. Despite the fact that we have previously reported that mortality in elderly patients with bacteremic pneumococcal pneumonia is associated with age and the severity of the infectious condition itself, the role of age as a prognostic factor is controversial [34, 35]. From a theoretical point of view, a healthy non-frail patient might represent a good model for studying the effect of ageing itself on the management and prognosis of multiple diseases. In our study, given the lack of significant differences in the class of antibiotics provided and virulence of the serotype involved, age seems likely to be relevant to prognosis. In fact, a causative role of immunosenescence in the outcome of older patients seems highly plausible [36]. Aging

is associated with changes in immune response impairment of alveolar macrophage function and increases in cellular apoptosis during sepsis, leading to a greater severity of infection [37]. Nevertheless, other authors have reported that age itself did not have any impact on mortality in patients with one or no comorbid conditions, except for those aged 80 years and older [38]. In our study, we cannot exclude in a subgroup of patients a pre-frail stage revealing a vulnerable state of relatively low physiological reserve to respond adequately to any acute clinical deterioration. Such a state may identify a subset of patients who are at high risk of progressing to frailty or reverse to non-frail under external stressors [9].

On the other hand, it is recognized that age itself is an important limiting factor for ICU admission, independent of baseline status and severity of illness [39–42]. However, to our knowledge no previous studies have focused on older patients who were fit and "healthy". Given the progressive aging of the population, we should consider changing ICU admission criteria to take into account biological age, more than chronological age.

Our study has some limitations: 1) We have not used any functional assessment scale, and hence, we cannot completely rule out a certain degree of functional limitation in some patients. The effect of any misclassification in this study would be limited, because according to some authors self-reported measures of mobility limitation are well correlated with other objective scales [43, 44]. 2) Due to the characteristics of our registry, we may not have adequately identified the subgroup of "vulnerable" patients (CFS = 3, 4), namely, those who are not dependent but do have some limitations and complain of being "slowed up" or tired [11, 30]. Although such patients should not be considered frail, we cannot rule out a pre-frail state having contributed to the poor outcome in some patients. Further, we have not assessed the role of concomitant medications that could have influenced the outcome of these patients [45]. 3) There was a low rate of inpatient death, and this is reflected in wide CIs. This is attributable to the type of population eligible for this study and the marked reduction in mortality among pneumonia patients in recent years. 4) The observational study design could have introduced bias. In particular, decisions on the process of care were left to the discretion of the managing physicians. The effect of this potential source of heterogeneity may be limited by the high degree of reliability and prospective collection of data, together with the adjustment for potential confounding variables. Given this and to avoid possible age bias, the multivariate logistic regression models adjusted for CURB score (excluding age). In our opinion, this design represents a realistic approach to investigate the real-world care of patients with pneumonia. Despite these limitations, we believe that this study has produced important findings that should be considered in the management of older patients.

Conclusions

In this study, we have described the observation that bacteremic pneumococcal pneumonia in healthy and well-functioning older patients behaves as a clinical entity distinct from that in younger patients, and notably, outcomes are poorer in the older age group. These differences in survival do not seem to be explained by process of care or serotype. Future multicentre studies are required to confirm these results. In the meantime, we suggest that biological age should be more routinely assessed to guide clinical decision making in older patients in general and, in particular, to help clinicians identify older patients with pneumonia who might benefit from ICU admission.

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Availability of data and materials
Data supporting findings in the study can be requested from corresponding author.

Authors´ contributions
LAR, PPE, AB, AC, MR and RZ conceived and designed the study. LAR, PPE, AG, CJ, AA and RZ enrolled patients and collected and compiled data. AB performed the statistical analysis. LAR, PPE, AG, AB, CJ, AA, AC, MR and RZ analyzed and interpreted the data. LAR, PPE, AB, AC, MR and RZ wrote the manuscript, which was critically reviewed and revised by AG, CJ, AA, AC and MR. All authors have read and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

Consent for publication
Not applicable for that section.

Ethics approval and consent to participate
The protocol for the study has been approved by Hospital Universitario Cruces and Hospital Galdakao-Usansolo Ethics Committee. As the study used data that was collected as part of routine medical care, the ethics committee determined that individual consent was not required.

Publisher's Note

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New-onset atrial fibrillation in patients with pneumococcal pneumonia. Impact of timing and duration on short- and medium-term mortality

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SUMMARY

Objetives: To assess the incidence, related factors, timing and duration of new- onset atrial fibrillation in a cohort of consecutive patients diagnosed with pneumococcal pneumonia.
Methods: Observational study including all immunocompetent adults hospitalized for pneumococcal pneumonia. Patients were classified by time (atrial fibrillation recognized on emergency room arrival or developed during hospitalization) and duration (paroxysmal or persistent). Patients were followed-up for 6 months after discharge.
Results: We included 1092 patients, of whom 109 (9.9%) had new-onset atrial fibrillation. An early event was documented in 87 (79.8%) cases. Arrhythmia was classified as paroxysmal in 78 patients. Older age, heavy drinking, respiratory rate $\geq$ 30/minute, leukopenia, severe inflammation and bacteremia were independent risk factors for developing new-onset atrial fibrillation on admission. Overall, 48 (4.4%) patients died during hospitalization, the rate being higher in those patients who developed new-onset arrhythmia (17.9% vs 2.9% $p<0.001$). Among patients with events recognized at admission, in-hospital mortality was higher in those with persistent arrhythmia (34.8% vs 6.3%, $p=0.002$) and 6-month survival was better among those who developed paroxysmal event.
Conclusions: The development of new-onset atrial fibrillation was associated with pneumonia severity, and higher in-hospital mortality. Bacteremia and severe systemic inflammation were factors associated with its development.

Introduction

Community-acquired pneumonia is the leading cause of mortality in patients with infection[1]. Overall, *Streptococcus pneumoniae* is the most commonly identified pathogen in pneumonia, being responsible for the highest rates of bacteremia, hospital admission and mortality[2]. The prognosis of patients with pneumococcal pneumonia has not changed in the last decade in spite of improvements in the quality of the process of care during hospitalization[3]. Moreover, it has been recognized that pneumonia is associated with poor long-term outcomes after hospital admission[4–6].

The development of cardiac complications in general and new-onset atrial fibrillation (AF) in particular has been documented in a substantial number of patients hospitalized for pneumonia[7–10]. Mechanisms responsible for these conditions have yet to be clearly elucidated and probably reflect the impact of inflammation and potential "cardiotoxicity" of a specific pathogen on host condition[11,12]. The host-pathogen interaction might be especially relevant in patients with bacteremia due to their elevated inflammatory response[13]. If so, we could speculate that the development of a new-onset AF itself could be considered a surrogate marker

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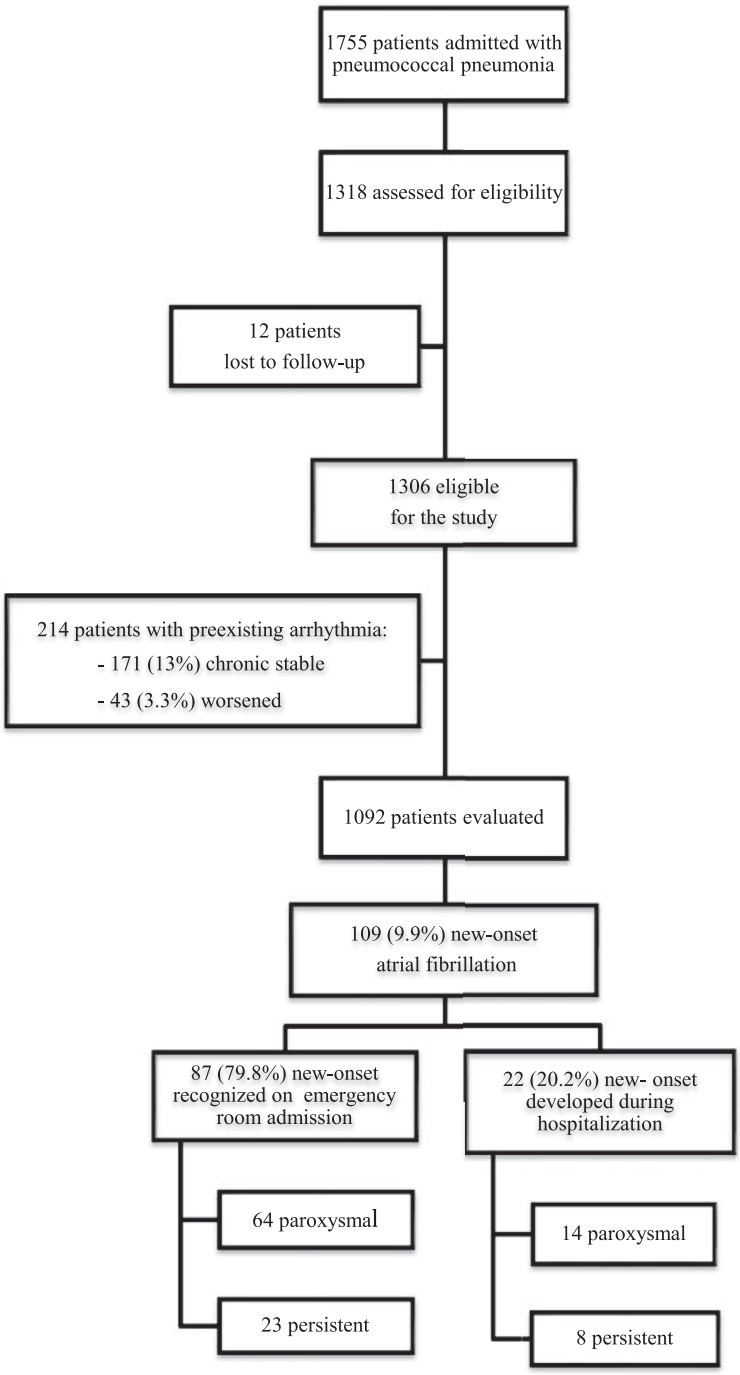


Fig. 1. Flow of patients admitted with pneumococcal pneumonia through the study.

of primary severity of pneumonia at hospital admission and might identify a subgroup of patients at increased risk of death. Nonetheless, it remains unclear whether pneumonia truly increases the risk of new-onset AF or whether this complication is a consequence of the interaction of exogenous factors in the host. For this reason, studies designed to describe these factors associated with new-onset AF, especially on admission, could be important to clarify this point.

Given this, the objectives of our study were to assess the incidence, timing and duration of a new-onset AF in a prospective cohort of patients with pneumococcal pneumonia requiring hospital admission and to identify predictive factors associated with this condition.

Materials and methods

Study design and population

This was a cohort observational study based on the analysis of data from a prospective registry of consecutive immunocompetent adults hospitalized for pneumococcal pneumonia in two tertiary medical centers. The study was conducted between January 2002 and July 2019. The bacteriological diagnosis of pneumococcal pneumonia was based on the results of urinary antigen testing and/or blood culture obtained within 24 h after hospital admission. To evaluate the role of pneumococcal bacteremia, we limited the analysis to patients for whom blood culture results were available.

Table 1
Demographic and clinical characteristics of patients with pneumococcal pneumonia stratified by whether and when they developed atrial fibrillation.

	No event ($n=983$)	New-onset AF ($n=109$)	P*	New-onset AF presented on ER admission ($n=87$)	P**
Demographic variables					
Male sex	583(59.3)	75(68.8)	0.055	57(65.5)	0.258
Age in years, mean (SD)	60.7(17.6)	70.1(12.5)	0.001	67(17.33)	0.001
Nursing home resident	23(2.3)	4(3.7)	0.396	4(4.6)	0.269
Current smoker	306(31.9)	35(32.1)	0.855	30(34.5)	0.535
Heavy drinker ***	116(12.2)	24(23.5)	0.001	19(23.5)	0.004
Underlying conditions					
Cancer	39(4)	5(4.6)	0.755	2(2.3)	0.768
Liver disease	37(3.8)	9(8.3)	0.027	6(6.9)	0.153
Renal disease	40(4.1)	5(4.6)	0.796	3(3.4)	0.999
Chronic obstructive pulmonary disease	176(17.9)	30(27.5)	0.015	23(26.4)	0.049
Diabetes mellitus	152(15.5)	19(17.4)	0.592	12(13.8)	0.676
Cerebrovascular disease	46(4.7)	7(6.4)	0.422	5(5.7)	0.599
Congestive heart disease	46(4.7)	5(4.6)	0.965	4(4.6)	0.999
Coronary disease	8(0.8)	0(0)	0.381	0(0)	0.999
Arterial hypertension	334(34)	53(48.6)	0.002	43(49.4)	0.004
Hyperlipidemia	256(26)	30(27.5)	0.739	23(26.4)	0.936
Vaccination status					
Influenza vaccine	230(24.3)	37(36.3)	0.008	32(39.5)	0.003
Pneumococcal vaccination	104(10.9)	12(11.4)	0.881	9(10.7)	0.948
Clinical characteristics at admission					
Mean number of days with symptoms prior to hospital admission (SD)	3.8(2.8)	3.8(2.6)	0.906	3(2.9)	0.355
Prior antibiotic treatment for the current illness	99(10.1)	5(4.6)	0.064	5(5.7)	0.192
Body temperature < 35 or >40 °C)	6(0.6)	0(0)	0.531	0(0)	0.999
Altered mental status	87(8.9)	16(14.7)	0.048	11(12.6)	0.240
Systolic blood pressure < 90 mm Hg	89(9.1)	17(15.6)	0.029	10(11.5)	0.451
Diastolic blood pressure ≤ 60 mm Hg	343(34.9)	40(36.7)	0.708	29(33.3)	0.770
Respiratory rate ≥ 30/min	179 (18.3)	50 (45,9)	<0.001	36 (41.6)	<0.001
Laboratory and radiological findings					
Blood urea nitrogen ≥ 30 mg/dL	314(31.9)	70(64.2)	0.001	49(56.3)	0.001
PaO_2 < 60 mm Hg	399(40.6)	61(56)	0.002	47(54)	0.015
Glucose>250 mg/dL	73(7.4)	10(9.2)	0.514	5(5.7)	0.564
Hematocrit < 30%	31(3.2)	4(3.7)	0.772	4(4.6)	0.521
Blood pH < 7.35	51(5.2)	18(16.5)	0.001	10(11.5)	0.026
Leukocyte count < 4000 ($x10^9$/L)	38(3.9)	12(11)	0.001	9(10.3)	0.011
Inflammation					
Mild (ref)	212(21.6)	14(12.8)	0.013	11(12.6)	0.034
Moderate	264(26.9)	23(21.1)		19(21.8)	
Severe	507(51.6)	72(66.1)		57(65.5)	
Multilobar pneumonia	308(31.3)	51(46.8)	0.001	39(44.8)	0.010
Pleural effusion	107(10.9)	16(14.7)	0.235	11(12.6)	0.616
Positive urinary antigen test	851(86.6)	101(92.7)	0.189	80(92)	0.470
Positive blood culture	403(41)	57(52.3)	0.023	47(54)	0.018
Severity of illness on admission					
PSI risk class > 3	407(41.4)	85(78)	0.001	63 (72.4)	0.001

p*: No event vs new-onset AF. p**: No event vs new-onset AF presented on emergency room admission. *** Heavy drinking was defined as consuming an average of 8 or more drinks per week for women and 15 or more drinks for men. AF: atrial fibrillation; ER: emergency room. *PSI:* Pneumonia Severity Index.

We excluded patients who had been diagnosed with pneumonia in the previous 3 months or with preexisting paroxysmal, chronic stable or worsening AF.

Eligible patients were stratified into three groups according to whether they developed AF, and if so, the timing: 1) no AF detected; 2) new-onset AF (including both, cases recognized on emergency room [ER] arrival and cases developed during hospitalization); or 3) new-onset AF recognized on admission to the ER).

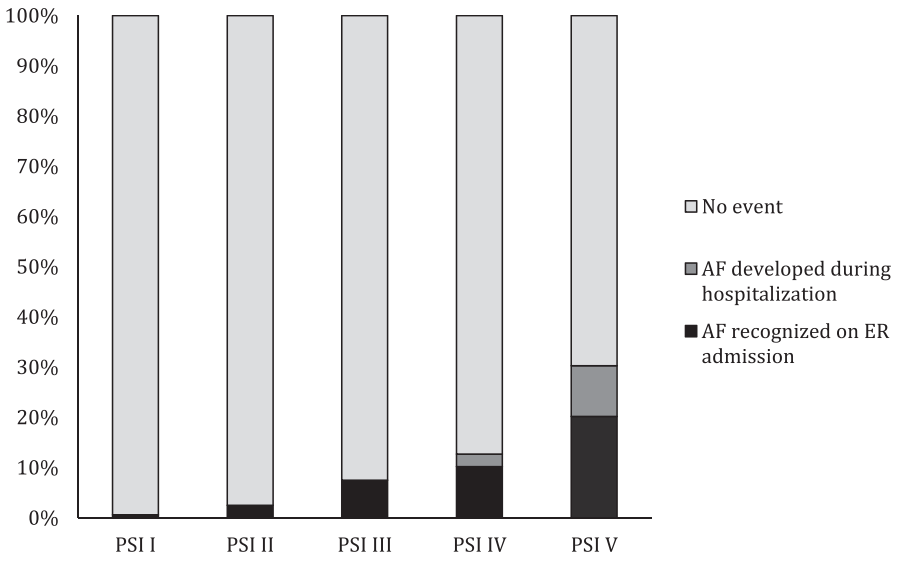
The severity of patients' clinical condition was assessed on admission using the Pneumonia Severity Index (*PSI*)[14]. The study protocol was approved by the Comité de Etica de Investigación con Medicamentos de Euskadi (approval number EPA2019043).

Data collection

Since 2002, there has been an ongoing standardized prospective registry of all patients hospitalized for pneumonia in our two hospitals. For eligible patients, we assessed data on socio-demographic characteristics, comorbidities, influenza and pneumococcal vaccination status, vital signs, results of routine laboratory tests, including the pneumococcal urinary antigen test and blood cultures, and radiological findings on admission. Measures of in-hospital clinical course and outcome included: 1) development of in-hospital complications including cardiovascular, hematological, respiratory and neurological events; 2) admission to the intensive care unit (ICU); 3) use of invasive mechanical ventilation; 4) septic shock; 5) in-hospital mortality; and 6) length of hospital stay. Patients were empirically treated in accordance with the current National Guidelines of the Spanish Society of Pulmonology [SEPAR] at the discretion of the attending doctor[15]. All patients were followed-up after hospitalization until the resolution of the pneumonia.

Outcome

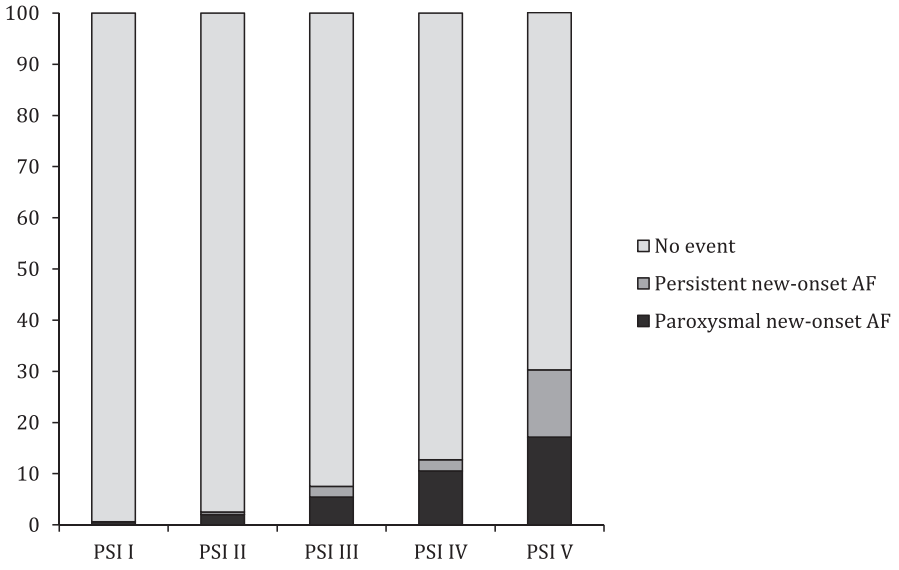
The primary outcomes were the occurrence of a new-onset AF, either early or late and factors associated with it. Secondary outcomes included the timing and duration of new-onset atrial arrhythmia and its role in all-cause mortality, both in-hospital and at 6-months after discharge. Survival status after hospitalization was assessed using data from the database of the Basque Health Service (Osakidetza) on 31th December 2019.



P<0.001

PSI: Pneumonia Severity Index; AF: atrial fibrillation; ER: emergency room

Fig. 2a. Patients who developed new-onset AF stratified by time of onset (on ER admission or during hospitalization) in each *PSI* risk class.



P<0.001

PSI: Pneumonia Severity Index; AF: atrial fibrillation

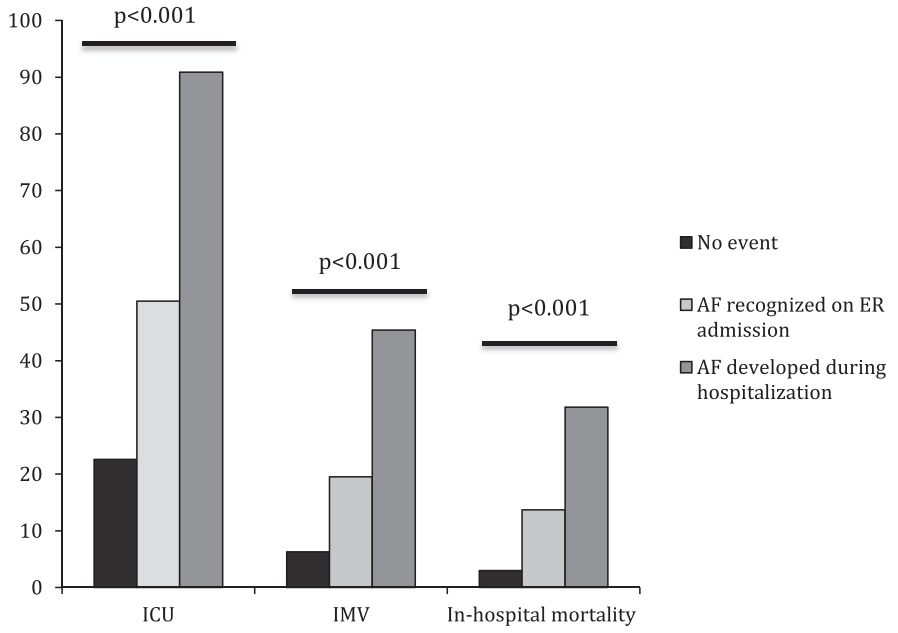
Fig. 2b. Patients who developed a new-onset AF stratified by duration (paroxysmal or persistent) in each *PSI* risk class.

Definitions

Pneumonia was defined as the presence of new pulmonary infiltrate on the chest X-ray together with signs and symptoms suggestive of lower respiratory tract infection. Septic shock was defined as systolic blood pressure of less than 90 mm Hg and a need for vasopressors for at least 4 h, after fluid therapy[16].

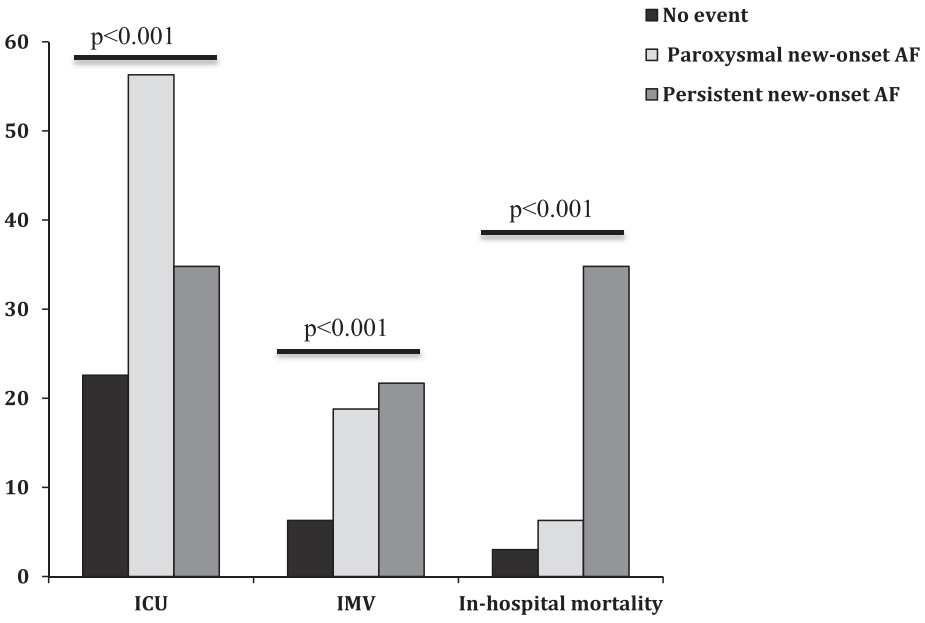
New-onset AF was defined as an episode of AF in patients with no previous diagnosis of this condition before hospital admission. Such events were then classified according to time of presentation as: 1) AF recognized on the basis of the analysis of electrocardiogram performed on admission to the ER; or 2) late, if the event was not detected on admission but rather developed during hospitalization. Additionally, considering the duration, cases of incident AF were classified as: 1) paroxysmal, i.e., the event resolved (spontaneously or with medication) during hospitalization; or 2) persistent, i.e., patients continued to have the arrhythmia at the time of death or hospital discharge.

Moderate inflammation was defined as a C-reactive protein level of 70–150 mg/L or white cell count of $15–30 \times 10^9$/L. Severe inflammation was defined as a C-reactive protein level greater than 150 mg/L or white cell count greater than 30×10^9/L[17].



ICU: intensive care unit; IMV: invasive mechanical ventilation; ER: emergency room.

Fig. 3a. In-hospital course and outcomes in patients with new-onset AF stratified by time of onset (on emergency room admission or developed during hospitalization).



ICU: Intensive care unit; IMV: Invasive mechanical ventilation; ER: emergency room.

Fig. 3b. In-hospital course and outcomes in those patients with new-onset AF recognized on ER admission stratified by duration (paroxysmal or persistent).

Statistical methods

Descriptive analysis was undertaken using frequencies and percentages, means and standard deviations (SDs) or medians and interquartile ranges (IQRs) depending on the distribution of the data. Comparisons were performed with chi-square or Fisher's exact tests for qualitative variables and with t tests or non-parametric Mann-Whitney U tests for quantitative variables. Patient survival was analyzed using the Kaplan-Meier method. The log-rank test was used to compare survival between groups.

Univariate logistic regression was performed to identify factors related to the development of new-onset atrial arrhythmia. All variables with a $p < 0.10$ were then included in a multivariate regression model. Variables with the highest p values were excluded one by one until all variables had a p value <0.05. The results were expressed as odds ratios (ORs) and 95% confidence intervals (95% CIs). The discriminatory power of the model was evaluated by

Table 2
Multivariate analysis of factors associated with the development of new-onset and new-onset atrial fibrillation presented on emergency room admission.

	New-onset AF			New-onset AF presented on ER admission		
	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	p	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	p
Sex male	1.51 (0.99–2.31)			1.30 (0.82–2.07)		
Age, years	1.03 (1.02–1.04)	1.04 (1.04–1.04)	0.0001	1.03 (1.02–1.05)	1.05 (1.05–1.05)	0.0001
Nursing home resident	1.59 (0.54–4.68)					
Current tobacco use	1.04 (0.68–1.59)			1.15 (0.72–1.83)		
Heavy drinker*	2.22 (1.35–3.65)	2.30 (2.29–2.31)	0.004	2.21 (1.27–3.83)	2.66 (2.65–2.67)	0.002
Solid cancer	1.16 (0.44–3.01)			0.57 (0.13–2.40)		
Liver disease	2.30 (1.07–4.90)			1.89 (0.77–4.62)		
Renal disease	1.13 (0.43–2.93)			0.84 (0.25–2.78)		
Chronic obstructive pulmonary disease	1.74 (1.10–2.73)			1.64 (0.99–2.72)		
Diabetes mellitus	1.15 (0.68–1.94)			0.87 (0.46–1.64)		
Cerebrovascular disease	1.39 (0.61–3.17)			1.24 (0.48–3.21)		
Congestive heart disease	0.97 (0.38–2.51)			0.98 (0.34–2.79)		
Arterial hypertension	1.83 (1.23–2.73)			1.89 (1.22–2.95)		
Hyperlipidemia	1.07 (0.69–1.68)			1.02 (0.62–1.67)		
Influenza vaccination	1.77 (1.15–2.72)			2.03 (1.27–3.25)		
Pneumococcal vaccination	1.05 (0.55–1.98)			0.97 (0.47–2)		
Previous antibiotic treatment	0.42 (0.17–1.07)			0.54 (0.21–1.37)		
Altered mental status	1.77 (0.99–3.14)			1.49 (0.76–2.91)		
Systolic blood pressure < 90 mm Hg	1.85 (1.05–3.25)			1.30 (0.65–2.61)		
Diastolic blood pressure ≤ 60 mm Hg	1.08 (0.71–1.63)			0.93 (0.58–1.48)		
Respiratory rate ≥ 30/ min	3.79 (2.51–5.71)	3.34 (3.33–3.35)	0.0001	3.15 (2–4.98)	3.26 (3.25–3.27)	0.0001
Blood urea nitrogen ≥ 30 mg/dL	3.82 (2.52–5.78)	2.03 (2.02–2.03)	0.003	2.74 (1.76–4.28)		
PaO_2 < 60 mm Hg	1.66 (1.08–2.54)			1.62 (1–2.61)		
Glucose > 250 mg/dL	1.25 (0.63–2.51)			0.76 (0.29–1.93)		
Hematocrit < 30%	1.17 (0.40–3.37)			1.48 (0.51–4.29)		
Blood pH < 7.35	3.61 (2.02–6.44)	1.99 (1.99–2)	0.048	2.37 (1.15–4.85)		
Leucocyte count < 4000 ($x10^9$/L)	3.06 (1.54–6.05)	2.65 (2.64–2.67)	0.027	2.85 (1.33–6.12)	3.42 (3.40–3.44)	0.008
Inflammation						
Mild (ref)						
Moderate	1.31 (0.66–2.62)	1.88 (1.87–1.89)	0.107	1.38 (0.64–2.97)	1.96 (1.95–1.97)	0.114
Severe	2.15 (1.18–3.89)	2.88 (2.87–2.90)	0.002	2.16 (1.11–4.21)	3.33 (3.32–3.35)	0.001
Multilobar pneumonia	1.92 (1.29–2.87)			1.78 (1.14–2.77)		
Pleural effusion	1.40 (0.79–2.48)			1.18 (0.61–2.30)		
Urinary antigen positive	1.80 (0.76–4.21)			1.71 (0.67–4.33)		
Positive blood culture	1.57 (1.06–2.34)			1.69 (1.08–2.62)	1.75 (1.74–1.75)	0.023
PSI risk class > 3	5.01 (3.13–8.02)			3.71 (2.28–6.04)		

* Heavy drinking was defined as consuming an average of 8 or more drinks per week for women and 15 or more drinks for men; ER: emergency room; *PSI:* Pneumonia Severity Index.

calculating the area under the receiver operating characteristic (ROC) curve and the goodness of fit with the Hosmer-Lemeshow test. Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 23.0 (Armonk, NY).

Results

We assessed 1318 patients with pneumococcal pneumonia that had culture results from blood samples obtained at hospital admission, of whom 1092 remained for analysis. Overall, new-onset AF was detected in 109 patients (9.9%), 87 cases (79.8%) being classified as early (on ER admission) (Fig. 1).

The mean age of the entire cohort was 61.7 (±17.4) years, 608 patients (54.6%) being ≥ 65 years. Bacteremia was identified in 460 patients. In 632 cases (57.8%), the diagnosis was made based on positive pneumococcal urinary antigen test results (blood culture being negative in all these patients). Table 1 summarizes the demographic and clinical characteristics of patients who developed new-onset AF and the subset with new-onset AF recognized on ER admission. The incidence of a first episode of new-onset AF was 5.7% and 14.5% in patients under 65 and those 65 years of age or older respectively.

Fig. 2a and 2b shows the time and type of new-onset AF stratified by severity on admission. No patients in *PSI* risk class I to III developed a late event but 24 (27.8%) presented an early event ($p < 0.003$).

Fig. 3 shows the in-hospital course and outcome indicators. Overall outcome indicators were significantly poorer in patients with new-onset AF developed late during hospitalization (Fig 3a). Among patients with AF recognized on ER admission, those with paroxysmal new event were more likely than those with persistent arrhythmia to be admitted to the ICU but there were no significant differences in the requirements for invasive ventilation (Fig 3b). Out of the 1092 (4.4%) patients analyzed, 48 died during hospitalization. The mortality rate was significantly higher in patients who developed new-onset AF than those who did not (17.9% vs 2.9% $p < 0.001$). Among patients who presented new-onset AF on ER admission, in-hospital mortality was higher in those with persistent arrhythmia rather than paroxysmal arrhythmia (34.8% vs 6.3%, $p = 0.002$). The median length of hospital stay in patients with new-onset AF was significantly longer than others. (9 vs 6 days, $p < 0.001$).

The univariate and multivariate analyses of factors associated with both new-onset AF overall and new-onset AF recognized at admission are reported in Table 2. In the adjusted multivariate analysis, the following independent factors were identified as predictors of a new event presented on ER admission: older age (HR 1.05; 95% CI 1.05–1.06), being a heavy drinker (HR 2.66; 95% CI 2.65–2.67), respiratory rate ≥30/minute (HR 3.26; 95% CI 3.25–3.27), leukocyte count < 4000 (x10/L) (HR 3.42; 95% CI 3.40–3.44), severe inflammation (HR 3.33; 95% CI 3.32–3.35) and bacteremia (HR 1.75; 95% CI 1.74–1.75). The area under the ROC curve for this model was 0.78. The model was a good fit to the data (Hosmer-Lemeshow, $p = 0.752$).

All patients were followed-up for at least 6 months after hospital discharge. Overall, 28 (2.6%) patients died during follow-up.

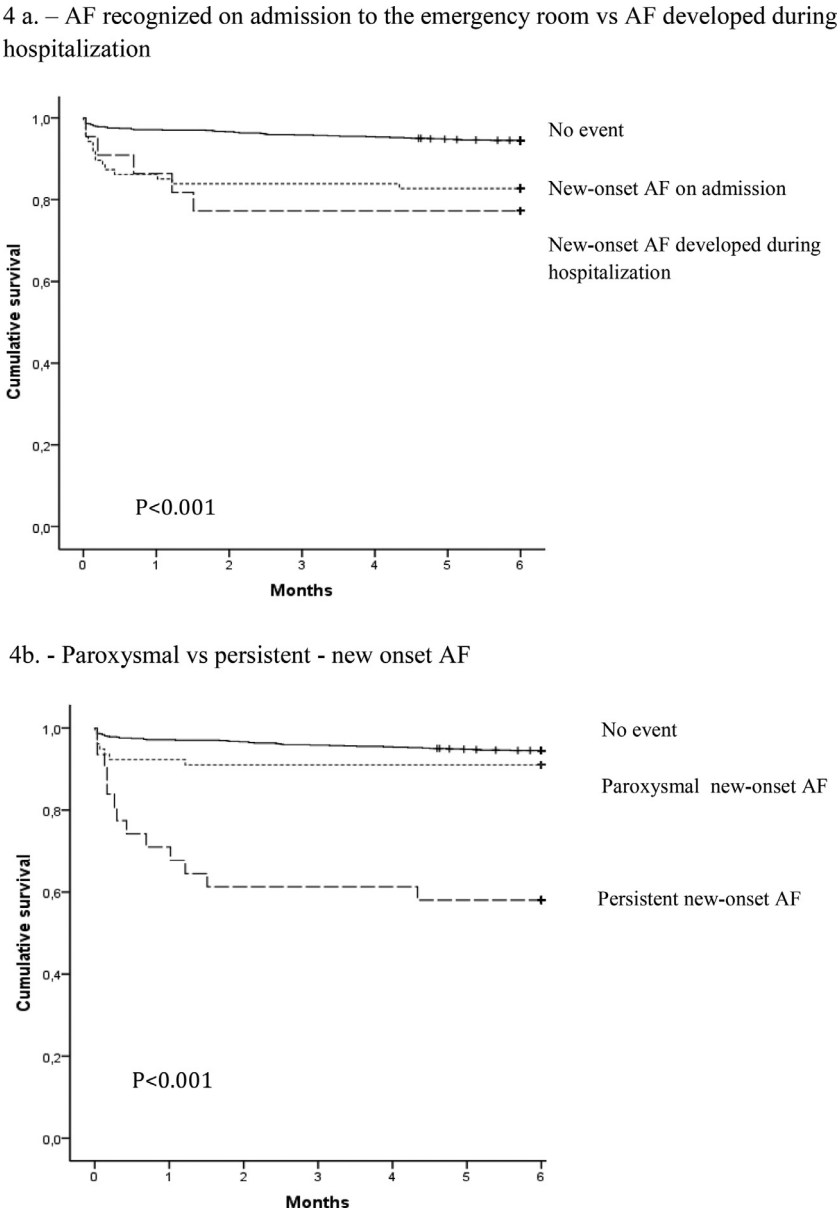


Fig. 4. Kaplan-Meier curves showing the survival probability stratified by time of onset of atrial fibrillation (AF), its duration and both categories of new-onset atrial fibrillation.

Fig. 4 shows survival curves plotted as a function of time (Fig 4a), duration (Fig 4b) and both (Fig 4c) of the new-onset AF. The 6-month survival rate was higher in patients with paroxysmal arrhythmia recognized on ER admission than those who developed persistent arrhythmia (log rank < 0.001).

Discussion

The main findings of this large prospective cohort study were: (1) Nearly 10% of patients with pneumococcal pneumonia developed new-onset AF, the condition presenting on ER admission in nearly 80% of cases. (2) The development of new-onset AF was associated with higher mortality both in-hospital and during the 6-months after discharge. (3) In our cohort, the presence of new-onset AF was not associated with a history of traditional cardiovascular risk factors.

The interest of this study lies in (1) the nature of the study population itself. Specifically, we only included patients with pneumococcal pneumonia, all of them with blood culture results. This has enabled us to assess the role of bacteremia in the pathogenesis of AF. (2) Furthermore, we have excluded patients with previous paroxysmal or chronic AF, considering only patients with a new event and specifically those with an event detected on hospital admission. This has allowed us to control for confounding effects of various clinical scenarios and therapeutic procedures during hospitalization which might trigger the genesis of AF.

Similar to others, we have found that 10% of patients developed incident new-onset AF during hospitalization[8–10,18]. The mechanisms responsible for this condition have yet to be clearly elucidated but is likely to involve several factors such as increased sympathetic activity, cytokine production and secondary inflammation, direct impairment of cardiomyocytes coexisting with electrolyte disturbance and myocardial depression secondary to sepsis[19–21]. Unlike other authors, we have not found any relation between AF and traditional cardiovascular risk factors[22,23]. For these reasons, we could speculate that AF preented on admission represents a marker of organ dysfunction and severity.

4c. - New-onset AF recognized on admission to the emergency room stratified by duration

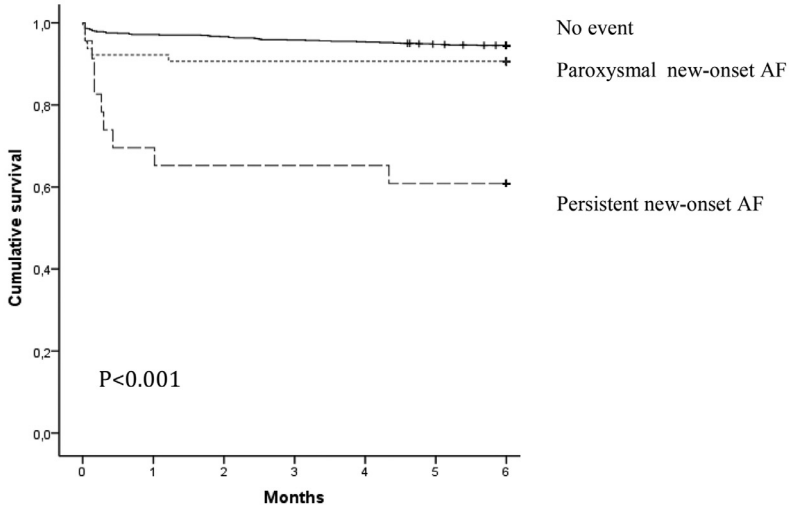


Fig. 4. Continued

Two host-related factors, alcoholism and older age, seem to be related to this complication. Several studies have reported the development of AF to be related to the frequency and quantity of alcohol intake, even in patients with normal cardiac function[24]. Mechanisms underlying this complication have yet to be clearly elucidated. Alcohol has an effect on catecholamine release and vagal stimulation could act as a trigger of AF in these patients[25,26].

There is an increasing evidence linking inflammation to a broad spectrum of cardiovascular conditions[27]. In this study, we have been able to correlate the development of early new-onset AF to bacteremia and severe inflammation. Similar to others, we have observed a progressive increase in AF onset with PSI risk class[10,11,22]. For these reasons, we could speculate that some pathogen-virulence-related factors including bacteremia and secondary systemic inflammatory response are the main variables responsible for the genesis of AF. Further studies are necessary to confirm this hypothesis. On the other hand, AF developing during hospitalization could be affected by a more severe initial systemic dysfunction that could prompt more aggressive therapeutic interventions. In fact, new-onset AF frequently develops in critically ill patients admitted to the ICU due to sepsis[17,28,29].

The contribution of various etiological factors in general is controversial[21]. Several studies have found a significant relation between pneumococcal infection and cardiac complications [11,12,23,30]. The presence of cardiac lesions during the acute pneumococcal infection together with the production of pneumolysin seems to be involved in the genesis of this type of complications[12,31]. The design of our study provides evidence supporting this association in patients with pneumococcal pneumonia in general and those with bacteremia in particular.

Patients who developed new-onset AF had a prolonged hospital stay, and higher rates of ICU admission and in-hospital mortality. Similar patterns have been reported in other studies and may reflect an association between severity of pneumonia and the development of this complication[8,23]. In the same way, failure to restore sinus rhythm was associated with increased mortality. This has also been reported in critically ill patients with AF discharged from general ICUs, but unlike our study, most of these studies included both exacerbation of chronic and new-onset AF[32]. Furthermore, we have observed in these patients that a plateau of mortality is reached 2 months after admission. The reason for this poorer outcome is not clear. It is possible that hemodynamic derangement secondary to AF may be a tipping point for patients with a history of limited cardiorespiratory reserve. If so, close follow-up early after discharge could be necessary in this subgroup of patients.

We recognize, however, that our study has some limitations. 1) The treatment given for AF was not recorded in our database, and hence, we have not explored its impact on the final outcome of these patients. 2) We did not assess routine cardiac markers such as troponin or Nt-proBNP. This fact could underestimate the incidence of other concomitant pauci-symptomatic cardiac events in our cohort of patients. 3) We were unable to obtain data on the causes of death after discharge, which might have added important additional information.

In spite of these limitations, our findings have important implications. Clinicians need to be aware of the importance of incident AF in patients with community-acquired pneumonia and its role in-hospital and post-discharge outcome in these patients. A better knowledge of this complication may help identify at-risk patients warranting a strict monitoring during hospitalization but also close follow-up after discharge.

In conclusion, we identified several risk factors, most of them related to the severity of the infection that may identify a subset of patients at risk of this complication. Multicenter studies are needed to confirm these results and to guide the design and implementation of future strategies for strengthening the monitoring and follow-up of these patients to improve their prognosis both during hospitalization and after discharge.

Contributors

LAR and LR take the responsibility of the manuscript as a whole. LAR, LS, PPE, LMI, AC, BG and RZ conceived and designed the study. LAR, LS, PPE, AG, BG, AA and RZ enrolled patients and collected and compiled data. LMI performed the statistical analysis. LAR, LS, PPE, LMI, AC, BG, AA and RZ analyzed and interpreted the data. LAR, LS, LMI, BG and RZ wrote the manuscript, which

was critically reviewed and revised by AG, AA, and PPE. All authors have read and approved the final manuscript.

Declaration of Competing Interest

All authors have not conflict of interest related to this publication.

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Factors influencing long-term survival after hospitalization with pneumococcal pneumonia

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SUMMARY

Objective: To assess survival and identify predictors of survival more than 30-days after discharge in a cohort of consecutive patients diagnosed with pneumococcal pneumonia.
Methods: Observational study including all consecutive immunocompetent adult patients surviving more than 30-days after hospitalization. The bacteriological diagnosis was based on the results of urinary antigen testing and/or blood culture. Life expectancy was calculated for each patient considering their sex, age and date of discharge.
Results: We included 1114 patients that survived more than 30- days after discharge. Of them, 431 (38.6%) died during follow-up (median follow-up of 6.7 years). Age, history of cancer, liver disease, chronic renal disease, chronic obstructive pulmonary disease, cerebrovascular disease, atrial arrhythmia and coronary disease, red cell distribution width (RDW) > 15%, positive blood culture, hematocrit < 30% and living in a nursing home were independent risk factors for reduced long-term survival after hospital discharge. Cumulative 1-, 3- and 5-year survival rates were 93.9%, 85.3% and 76%, respectively. Among non-survivors, 361 (83.8%) died earlier than expected given their life expectancy.
Conclusions: Survival after hospital discharge is mainly associated with age and comorbidities. The findings of bacteremia and elevated RDW on admission could help identify patients at high risk of long-term mortality.

Introduction

Pneumonia remains a common cause of morbidity and mortality around the world. In fact, this entity represents the leading cause of infection-related death.[1] Traditionally, pneumonia has been considered an acute process that, once resolved, has no impact on patient survival. There is growing evidence, however, of a higher risk of death after recovery from the acute episode than that the general population.[2–4] The excess mortality observed in these patients may be as high as 50% within 5 years after hospital discharge.[5]

Streptococcus pneumoniae is the most commonly identified pathogen in pneumonia, being responsible for the highest rates of hospital admission and mortality. Approximately 20% of patients diagnosed with pneumococcal pneumonia develop bloodstream infections, and this type of pneumonia has traditionally been associated with poorer outcomes during hospitalization.[6,7] By contrast, for both bacteremic and non-bacteremic pneumococcal pneumonia, there is limited information in the literature on mortality after hospitalization.[8,9] At this point, it could be speculated that the acute infectious episode acts as a trigger to create a persistent inflammatory state which, in turn, has a negative effect on host-related factors such as age or comorbidities.[2] This could be even more relevant in patients with bacteremia due to their elevated cytokine production.[10] Considering the higher incidence of invasive pneumococcal disease in older people and those with underlying conditions, together with the results of recent animal studies reporting a possible association between “cardiotoxicity” and invasive pneumococcal infection, we hypothesized that invasive pneumococcal disease, among other factors, is a marker of impaired long-term survival in these patients.[11,12]

Given this, the objectives of our study were to assess the survival rate after hospitalization in a prospective cohort of patients with pneumococcal pneumonia requiring hospital admission as well as to identify risk factors associated with outcome, to guide

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the design and implementation of future strategies for improving the long-term survival of these patients.

Methods

Study design and population

This is an observational study based on the analysis of a prospective registry of consecutive immunocompetent adults (age 18 years or more) hospitalized for pneumococcal pneumonia in two tertiary medical centers (Cruces and Galdakao Hospitals). The study was conducted between January 2002 and January 2017. The bacteriological diagnosis of pneumococcal pneumonia was based on the results of urinary antigen testing and/or blood culture within 24 h after hospital admission. For the purpose of the study, we limited the analysis to consecutive patients who had blood culture performed. Patients were excluded if they died during hospitalization or within 30- days after hospital discharge. Participants were stratified into two groups according to their survival status during follow-up: (1) survivors and (2) non-survivors.

The severity of patients' clinical condition was assessed on admission using the Pneumonia Severity Index (*PSI*) *score*.[13] A local ethic committee approved the analysis of data for this study.

Data collection

Since 2002, there has been an ongoing standardized prospective registry of all patients hospitalized for pneumonia in our two hospitals. This registry includes numerous variables characterizing patients and their pneumonia. For eligible patients, we assessed data on socio-demographic characteristics, medical comorbidities, influenza and pneumococcal vaccination status, vital signs, results of routine laboratory tests, including the pneumococcal urinary antigen test and blood cultures, and radiological findings on admission. Measures of in-hospital clinical course and outcome included: (1) admission to the intensive care unit; (2) use of invasive mechanical ventilation; (3) septic shock; and (4) in-hospital mortality. Patients were empirically treated in accordance with the National Guidelines of the Spanish Society of Pulmonology [SEPAR] at the discretion of the attending doctor.[14]

Comorbidities considered were the following diagnosed prior to hospital admission: chronic respiratory disease, diabetes mellitus, cerebrovascular disease, chronic liver disease, chronic renal disease, cancer, arterial hypertension, dyslipidemia, heart arrhythmias (atrial fibrillation or flutter), congestive heart failure and coronary disease. In addition, incident in-hospital heart complications were considered.

Outcome

The main outcome was all-cause mortality after hospital discharge during the follow-up period. Survival status was assessed using data from the database of the Basque Health Service (Osakidetza) on 31st December 2017. In order avoid bias due to short-term deaths attributable to the acute onset, patients who died within 30- days after hospital discharge were excluded. We compared observed and expected survival according to life expectancy for each patient. Life expectancy was estimated using life expectancy tables for the Spanish population (years 2000–2017) according to sex, age and date of discharge.[15]

Definitions

Pneumonia was defined as the presence of new pulmonary infiltrate on the chest X-ray together with signs and symptoms suggestive of lower respiratory tract infection. Septic shock was defined as a systolic blood pressure of less than 90 mm Hg and a need for vasopressor drugs for at least 4 h, after fluid therapy.[16] The diagnosis of altered mental status was based on observation that the patient's mental state was not normal and that this was a new phenomenon.[13]

For the purposes of this study, cancer was defined as any solid tumor not requiring chemotherapy or radiotherapy treatment in the year prior to the onset of pneumonia. The onset of congestive heart failure and/or atrial arrhythmia (atrial fibrillation or flutter) and/or coronary disease during hospitalization in patients with no previous diagnosis of these conditions was considered an incident heart complication. New hyperglycemia was defined as hyperglycemia (>200 mg/dL) at admission in a patient without a medical diagnosis of diabetes.[17]

Statistical analysis

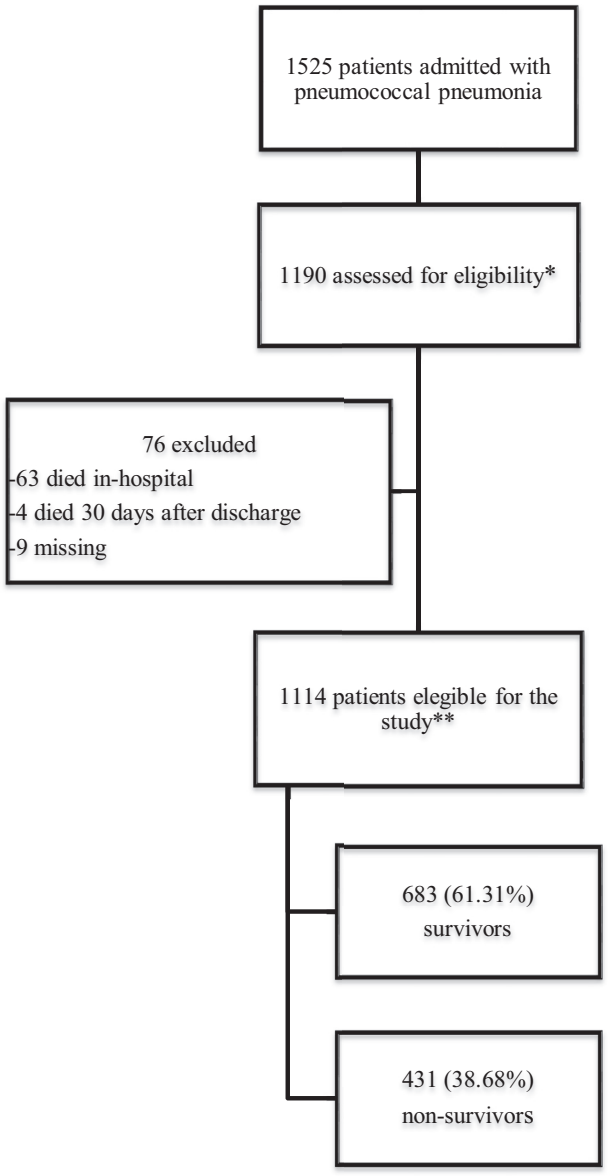
Descriptive analysis was undertaken, using frequencies and percentages, means and standard deviations (SDs) or medians and interquartile ranges (IQRs) depending on the distribution of the data. Comparisons were performed with chi-square or Fisher's exact tests for qualitative variables and with t tests or non-parametric Wilcoxon tests for quantitative variables. Patient survival was analyzed using the Kaplan–Meier method. The log-rank test was used to compare survival with different variables. A univariate Cox regression analysis was performed to identify factors related to patient characteristics and survival. All variables with a $p < 0.20$ were included in a multivariate Cox regression model. Variables with the highest p value were excluded one by one until all variables had a p value <0.05. Hazard ratios (HRs) and 95% confidence intervals (95% CIs) were calculated from univariate and multivariate models. The proportional hazard assumption was tested. Statistical analysis was performed using IBM SPSS Statistics for Windows version 23.0 (Armonk, NY).

Results

The flow of patients through the study is illustrated in Fig. 1. During the study period, 1525 patients were admitted to our two hospitals with pneumococcal pneumonia. Of whom, we assessed 1190 consecutive patients who had blood cultures obtained at hospital admission. After applying the exclusion criteria, 1114 patients were considered eligible for this study.

Table 1 summarizes the demographic and clinical data of patients. The mean age of the entire cohort was 63.6 (±17.5) years, with 608 (54.6%) being ≥ 65 years. Bacteremia was identified in 479 patients. In 635 (57%) cases diagnosis was made by positive pneumococcal urinary antigen (all of them with negative blood culture). Patients who did not survive were older and had more comorbidities but were less likely to be active smokers. They were also more likely to have hypoxemia, high blood urea nitrogen, altered mental status, low hematocrit, increased red blood cell distribution width (RDW), and newly discovered hyperglycemia at hospital admission. In contrast, survivors more frequently had multilobar pneumonia and were more likely to be admitted to the intensive care unit or require invasive mechanical ventilation. They were also more likely to have positive results in pneumococcal urinary antigen testing and less likely to have bacteremia. A greater proportion of non-survivors than survivors were classified in the higher risk classes according to *PSI score* ($p < 0.001$).

Fig. 2 compares the Kaplan–Meier survival curves observed and stratified by the presence or absence of comorbidities with those expected based on sex, age and date of discharge ($p < 0.001$; log-rank test). Of the 1114 patients surviving their index hospitalization, 431 (38.6%) died during a median follow-up of 6.70 years. Cumulative 1-, 3- and 5-year survival rates were 93.9%, 85.3%, and



* Consecutive patients who had blood drawn for culture within 24 hours after admission

** Survived more than 30- days after discharge

Fig. 1. Flow of patients admitted with pneumococcal pneumonia through the study.

76%, respectively. Of the 431 non-survivors, 361 (83.8%) died earlier than expected, given their life expectancy.

Fig. 3 shows Kaplan–Meier survival curves by *PSI* risk class. The survival rates were 99.3%, 94%, 81.1%, 65% and 47.6% for patients in *PSI* risk classes I to V, respectively (log rank $p < 0.001$).

The univariate and multivariate analyses of factors associated with long-term mortality after hospitalization for pneumococcal pneumonia are reported in Table 2. In an adjusted multivariate model, the following were identified as predictors of long-term mortality: age (HR 1.05; 95% CI 1.045–1.06), solid cancer (HR 2.60; 95% CI 1.81–3.73), liver disease (HR 2.02; 95% CI 1.27–3.20), chronic renal disease (HR 2.01; 95% CI 1.43–2.82), COPD (HR 1.73; 95% CI 1.38–2,14), cerebrovascular disease (HR 2.38; 95% CI 1.71–3,32), atrial arrhythmia (HR 1.42; 95% CI 1.12–1.79), coronary disease (HR 1.55; 95% CI 1.14–2.11), RDW > 15% (HR 1.89; 95% CI 1.52–2.34), bacteremia (HR 1.47; 95% CI 1.23–1.80) and living in a nursing home (HR 1.91; 95% CI 1.18–3.10). To simplify the interpretation of the results, we performed a new analysis (model 2) considering the presence of comorbidities (categorized as 0, 1 or >1). In this model, hematocrit <30% on admission (HR 1.62; 95% CI 1.04–2.52) was independently predictive of long-term mortality, no other significant differences being found compared to model 1.

Fig. 4 shows survival curves plotted as a function of bacteremia and RDW (dichotomized to ≤15% vs. >15%) and stratified by age or the presence of one or more comorbidities. Patients with both positive blood cultures and RDW >15% at admission had shorter long-term survival than other groups, the shortest survival being seen in those with comorbidities or ≥ 65 years old.

Table 1
Demographic and clinical characteristics of patients with pneumococcal pneumonia surviving more than 30-days after discharge.

Characteristics	All	Survived (n=683)	Non-survived (n=431)	*p*
Demographics				
Male sex	670 (60.1)	386 (56.5)	284 (65.9)	0.002
Age in years, mean (SD)	63.6 (17.5)	57.1 (17.3)	73.7 (12.3)	<0.001
Nursing home resident	27 (2.4)	7 (1)	20 (4.6)	<0.001
Underlying conditions				
Cancer	50 (4.5)	15 (2.2)	35 (8.1)	<0.001
Liver disease	39 (3.5)	16 (2.3)	23 (5.3)	0.008
Renal disease	58 (5.2)	16 (2.3)	42 (9.7)	<0.001
Chronic obstructive pulmonary disease	216 (19.4)	86 (12.6)	130 (30.2)	<0.001
Diabetes mellitus	194 (17.4)	79 (11.6)	115 (26.8)	<0.001
Cerebrovascular disease	63 (5.7)	20 (2.9)	43 (10.0)	<0.001
Congestive heart disease	112 (10.1)	37 (5.4)	75 (17.4)	<0.001
Cardiac arrhythmia	186 (16.7)	64 (9.4)	122 (28.3)	<0.001
Coronary disease	74 (6.6)	27 (4)	47 (10.9)	<0.001
Hypertension and/or dyslipidemia	564 (50.6)	297 (43.5)	267 (61.9)	<0.001
Incident heart complication	100 (9)	59 (8.7)	41 (9.5)	ns
Number underlying diseases				<0.001
0	539 (48.4)	445 (65.2)	94 (21.8)	
1	304 (27.3)	149 (21.8)	155 (36)	
>1	271 (24.3)	89 (13)	182 (42.2)	
Vaccination status				
Influenza vaccine	303 (27.2)	146 (22)	157 (38.9)	<0.001
Pneumococcal vaccination	141 (12.7)	69 (10.4)	72 (17.4)	0.001
Current tobacco use	306 (27.5)	227 (33.2)	79 (18.5)	<0.001
Heavy drinker (> 80 mg alcohol/day)	132 (11.8)	89 (13.4)	43 (10.5)	ns
Clinical characteristics at admission				
Body temperature <35 or >40 °C, mean (SD)	15 (1.3)	12 (1.8)	3 (0.7)	ns
Respiratory rate, mean (SD)	22.7 (6.9)	21.8 (6.5)	24 (7.4)	<0.001
Heart rate, mean (SD)	102.5 (20.5)	104.3 (20.1)	99.7 (20.8)	<0.001
Altered mental status	91 (8.2)	43 (6.3)	48 (11.1)	0.003
Systolic blood pressure < 90 mm Hg	96 (8.6)	76 (11.1)	20 (4.6)	<0.001
Laboratory and radiological findings				
Blood urea nitrogen> 30 mg/dL	431 (38.7)	214 (31.3)	217 (50.3)	<0.001
PaO_2 < 60 mm Hg	475 (42.6)	249 (45.3)	226 (56.9)	<0.001
Glucose>200 mg/dL and no diagnosis of DM	56 (5)	26 (3.8)	30 (7.0)	0.019
Hematocrit <30%	391 (3.5)	16 (2.3)	23 (5.3)	0.002
RDW >15[a]	256 (23)	97 (14.5)	159 (38.4)	<0.001
Leucocyte count <4000 ($\times 10^9$/L)	40 (3.6)	29 (4.3)	11 (2.6)	ns
Multilobar pneumonia	322 (28.9)	214 (31.3)	108 (25.1)	0.026
Pleural effusion	132 (11.8)	87 (12.7)	45 (10.4)	ns
Urinary antigen positive	959 (86)	607 (88.8)	352 (81.6)	<0.001
Positive blood culture	479 (43)	265 (38.8)	214 (49.7)	<0.001
Severity of illness at admission				
PSI risk class >3	530 (47.6)	229 (33.5)	301 (69.8)	<0.001
Outcomes				
Intensive care admission	255 (22.9)	182 (26.7)	73 (16.9)	<0.001
Invasive mechanical ventilation	57 (5.1)	42 (6.1)	15 (3.5)	0.049
Septic shock	119 (10.7)	88 (12.9)	31 (7.2)	0.003

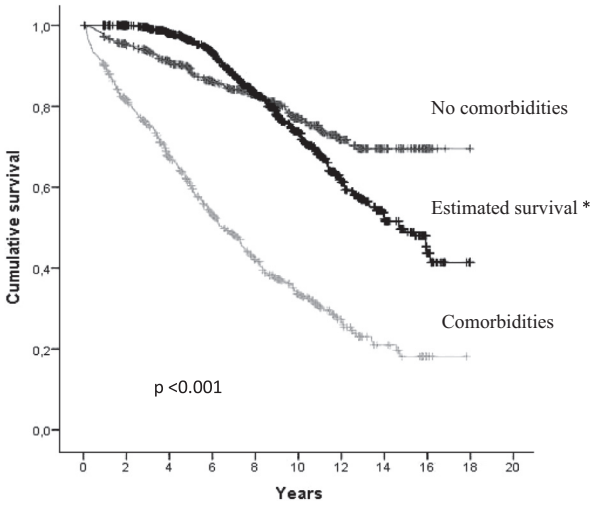
Data are given as frequency (percentage) unless otherwise stated. Percentages exclude patients with missing data. SD: Standard deviation. RDW: red blood cell distribution width. PSI: Pneumonia severity index.
[a] Reference range for RDW in our laboratory is 11% to 15%.

Discussion

In this large prospective study, we documented a significantly shorter long-term survival in patients with pneumococcal pneumonia than their life expectancy based on sex, age and year of discharge from hospital. To our knowledge, this is one of the largest series focusing on this topic including both bacteremic and non-bacteremic patients with this entity. The interest of this study lies not only in the number of patients included but also in the reproducibility of the observational design itself, which is based on the current clinical management of these patients in real life and differs from approaches based on complex biomarkers or microbiological analysis, most only available for research purposes.[18,19] We consider that these factors strengthen the clinical applicability of our results.

We have reported 1-, 3- and 5-year survival rates of 93.9%, 85.3% and 76%, respectively. At this point, beyond overall survival rates, it is interesting to consider how long these patients might live and how long they actually live. In our cohort, only 16.2% of non-survivors reached their life expectancy. Other authors have also reported this negative association between pneumonia and long-term outcome, reporting survival rates ranging from 25% to 53% at 5 years.[5, 20–23] This variability is mainly attributable to the type of population included, differences in control groups and follow-up intervals.

Similar to other studies, we have found that the presence of comorbidity and the number of comorbid conditions are both independently associated with shorter long-term survival.[23–25] This could simply be a consequence of the natural history of the underlying conditions themselves. Another factor that might be responsible for this finding, however, is a persistent inflammatory state impairing underlying conditions or even favoring the development of other health problems.[2,26,27] On the other hand, it is also possible that pneumonia itself is a surrogate marker of unknown poor health status that increases the risk of subsequent death. If so, close follow-up and optimal and more intensive management of underlying conditions might be crucial for improving the prognosis. In our series and unlike in others, neither diabetes



Survival	Comorbidities	No comorbidities	Estimated *
1 year	90.1%	97.2%	100%
3 year	75.3%	95.1%	99.9%
5 year	60.4%	89,3%	96.3%

Fig. 2. Observed and estimated *survival curves for patients with pneumococcal pneumonia stratified by the presence or absence of comorbidities and surviving more than 30 days after discharge.
*Estimated survival according to Spanish survival tables based on age, sex and date of hospital discharge.

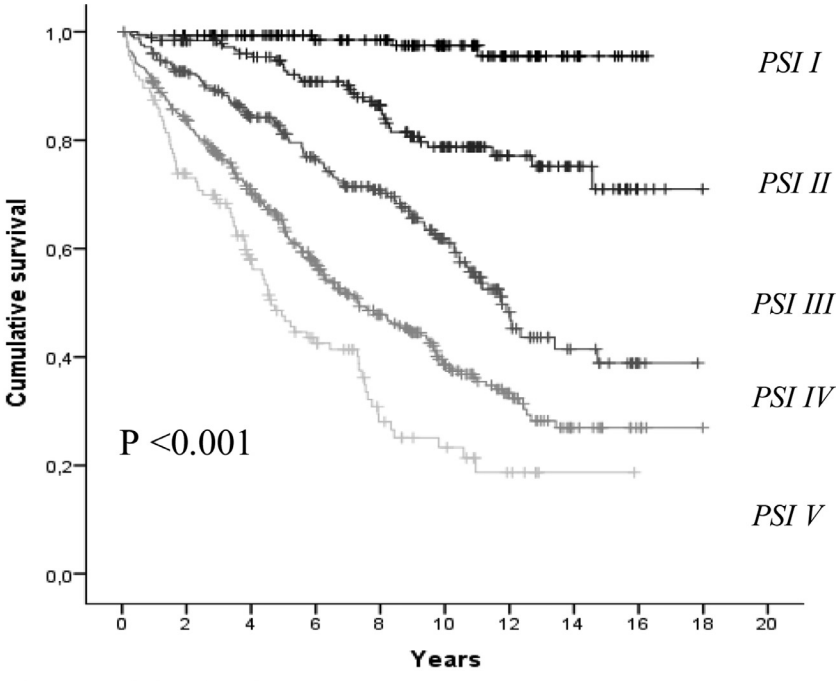
nor new hyperglycemia was associated with this poor outcome.[17] The reason for this is not clear. It is possible that diabetes and its effects on the immune system only influence the early prognosis. It might also be the case that in our study its long-term effects were masked by the statistical procedures applied to control for other comorbidities such as ischemic heart disease or renal failure.

The contribution of etiological factors to long-term outcomes is controversial. In our series, cumulative survival rates were similar to those in other series including patients with different microbiological etiologies.[22] These results would seem, at first sight, to corroborate previous reports showing that survival after discharge is independent of the pathogen. It is difficult, however, to discriminate the real contribution of each of pathogen in these series due to pneumococcus being the most frequently isolated and the limitation of current procedures for identifying the causal bacteria in real-world settings. More studies are needed to clarify this issue.

Several studies have documented an association between living in a nursing home and mortality, reflecting the age, functional status and severe and multiple comorbid conditions of this population.[21,28] In our study, despite the relatively small number of patients (2.6%) who lived in a nursing home, this association was observed after adjusting for age and comorbidities. This finding could reflect a low physiological reserve or frailty in this subgroup of patients.

No classic clinical or laboratory markers for severity on admission predicted survival in this study. Similar to previous observations, severity was found to be correlated with long-term prognosis but not to be an independent risk factor for long-term mortality in the multivariate analysis.[21,23,25,29] This probably indicates that the role of severity as measured by the *PSI* may be confounded by the contribution of age or comorbidities. Notably, our findings contrast with those of another study showing severity alone or in combination with blood markers to be a predictor of long-term outcome.[19] Nevertheless, that study had some weakness regarding multivariate analysis, limiting the generalizability of the results. Further, unlike other authors, we have not found an increased risk of long-term mortality in patients requiring ICU admission and/or under IMV after adjusting for confounders. Differences in our study population, selective ICU admission criteria including the role of age as limiting factor for ICU admission, may explain these discordant results.[30–32]

In this study, we found that patients with bacteremic pneumonia have poorer long-term prognosis than those with non-



PSI: Pneumonia Severity Index

Fig. 3. Kaplan–Meier plot of long-term survival by *PSI* risk class.

Table 2
Multivariate analysis of factors associated with long-term survival more than 30 days after hospitalization.

	Unadjusted HR (95% CI)	Model 1 Adjusted HR (95% CI)	*P*	Model 2 Adjusted HR (95% CI)	*p*
Sex male	1.35 (1.11–1.65)				
Age, years	1.06 (1.05–1.06)	1.05 (1.04–1.06)	<0.0001	1.04 (1.03–1.05)	<0.0001
Age≥65 years	6.03 (4.68–7.78)				
Nursing home resident	2,92 (1.86–4.58)	1.91 (1.18–3.10)	0.008	1.94 (1.21–3.08)	0.005
Solid cancer	2.94 (2.08–4.17)	2.60 (1.81–3.73)	<0.0001		
Liver disease	2.42 (1.58–3.69)	2.02 (1.27–3.20)	0.003		
Renal disease	2.91 (2.11–4.01)	2.01 (1.43–2.82)	<0.0001		
Chronic obstructive pulmonary disease	2.21 (1.80–2.72)	1.72 (1.38–2.14)	<0.0001		
Diabetes mellitus	2.09 (1.68–2.59)				
Cerebrovascular disease	2,99 (2.17–4.10)	2.38 (1.71–3.32)	<0.0001		
Congestive heart disease	2.88 (2.24–3.70)				
Atrial arrhythmia	3.12 (2.52–3.86)	1.42 (1.12–1.79)	0.003		
Coronary disease	2.48 (1.83–3.37)	1.55 (1.14–2.11)	0.005		
Arterial hypertension and/or dyslipidemia	1.96 (1.61–2.38)				
Incident heart complication	1.37 (0.93–1.89)				
Number underlying diseases					
1	3.95 (3.06–5.11)			2.24 (1.71–2.94)	<0.0001
>1	6.89 (5.35–8.87)			3.12 (2.37–4.10)	<0.0001
Influenza vaccine	2.13 (1.74–2.61)				
Pneumococcal vaccination	1.49 (1.15–1.93)				
Current tobacco use	0.50 (0.39–0.64)				
Heavy drinker	0.81 (0.59–1.11)				
Body temperature ≤35 or ≥40 °C	0.45 (0.14–1.42)				
Respiratory rate	1.03 (1.02–1.04)				
Heart rate	0.99 (0.98–0.99)				
Altered mental status	1.75 (1.29–2.36)				
Systolic blood pressure <90 mm Hg	0.51 (0.32–0.79)				
Blood urea nitrogen ≥ 30 mg/dL	2.02 (1.68–2.45)				
PaO_2 <60 mm Hg	1.58 (1.30–1.93)				
Glucose >200 mg/dL and no diagnosis of diabetes	1.58 (1.09–2.29)				
Hematocrit <30%	2.18 (1.43–3.33)			1.62 (1.04–2.52)	0.030
RDW >15%	2.92 (2.39–3.57)	1.89 (1.52–2.34)	<0.0001	1.98 (1.61–2.43)	<0.0001
Leucocyte count <4000 ($\times 10^9$/L)	1.27 (0.70–2.32)				
Multilobar pneumonia	0.83 (0.67–1.04)				
Pleural effusion	0.73 (0.54–1)				
Urinary antigen positive	0.73 (0.57–0.98)				
Positive blood culture	1.25 (1.04–1.52)	1.47 (1.21–1.80)	<0.0001	1.45 (1.19–1.76)	<0.0001
PSI risk class >3	3.82 (3.10–4.70)				
Intensive care admission	0.72 (0.56–0.92)				
Invasive mechanical ventilation	0.66 (0.39–1.05)				
Septic shock	0.73 (0.51–1.06)				

RDW: red blood cell distribution width. *PSI:* Pneumonia severity index. HR: Hazard ratios. CI: confidence interval.

bacteremic pneumonia with positive urinary antigen test results. It is probable that the higher inflammatory state worsens underlying conditions or acts as a trigger of other subclinical conditions. Other authors have not reported any differences between these two groups.[9] This could be largely explained by the type of population included, as reflected in the high 30-day mortality rates (similar in both groups), and the methodology of the study itself (blood cultures being obtained depending on the severity of the infection).

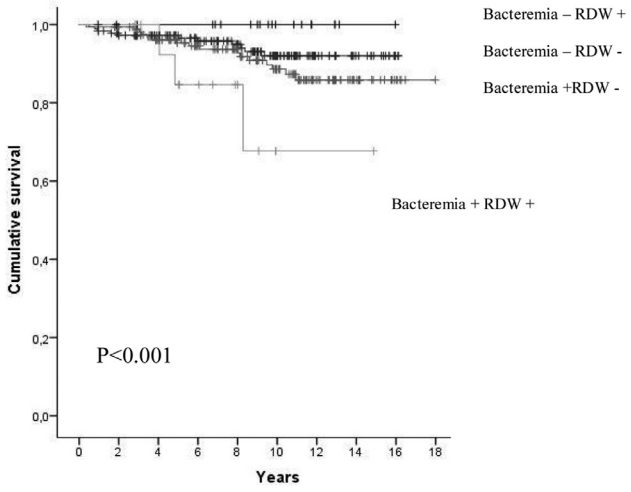
Recent observations suggesting a potential cardiotoxicity of pneumococcus infection raise some concerns about its possible role in the prognosis of these patients.[11,12] The presence of cardiac lesions during the acute pneumococcal infection together with production of pneumolysin seems to play a role, with other factors, in the genesis of cardiac complications.[33] Nevertheless, the long-term impact of this effect has yet to be studied. In this study, we have not found an association between in-hospital development of an incident cardiac complication and shorter survival, though this could be due to the small number of events. Studies involving more patients are needed to test this hypothesis.

Red blood cell distribution width is a laboratory parameter used for the differential diagnosis of microcytic anemia. Significantly, in this study, we have found that RDW >15% is an independent factor in long-term mortality after controlling for confounding factor such as hematocrit and comorbidities. Several studies have previously reported an association between this parameter and complicated hospitalization or mortality in community-acquired pneumonia and other conditions.[34–36] To our knowledge, however, this is the first time that this association with long-term mortality is shown in patients with pneumococcal pneumonia. The reason for this poorer outcome is not clear. It is possible that RDW is a marker of low-grade inflammation and oxidative stress.[36] Further studies are needed to evaluate this hypothesis. From a practical perspective, the interest of this finding is that RDW is routinely calculated by all hematology analyzers, and hence, its determination does not imply additional costs.

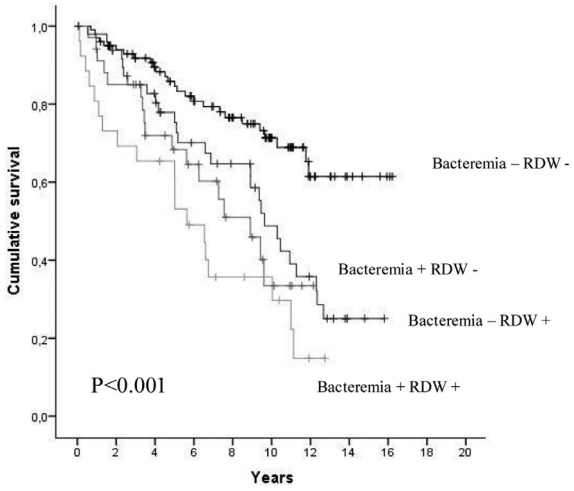
Anemia is a common complication of chronic underlying conditions with prognostic implications. A hematocrit level of <30% on admission is a classical component of the *PSI*. In this study, we have observed that anemia is also a predictor of survival independent of age and other comorbid conditions. This observation also documented by other authors is not easy to explain.[23] It is possible that it could reflect an exaggerated effect of inflammatory cytokines on subclinical not well-functioning red cell progenitors during acute onset of the disease.

The main strength of our study lies in the study population itself. Specifically, we only included patients with pneumococcal pneumonia, all of them with blood culture and urinary antigen test results. Further, the strict data collection process has allowed us to control for confounding effects in the multivariate analysis. We

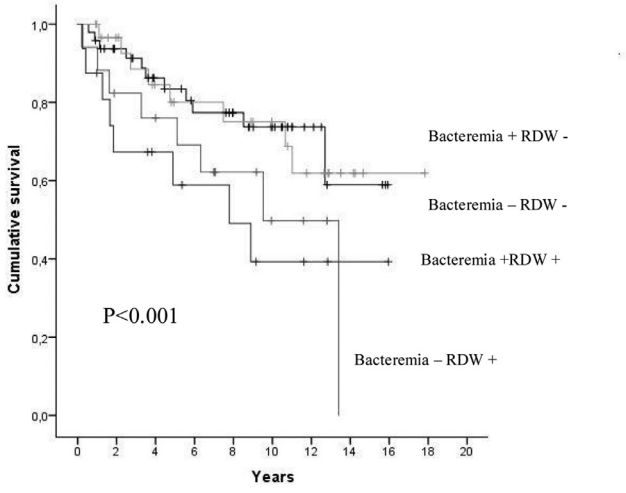
< 65 years and no comorbid condition



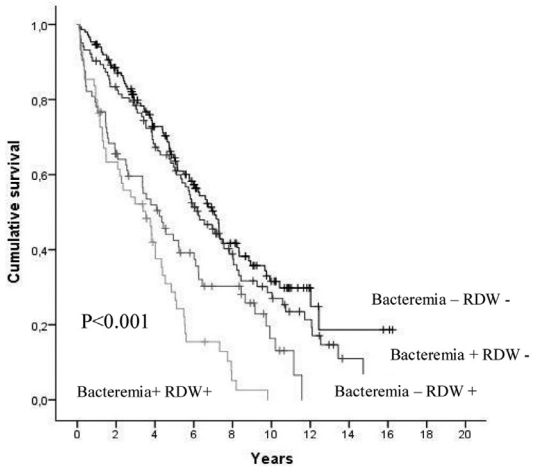
≥65 years and no comorbid condition



<65 years and at least one comorbid condition



≥65 years and at least one comorbid condition



RDW +: red blood cell distribution width >15%

Fig. 4. Kaplan–Meier curves showing the survival probability stratified by age and presence of comorbidities.

recognize, however, that our study also has some limitations. (1) It was conducted in two hospitals in the same geographical area and health system, and hence, it may not be possible to extrapolate the results to other areas. (2) The low rate of pneumococcal immunization in our area could limit its potential beneficial effect on survival. (3) We were unable to obtain data on the causes of death, which could have added important additional information. (4) Finally, we did not evaluate the role of inflammatory markers such us C-reactive protein, because that was not routinely requested during the first years of this study.

To summarize, this study demonstrates a significant decrease in long-term survival compared with individuals' life expectancy in a large population of patients diagnosed with pneumococcal pneumonia. This is mainly associated with host-related factors such as age and presence of comorbidities. Interestingly, the finding of bacteremia and elevated RDW on admission also could help identify a group of patients at high risk of long-term mortality. Future multicenter studies are required to confirm these results. Our results could argue in favor of strengthening efforts to widen pneumococcal vaccination coverage especially in aged patients and/or those with chronic comorbid conditions, as well as improving the clinical control of underlying disease, as main strategies for improving survival after hospital discharge.

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Declaration of Competing Interest

The authors declare no conflicts of interest

CRediT authorship contribution statement

Luis A Ruiz: Conceptualization, Investigation, Methodology, Data curation, Formal analysis, Writing - original draft, Writing - review & editing. **Leyre Serrano:** Investigation, Data curation, Writing - original draft, Writing - review & editing. **Pedro P España:** Data curation, Formal analysis, Writing - review & editing. **Lorea Martinez-Indart:** Methodology, Data curation, Formal analysis, Writing - review & editing. **Ainhoa Gómez:** Data curation, Writing - review & editing. **Ane Uranga:** Data curation, Writing - review & editing. **Sonia Castro:** Data curation, Writing - review & editing. **Amaia Artaraz:** Data curation, Writing - review & editing. **Rafael Zalacain:** Conceptualization, Methodology, Formal analysis, Writing - original draft, Writing - review & editing.

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S*treptococcus pneumoniae*, es el agente etiológico identificado con más frecuencia entre los pacientes con una neumonía adquirida en la comunidad que requiere ingreso hospitalario. Clásicamente se ha descrito que entre un 15 y un 25% de las neumonías por neumococo presentan una forma bacteriémica, sin embargo su significado desde un punto de vista pronóstico continua siendo, aún en nuestros días, objeto de debate. Actualmente se han identificado en esta bacteria hasta 100 serotipos, algunos de ellos con diferentes capacidades invasivas, en funcion de un "medio ambiente" propio de cada paciente. Pero esta entidad también puede llegar a afectar a otros órganos. Estamos empezando a conocer la relacion que existe entre el hecho de padecer una neumonía y la posibilidad de desarrollar una complicación cardiaca durante el episodio agudo. Por otro lado, la neumonía no sólo es una enfermedad aguda sino que también se va a comportar como un posible marcador de supervivencia futura. ¿Como interrelacionan los factores dependientes del propio paciente en el pronóstico de esta entidad?, ¿qué implicaciones tiene la aparición de una arritmia cardiaca en la fase aguda de la enfermedad?, ¿qué pacientes están a riesgo de morir prematuramente tras el episodio agudo?, ¿qué papel tiene la presencia de una bacteriemia en la historia natural de la neumonía neumocócica?. Tratar de responder a estas preguntas va a constituir el objetivo general de este proyecto de Tesis Doctoral.