UNIVERSITAT DE BARCELONA

EPIDEMIOLOGÍA DE LA NEUMONÍA ADQUIRIDA EN LA COMUNIDAD QUE REQUIERE HOSPITALIZACIÓN EN PERSONAS DE 65 AÑOS Y MÁS. FACTORES DE RIESGO Y FACTORES ASOCIADOS AL REINGRESO

Memoria presentada por

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Listado de abreviaturas

CDC	Centers for Disease Control and Prevention
DE	Desviación estándar
ENI	Enfermedad neumocócica invasiva
EPOC	Enfermedad pulmonar obstructiva crónica
EUA	Estados Unidos de América
EV	Efectividad vacunal
GPC	Guía de práctica clínica
HC	Historia clínica
Hib	*Haemophilus influenzae* tipo b
IB	Índice de Barthel
IC	Intervalo de confianza
NAC	Neumonía adquirida en la comunidad
ORa	Odds ratio ajustada
PCR	Reacción en cadena de la polimerasa
PSI	*Pneumonia severity index*
Rx	Radiografía
UCI	Unidad de cuidados intensivos
UE	Unión Europea
VIH	Virus de la inmunodeficiencia humana
VNC	Vacuna antineumocócica conjugada

VNC10	Vacuna antneumocócica conjugada 10-valente
VNC13	Vacuna antineumocócica conjugada 13-valente
VNP	Vacuna antineumocócica de polisacáridos
VNP23	Vacuna antineumocócica de polisacáridos 23-valente

1. Introducción

1.1 La neumonía adquirida en la comunidad. Historia.

La neumonía es un proceso inflamatorio agudo del parénquima pulmonar que se manifiesta por signos y síntomas de infección respiratoria acompañados por un nuevo infiltrado en una radiografía (Rx) de tórax. Cuando afecta a la población no ingresada en un hospital se denomina neumonía adquirida en la comunidad (NAC) o extrahospitalaria para diferenciarla de la que aparece en pacientes hospitalizados.[1,2]

Los primeros textos que hacen alusión a la neumonía datan del siglo V a.C. Hipócrates, en sus escritos describió las principales enfermedades del tracto respiratorio inferior y nombró a la afectación pulmonar "neumonía" (en griego: πνευμονία). Además, detalló la sintomatología y los métodos de la época para tratarla y describió como debía realizarse un drenaje quirúrgico para tratar el empiema.[3–5]

En el siglo XIX la neumonía fue reconocida como una de las principales causas de mortalidad en la población, lo que motivó a científicos de la época a profundizar en los estudios sobre la enfermedad.[6,7] Sir William Osler, conocido como "el padre de la medicina moderna" describía la neumonía con el aforismo "el capitán del barco de la muerte" y detectó diferencias en la presentación clínica de la neumonía en los ancianos en relación a otros grupos de edad.[8,9]

La identificación de *Streptococcus pneumoniae* es un hito importante en la historia de la neumonía. *S. pneumoniae* se identificó en 1881, cuando de manera casi paralela Louis Pasteur en Francia y George Sternberg en Estados Unidos describieron el microorganismo en una muestra de saliva humana denominándolo "*Microbe septicemique du salive*" y "*Micrococcus pasteuri*", respectivamente.[10] Fue una de las primeras bacterias patógenas observadas mediante el desarrollo de la tinción de Gram en 1884, técnica que aún es empleada en la actualidad.[11] Posteriormente, en 1886, Fraenkel lo denominó *Pneumococcus* por su capacidad de producir enfermedad pulmonar, siendo reconocido como el agente causal más común de la neumonía lobular.[12] Paralelamente a la identificación de

Pneumococcus se identificaron también *Klebsiella pneumoniae* y *Staphylococcus aureus.*[13–15]

En 1920, debido a su apariencia en la tinción de Gram, se le cambió el nombre pasándose a denominar *Diplococcus pneumoniae* por su característica de agruparse en parejas[16] y finalmente se le denominó *S. pneumoniae* en 1974 por su disposición en cadenas.[15] Ya en el siglo XX se han identificado nuevos agentes causales de neumonía como *Chlamydia psittaci* en 1930, *Mycoplasma pneumoniae* y el virus de la gripe en 1933, *Coxiella burnetti* en 1937, *Legionella pneumophila* en 1977 y *Chlamydi*a *pneumoniae* en 1986.[13]

Los hermanos Klemperer a finales del siglo XIX demostraron que la inoculación de neumococos muertos a conejos los protegía frente a una futura infección por neumococo, y que podía transferirse la protección mediante la administración del suero de dichos conejos inmunizados a otros receptores.[15,17] Neufeld y Rimpau denominaron a este proceso opsonización.[18]

Otro hito importante para el estudio de la enfermedad neumocócica fue la descripción de la reacción de Quellung descrita por Neufeld en 1902, que permitió realizar el serotipado. A partir de una primera clasificación básica que diferenciaba los serotipos 1, 2 y 3, Dochez y Gillespie clasificaron el resto de neumococos como del grupo 4. La reacción de Quellung ha sido adoptada ampliamente como el método de elección para la tipificación capsular.[19–21] En 1932, Cooper et al. identificaron 32 serotipos y durante la II guerra mundial en Estados Unidos de América (EUA) se describieron hasta 75 serotipos.[22] En 1995 mediante la reacción de Quellung se identificaron 90 serotipos y actualmente se han identificado más de 97 serotipos.[23,24]

La introducción de antibióticos modificó el impacto de la enfermedad en la población: las infecciones neumocócicas fueron de las primeras que se trataron con un agente antimicrobiano (optochin), un derivado de la quinina, abandonado debido a su toxicidad. Posteriormente se utilizó la sulfapiridina, observándose una reducción en la letalidad que pasó del 27% al 8% entre los pacientes con neumonía tratados con dicho fármaco; sin embargo, pronto se reportaron cepas resistentes. En 1943 Keefer et al. emplearon penicilina en el tratamiento de una variedad de

infecciones estafilocócicas y estreptocócicas (incluidas las neumocócicas) con resultados positivos. Los estudios realizados con neumococos mostraron la relevancia clínica de las proteínas de unión a la penicilina en el desarrollo de resistencia a dicho antibiótico.[10]

1.2 Epidemiología y carga de enfermedad

La NAC es una causa de morbilidad y mortalidad importante que afecta especialmente a los menores de 5 años y a las personas de 65 años y más.[2,25] También puede afectar a personas de cualquier grupo de edad que presentan determinadas comorbilidades o factores de riesgo.

Según datos de las Naciones Unidas, en 2017 las personas de 65 años y más representaba el 8,29% de la población mundial y Europa acumula el porcentaje más alto de personas en este grupo de edad el 17,59%.[26]

Se estima que la población de Europa en 2030 será más longeva debido a la baja tasa de natalidad y al incremento en la esperanza de vida, fenómeno que se está observando en diversos Estados miembros de la Unión Europea (UE).[26] El aumento de la esperanza de vida en los países desarrollados y los avances médicos han aumentado la proporción de pacientes con NAC que tienen edad avanzada y que padecen múltiples comorbilidades.[27]

La incidencia de la NAC en países europeos es variable debido a factores como la situación geográfica,[4] la estación,[28] la distribución etaria de la población, la introducción de programas de vacunación y las guías clínicas utilizadas para el manejo de los pacientes. Sin embargo, la incidencia de casos aumenta con la edad en todos los países y aproximadamente el 45% de todos los casos de NAC ocurren en pacientes de 65 años o más. La incidencia de la NAC en Europa varía entre 1,07 y 1,23 por 1000 personas-año en población adulta[25] y se va incrementando hasta alcanzar 6,2 por 1000 personas-año en personas de 65 años[29–31] y 16,87 por 1000 personas-año en personas de 90 años,[32] convirtiéndose así en una de las principales causas de hospitalización para las personas de 65 años y más.

Coincidiendo con los datos de Petrosillo et al. en Italia (6,2 por 1000 en $\geqslant$65 y 16,87 por 1000 en $\geqslant$90 años)[33] y Bjarnason et al. en Islandia (5,3 por 1000 en 65-79 y

12,7 por 1000 en >80 años),[34] en España también se observa un incremento de la hospitalización a medida que aumenta la edad, 3,94 por 1000 en los de 65-74 años y 25,85 por 1000 en los ⩾85 años.[35] Para las personas de 65 años y más desarrollar un episodio de NAC se comporta como un factor que desestabiliza otras comorbilidades ocasionando una recuperación más lenta y una mayor carga para los cuidadores, así como un consumo considerable de recursos sanitarios. Las personas de 65 años y más representan aproximadamente un tercio de todos los casos de NAC, pero son responsables de más de la mitad de todos los costes.[36–40]

Rozembaum et al. en un estudio realizado en Holanda, concluyó que el coste medio de atención de NAC dependía de la edad y el tipo de atención, con costes de 16,005€ por episodio para los adultos entre 65-74 años ingresados en la unidad de cuidados intensivos (UCI).[41]

Según el Global Burden of Disease Study, entre el 2007 y el 2017 las infecciones del tracto respiratorio inferior fueron la primera causa de muerte para las personas de más de 70 años, mostrando un incremento del 33% entre el primer y el último año.[42] Las defunciones por NAC se incrementan con la edad y representan la mayor proporción de todas las muertes por neumonía.[38,42,43]

La letalidad por NAC en pacientes ambulatorios se estimó del 5%, pero en pacientes hospitalizados la letalidad a corto plazo (letalidad hospitalaria y a los 30 días) varía del 12% al 18% y en los pacientes que ingresan a la UCI es superior al 30%.

Cilloniz et al. en un estudio realizado en España sobre el impacto de la edad y las comorbilidades en la etiología de la NAC, destaca que la edad no influye en la etiología, pero que la letalidad aumenta significativamente con la edad (6,9% en los de 65-74 años; 8,9% en 75-84 años y 17,1% en >85 años).[27] Un estudio español muestra que la letalidad a los 30 días en personas mayores de 65 años se incrementa significativamente con la edad (4,5% en los de 65-74 años; 6,0% en 75-84 años y 15,0% en >85 años).[44]

Las personas de 65 años y más, pueden tardar varios meses en recuperar el estado de salud previo al episodio de hospitalización por NAC y algunos nunca lo hacen.[45,46] En aquellos pacientes que sobreviven a los 30 días de la hospitalización, la mortalidad aumenta sustancialmente al cabo de 1 año y, en el caso de la neumonía

neumocócica, se mantiene elevada durante 3 a 5 años, lo que sugiere que el desarrollo de NAC sirve como marcador para las condiciones subyacentes asociadas a la mortalidad. En las personas de 60 años y más la neumonía es un factor predictivo de aumento de la mortalidad durante varios años después del episodio de NAC.[46–49]

Debido a que la recuperación total del paciente de 65 años y más suele ser lenta, la probabilidad de reingreso tras el alta hospitalaria se incrementa y son relativamente frecuentes los reingresos entre personas de edad avanzada y pacientes con múltiples comorbilidades.[45,46] Suele utilizarse como un indicador de vulnerabilidad el reingreso a los treinta días.[40,50–52] A menudo el reingreso en este grupo de edad se asocia a complicaciones en alguna de las comorbilidades preexistentes o a la aparición de una nueva patología,[53] lo cual comporta un incremento de la carga económica para los sistemas de salud.[40]

Además de la edad, otros factores como el tabaquismo, el alcoholismo, el estado nutricional y el padecer ciertas comorbilidades (enfermedad pulmonar obstructiva crónica [EPOC], enfermedad cardiovascular, enfermedad cerebrovascular, enfermedad renal crónica, enfermedad hepática crónica, diabetes mellitus y demencia) incrementan el riesgo de padecer NAC.[54–58]

Los casos más graves se deben a las complicaciones que se presentan en el curso de la NAC.[59] *S. pneumoniae* es el principal agente causal de NAC en personas de 65 años y más, en quienes hasta un tercio de los pacientes requieren ingreso en la UCI,[28] y casi el 20% muere durante la hospitalización o en el primer mes después del alta.[60]

A pesar de la mejora de la atención, la disponibilidad y cumplimiento generalizado de las pautas de tratamiento recomendadas, la incidencia de la NAC no ha disminuido en los últimos años y sigue siendo un problema frecuente en la práctica clínica, especialmente en pacientes que requieren hospitalización y/o ingreso en UCI.[61,62]

1.3 Clínica

1.3.1 Sintomatología

La NAC se define como una infección aguda del parénquima pulmonar que se manifiesta por signos y síntomas de infección respiratoria del tracto inferior (fiebre, tos, disnea), asociados a un infiltrado nuevo en la Rx de tórax no explicable por otra causa. Se presenta en pacientes no hospitalizados o que no han sido ingresados en un hospital los 14 días previos al inicio de los síntomas, o bien en aquellos pacientes hospitalizados que presentan la infección aguda en las 24-48 horas que siguen a su ingreso.[2,63–65]

La presentación clínica de la NAC en los adultos mayores es más inespecífica que la de las poblaciones jóvenes y frecuentemente es atípica.[66–68] Los hallazgos clásicos de tos, fiebre y disnea pueden estar ausentes en más de la mitad de los adultos de edad avanzada,[45,69,70] mientras que la taquipnea (frecuencia respiratoria >24 a 30 respiraciones/min) y los estertores son hallazgos más frecuentes.[66,67] A veces los síntomas no respiratorios pueden ser la principal característica de la NAC en las personas de 65 años y más, observándose una disminución del estado funcional, debilidad, cambios sutiles en el estado mental y anorexia o dolor abdominal,[25,69] lo cual comporta frecuentemente un diagnóstico tardío. El estado de fragilidad de la persona junto a la presentación de comorbilidades altera el cuadro clínico,[71] pudiéndose presentar como una exacerbación o descompensación de comorbilidades preexistentes (diabetes mellitus, enfermedad cardíaca, EPOC). Además, en aproximadamente el 30% de los casos, los hallazgos radiográficos no son concluyentes o son difíciles de interpretar.[72] La mayoría de los pacientes (58% a 89%) tienen una o más enfermedades crónicas subyacentes.[68,73]

1.3.2 Diagnóstico radiológico

La Rx de tórax se mantiene como el «gold standard» en el diagnóstico de la neumonía, ya que permite establecer la localización, la extensión, la presencia de complicaciones y de valoraciones de progreso de la enfermedad y de curación. La radiografía de tórax es una herramienta de fácil acceso y es fiable, por lo que debe obtenerse siempre en pacientes con sospecha de neumonía.[74–76]

Si bien el patrón de infiltrado en la Rx de tórax de pacientes con neumonía no sirve para hacer un diagnóstico etiológico,[49,75] es orientativo para determinar si se debe a un agente bacteriano (por presentar ciertas características como la consolidación lobular, la cavitación y/o derrames pleurales) o a otro tipo de agente. En las personas mayores los signos de la neumonía son visibles en las radiografías durante más tiempo en comparación con la población joven. Mittl et al. sugieren que debe realizarse una Rx de tórax de control en los pacientes mayores a las 8 semanas de la primera y señalan que mientras que a las 6 semanas el 73% de los adultos jóvenes mostraban una Rx de tórax normal, solo el 60% de los pacientes mayores presentaban una Rx de tórax normal, incrementándose al 84% a las 12 semanas.[77]

La Rx de tórax tiene menor precisión en pacientes con desnutrición, con estancias prolongadas en cama, obesos o inmunodeprimidos. En casos de elevada sospecha se puede repetir la radiografía a las 24-48 horas o incluso se puede plantear una tomografía computarizada torácica.[74]

1.3.3 Diagnóstico microbiológico

La NAC está ocasionada por una gran variedad de agentes como bacterias, virus, hongos y otros.[2] La identificación del agente etiológico en la NAC tiene el potencial de mejorar el manejo individual del paciente debido a la adecuada selección del tratamiento antibiótico, reduciendo el riesgo del fracaso clínico, disminuyendo la letalidad,[78] y así como evitando el desarrollo de resistencia a los antibióticos. El agente causal se debe identificar sobre todo en aquellos pacientes que presentan un cuadro de mayor gravedad o que presentan factores de riesgo y epidemiológicos que sugieran etiologías infrecuentes.

A pesar de que algunas características de la persona como la edad, el sexo o la presencia de ciertas comorbilidades pueden orientar para la identificación del agente causal, no existe un patrón epidemiológico, clínico o radiológico específico asociado a una entidad etiológica, por lo que se debe recurrir a técnicas de laboratorio para confirmar al agente.[74] Por ello, el régimen antibiótico inicial se elige empíricamente para evitar el retraso del tratamiento y disminuir el riesgo de muerte.[79,80]

Para la detección de los patógenos respiratorios asociados a la NAC se pueden utilizar muestras de secreciones respiratorias (obtenidas por técnicas no invasivas e inasivas), sangre, orina y liquido pleural. El uso combinado de las pruebas microbiológicas estándar junto con los ensayos de amplificación de ácidos nucleicos puede definir la etiología de la NAC en hasta un 89% de los casos.[81]

Los casos de NAC ocurren durante todo el año, aunque puede haber una variación en la incidencia de determinados agentes causales según la estación: en invierno se observa una mayor incidencia de *S. pneumoniae* y co-infecciones con el virus gripal, y en verano un incremento en los casos por *L. pneumophila*.[28]

En adultos mayores hospitalizados la identificación del agente causal suele darse en menos del 50% de los casos.[2,67,74] Esto puede explicarse por la ausencia de tos productiva, la utilización de antibióticos previos que pueden afectar la calidad de las muestras y el tipo de técnica empleada.

En la población de 65 años y más *S. pneumonia*e supone entre el 10% y el 50% de las NAC, pero también se han identificado bacterias intracelulares (2%–15%), *Haemophilus influenzae* (1%–10%), virus respiratorios (2%–20%), *Pseudomonas aeruginosa* (1%–15%), *S. aureus* (1%–7%), infecciones polimicrobianas (2%–13%) y Enterobacterias (1%–3%).[27,28,50,68,82] La proporción de cada agente etiológico varía según las características de la serie que se presenta, del tipo de muestra, de la variación en las técnicas y del tipo de población.

En un estudio prospectivo para describir la distribución estacional de la etiología microbiana en pacientes con NAC realizado en un hospital de Barcelona durante el periodo 2003-2014 en el que se estudiaron 4431 pacientes de los cuales el 60% eran de 65 años y más, se pudo identificar el agente etiológico en el 35% de los pacientes. Se observó una mayor incidencia de casos de NAC en invierno y primavera (35% vs 27%). Los agentes identificados fueron *S. pneumoniae* (15%), seguido de etiología polimicrobiana (5%), virus respiratorios (4%), *L. pneumophila* (2%), bacterias atípicas (2%), *S. aureus* (1%) *H. influenzae* (1%), *P. aeruginosa* (1%) y Enterobacterias (<1%).[28]

En el estudio de Fernández-Sabe et al. realizado en personas de 80 años y más, no se pudo identificar el agente en el 56% de los pacientes, siendo el principal agente

S. pneumoniae (23%) seguido de virus respiratorios (8%), *H. influenzae* (5%), bacilos Gram negativos (3%), *L. pneumophila* (1%) y otros agentes atípicos (1%).[67]

1.3.3.1 Técnicas diagnóstico según tipo de muestra

Esputo

El examen microscópico y el cultivo de esputo siguen siendo los pilares básico para el diagnóstico de laboratorio de la neumonía a pesar de la controversia existente sobre su sensibilidad y especificidad. El esputo es la muestra respiratoria que se obtiene con mayor frecuencia, pero no siempre se considera una muestra de buena calidad debido a que puede estar contaminada con la microbiota orofaríngea o a que el paciente haya recibido antibióticos antes de que se realicen los estudios, lo que reduce drásticamente el rendimiento diagnóstico.[83,84] Además, su interpretación puede estar afectada por la pérdida de bacterias si se produce retraso en su procesamiento o por la presencia de agentes etiológicos difíciles de cultivar.[74] Para valorar la calidad de la muestra para su cultivo se debe realizar un examen microscópico tras la realización de la tinción de Gram que muestre abundantes leucocitos y escasas células escamosas.[85,86]

La tinción de Gram permite detectar neumococo en pacientes con neumonía neumocócica bacteriémica hasta en un 80% de los casos con una especificidad del 85% - 93%y una sensibilidad del 57%-63%, mientras que el cultivo de esputo se considera un diagnóstico presuntivo debido a que la colonización de la orofaringe por neumococo es frecuente en pacientes con enfermedades pulmonares crónicas.[84,87]

Otros microorganismos que también pueden observarse en la tinción de Gram pero con una menor sensibilidad y aislarse en cultivo son *H. influenzae* y *Moxarella catarrhalis,* que colonizan las vías respiratorias fundamentalmente en pacientes con enfermedades crónicas.

El aislamiento de patógenos primarios como *L. pneumophila* o *Mycobacterium tuberculosis* se considera un diagnóstico de seguridad, incluso en esputos de mala calidad. Aunque es viable, el cultivo y aislamiento de *M. pneumoniae* y

Chlamydophila es poco sensible, difícil y lento, por lo que se recomiendan técnicas alternativas.

Hemocultivo

Las muestras se deben obtener preferiblemente en urgencias antes de iniciar el tratamiento antibiótico en todos los pacientes con indicación de hospitalización por NAC.[74]

En los pacientes hospitalizados por NAC los hemocultivos son positivos aproximadamente entre el 4% y el 20% de los casos.[88–91] Un hemocultivo positivo permite realizar el diagnóstico de certeza de neumonía neumocócica bacteriemica o neumonía por *H. influenzae*, identificar la presencia de organismos inusuales y permite adecuar el tratamiento antibiótico.

La realización del hemocultivo es importante en pacientes con NAC grave, comorbilidades o infección por virus de la inmunodeficiencia humana (VIH), en quienes la incidencia de bacteriemia es elevada.[74]

Liquido pleural

El derrame pleural paraneumónico se produce en 20 a 40% de los pacientes hospitalizados por NAC. Debido a que la incidencia de afectación pleural grave ha aumentado en los últimos años y el desarrollo de empiema es uno de los principales factores asociados a mala evolución de la NAC, se recomienda la obtención de una muestra mediante toracocentesis.[86,92]

La muestra debe analizarse mediante la tinción de Gram y cultivo de bacterias aerobias y anaerobias.[74] *S. pneumoniae* es el microorganismo aislado con mayor frecuencia, seguido de *H. influenzae.* En muestras de lıquido pleural también se puede emplear la detección de ácidos nucleicos.

Serología

Está indicada para el diagnóstico de infecciones causadas por *M. pneumoniae, C. pneumoniae, C. burnetii* y *L. pneumophila*. La sensibilidad y la especificidad de los ensayos varían, y su utilidad para hacer un diagnóstico rápido es limitada;[65,74,86] además, para valorar la seroconversión se precisan dos pares de suero, uno en la

fase aguda y otro en la fase de convalecencia (se valora el título elevado de anticuerpos IgM en el suero de la fase aguda y/o seroconversión del tıtulo de anticuerpos IgG en el suero de la fase de convalecencia).

Detección de antígeno

Las pruebas de antigenuria permiten detectar la excreción renal de antígenos microbianos. La detección de antígenos en la orina es un medio innovador para detectar patógenos importantes como *S. pneumoniae* y *L. pneumophila*. La muestra se recoge fácilmente y no se ve afectada por la toma previa de antibióticos, además el desarrollo de la prueba y la obtención de los resultados son rápido.

La detección del antígeno neumocócico en orina se puede realizar mediante la inmunocromatografía de membrana para detectar el antígeno polisacárido C de la pared celular presente en todos los serotipos.[65,74,86] Una ventaja es que presenta una sensibilidad mayor que la de los cultivos de sangre o del esputo de rutina. La sensibilidad oscila entre 65,5% y 100%, aumentando con la gravedad del caso, y la especificidad entre 94% y 100%.[65]

La detección de *L. pneumophila* por enzimoinmunoanálisis (EIA) se establece como una prueba altamente específica, tiene una sensibilidad del 80% al 95% y una especificidad estimada del 99% para la detección de infecciones causadas por el serogrupo 1.[65,93,94]

Mediante la detección del antígeno urinario se pueden obtener resultados rápidos, siendo este un método valioso para el diagnóstico temprano de la infección por *L. pneumophila*. Una limitación relativa es que la antigenuria puede persistir durante semanas o meses después del tratamiento.[65,74,86]

Técnicas de biología molecular

Las técnicas de biología molecular están indicadas en neumonías graves en las que no se ha logrado establecer el diagnostico etiológico por los medios habituales y en centros con la infraestructura y la experiencia técnica necesaria.

Mediante la técnica de reacción en cadena de la polimerasa (PCR) se puede detectar DNA neumocócico en muestra de líquido pleural, que tiene una sensibilidad alta en comparación con la muestra de sangre.

1.4 Evaluación de la gravedad y criterios de hospitalización

Una correcta evaluación del paciente con NAC es indispensable para valorar la gravedad, y establecer tanto el tratamiento como el seguimiento.[74] La decisión para la hospitalización de un paciente de 65 años y más con NAC está influenciada por el juicio clínico del médico y por factores como las comorbilidades, los hábitos de tabaquismo y consumo de alcohol, la situación familiar y la previsión de la adherencia al tratamiento.[4]

Las escalas pronósticas permiten valorar la probabilidad de muerte a los 30 días del paciente con NAC. Son sistemas de puntuación que pueden predecir la gravedad de la enfermedad que ayudan a determinar si un paciente con NAC debe hospitalizarse o ingresarse en la UCI.[95,96] Las escalas de gravedad más robustas son el *Pneumonia Severity Index* (PSI) y el CURB-65, que son de gran utilidad para la evaluación pronóstica y para determinar el nivel y la intensidad de la atención requerida.[95,96]

El PSI se desarrolló para definir el riesgo de mortalidad y orientar las decisiones sobre el tipo de atención, pero sus resultados son controvertidos, ya que puede subestimar enfermedad grave en personas previamente sanas y sobrestimar la gravedad en pacientes con edad avanzada o enfermedad crónica. El PSI incluye 20 variables a las que se les asigna una puntuación y con la puntuación obtenida se clasifica al paciente en una de entre cinco categorías posibles. Los pacientes en las categorías I a III presentan un bajo riesgo de mortalidad (<3%), mientras que las categorías IV a V tienen un alto riesgo de mortalidad (8% - 30%).[4,97]

Aunque estas escalas funcionan bien en la práctica clínica, existen otros factores intrínsecos en pacientes de edad avanzada que son determinantes de los resultados y que no están incluidos en ellas. La calidad de vida previa es un factor pronóstico decisivo, especialmente en pacientes institucionalizados y existe evidencia de que

el estado funcional de referencia, medido con el índice de Barthel (IB), es un factor que influye en la supervivencia inmediata y a largo plazo del paciente de edad avanzada.

El IB es una herramienta clínica que evalúa la capacidad de realizar actividades básicas de la vida diaria y asigna una puntuación según el grado de dependencia. Las actividades evaluadas incluyen autonomía para alimentarse, moverse, subir escaleras, vestirse, usar el inodoro y la incontinencia. La puntuación oscila entre 0 (dependencia total) y 100 (autonomía completa).

El estado funcional se ha asociado de forma independiente con un peor pronóstico de la NAC.[98,99] Se estima que el 60% de los pacientes con dependencia múltiple morirán durante los primeros 12 meses y solo el 25% sobrevivirá durante ≥2 años.[100]

Existe una creciente evidencia de que el estado funcional, medido por el IB, es más importante que la edad y la comorbilidad para predecir el pronóstico a los 12 meses en las personas de edad avanzada y de que incluso pequeños cambios en el IB se asocian con resultados clínicamente relevantes.[101] En un episodio de NAC un IB bajo se relaciona con el aumento de la estancia hospitalaria, de la letalidad y de los costes asociados.[101] Murcia et al. informaron que en pacientes de diferentes edades con diagnóstico de NAC con un IB ≤80, la mortalidad fue cuatro veces mayor que en la población general.[102]

La identificación de la gravedad y el riesgo de muerte en pacientes ancianos con NAC es un desafío asistencial, ya que muchos pacientes tienen comorbilidades asociadas y otras situaciones que afectan su salud inicial y no pueden evaluarse mediante escalas de gravedad de neumonía convencionales. Otra limitación de las escalas es que no se incluyen marcadores biológicos como la proteína-C reactiva o la procalcitonina.

1.5 Tratamiento antibiótico

La identificación del agente etiológico es esencial para la decisión del tratamiento a instaurar, pero a menudo su identificación es lenta y solo se alcanza en alrededor

del 50% de los casos. Por ello, se recomienda el uso del tratamiento antibiótico empírico dentro de las primeras horas después de la admisión en la sala de urgencias. El diagnóstico puede guiarse por la epidemiología de los microorganismos activos en la comunidad y los factores de riesgo que presenta el paciente, especialmente cuando se sospecha una infección por *P. aeruginosa* en pacientes con EPOC avanzada o bronquiectasias generalizadas.[74,103]

Las guías internacionales actuales para el manejo de la NAC no proporcionan recomendaciones específicas para pacientes de edad avanzada, existiendo una baja concordancia entre los regímenes de tratamiento antibiótico utilizados y los recomendados en las guías de práctica clínica (GPC). [63,64,86,104] Según Rossio et al. en Italia, en pacientes de 65 años y más hospitalizados y tratados empíricamente, solo el 38,8% de los tratamientos aplicados seguían las directrices de la GPC.[105]

El éxito de la terapia antimicrobiana en la NAC se basa en la adherencia del paciente al tratamiento. Los tratamientos que duran <7 días muestran una mejor adherencia y, además, el uso prolongado de antibióticos se relaciona con una mayor frecuencia de eventos adversos, prolonga la estancia hospitalaria, aumenta los costes sanitarios y favorece a la aparición de microorganismos multiresistentes ante los antimicrobianos disponibles. Estudios realizados por Houck et al. y Daniel et al. han encontrado una asociación directa entre el tratamiento antibiótico temprano y una mejora en los resultados clínicos de personas de edad avanzada.[106,107]

La GPC de la Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) y la GPC de la European Respiratory Society and European Society for Clinical Microbiology and Infectious Diseases instan a que la duración del tratamiento antimicrobiano no supere los 8 días en pacientes con una respuesta correcta. Esto fue confirmado por un reciente ensayo clínico aleatorizado realizado en 4 hospitales universitarios del País Vasco.[108]

En España, para el tratamiento de los pacientes hospitalizados por NAC se sigue las recomendaciones de la Sociedad Española de Neumología y Cirugía Torácica,[74] que están ampliamente difundidas entre los especialistas en neumología, medicina interna y medicina de cuidados intensivos y críticos.

1.6 Prevención mediante la vacunación

En la década de 1920, Heidelberger y Avery demostraron que los anticuerpos que conferían inmunidad reaccionaban con los polisacáridos capsulares del neumococo, siendo los primeros antígenos no proteicos identificados.[109] El conocimiento de la inmunogenicidad de los polisacáridos capsulares se utilizó con fines terapéuticos mediante la aplicación de seroterapias, tratamiento que empleaba inicialmente antisuero animal y posteriormente antisuero humano, pero debido a los resultados no satisfactorios dejó de utilizarse. En 1911, Wrigth et al. desarrollaron una vacuna antineumocócica de células completas, que se reemplazó por las vacunas antineumocócicas específicas frente a determinados serotipos desarrolladas por Felton a partir de los primeros polisacáridos capsulares neumocócicos purificados para la inmunización de sujetos humanos.[110] El reconocimiento del impacto de la morbilidad y la mortalidad de las neumonías neumocócicas generó interés en la prevención de la enfermedad mediante la vacunación. En los años cuarenta se realizaron ensayos clínicos controlados utilizando vacunas a base de polisacáridos capsulares de 2, 3, 4 y 6 serotipos que demostraron ser eficaces, lo que llevó a la comercialización de dos vacunas hexavalentes en 1946 (una para niños y otra para adultos). Estas vacunas se retiraron en los años 50 debido al auge de los antibióticos. La vacuna de polisacáridos se introdujo nuevamente en 1977 en forma de 14 valencias y en 1983 se amplió a 23 valencias,[24] que es la de uso actual recomendada para adultos y también para niños que presentan especial riesgo de desarrollar ENI que ya han recibido previamente la vacuna conjugada.[111]

Actualmente, están disponibles dos tipos de vacunas, la vacuna antineumocócica polisacárida (VNP) y las vacunas antineumocócicas conjugadas (VNC). Las guías internacionales recomiendan la vacunación como medida para prevenir la enfermedad neumocócica y estudios de coste-efectividad apoyan la recomendación de la vacunación antineumocócica en las personas de edad avanzada.[112,113]

1.6.1 Vacuna antineumocócica polisacárida

Desde 1983 se dispone de la vacuna antineumocócica polisacárida 23-valente (VNP23) que contiene antígenos contra 23 serotipos. Los estudios posteriores a su licencia muestran que la vacuna protege contra la enfermedad ENI en adultos

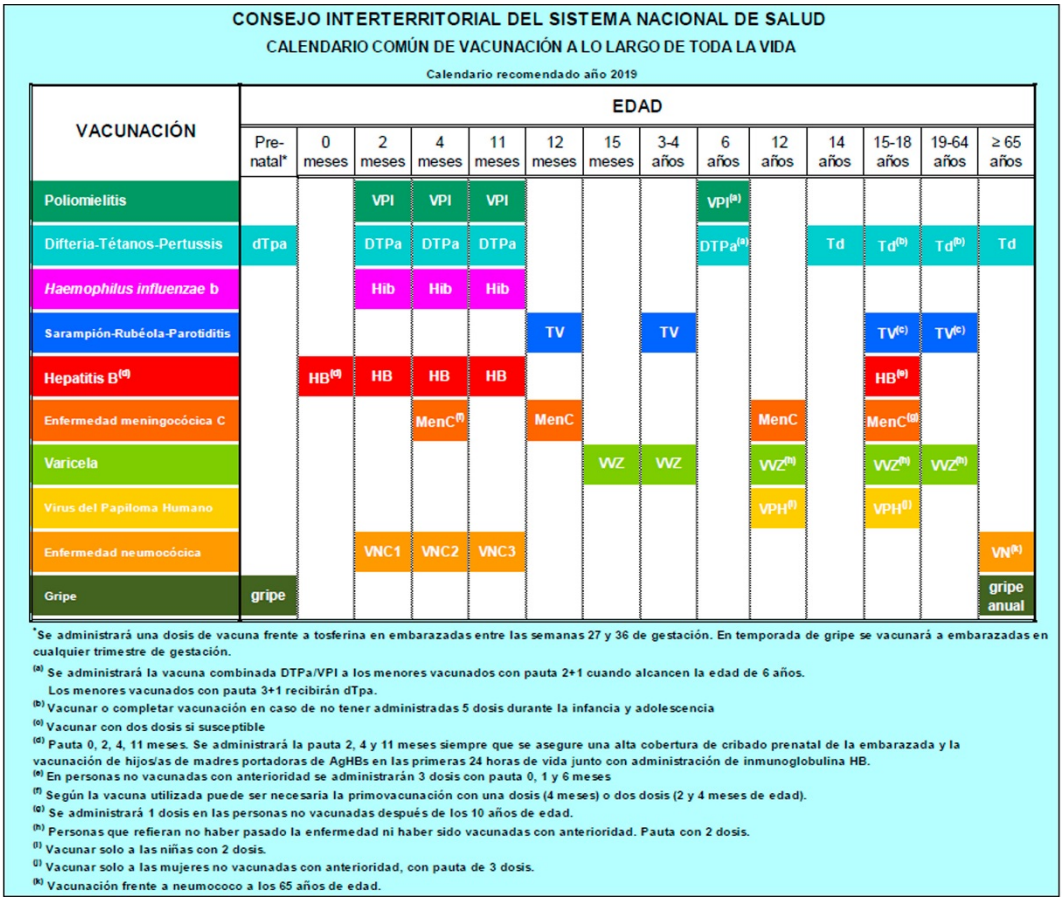
mayores inmunocompetentes. Las pruebas que respaldan un efecto beneficioso de la VNP para prevenir la neumonía neumocócica son más limitadas,[114–117] se han demostrado beneficios como la disminución de la estancia hospitalaria media. Además, se ha señalado que en personas de edad avanzada con enfermedades crónicas la VNP puede reducir la hospitalización durante la temporada de gripe.[118]

La vacunación con VNP23 en los EUA y en la mayoría de los países de la Unión Europea, está indicada para todas las personas de 65 años y más y para adultos menores de 65 años con mayor riesgo de ENI.[119] Francia, Portugal y Holanda no la incluyen en su calendario para adultos.[120]

El Consejo Interterritorial del Sistema Nacional de Salud de España contempla la vacunación con vacuna VNP23 en personas de 65 y más en el "Calendario de vacunación recomendado a lo largo de toda la vida" de 2019 (Figura 1) y en personas que presentan condiciones de riesgo para el desarrollo de enfermedad neumocócica en el "Calendario de vacunación específica en personas adultas (≥18 años) con condiciones de riesgo" (Figura 2).[121,122]

Estudios realizados en España han registrado una efectividad de 23,6% en todos los pacientes y 21% en pacientes inmunodeprimidos.[123] Sin embargo, a pesar de ser una vacuna gratuita, las coberturas de vacunación son bajas. Es necesario conocer los factores que se asocian a la cobertura de la VNP23 para diseñar estrategias que incrementen dichas coberturas.

Debido a que el agente etiológico no siempre se detecta, para el estudio de la efectividad de la vacuna VNP23 frente a la hospitalización, la NAC puede considerarse una aproximación útil para investigar la efectividad de la vacunación frente a la neumonía neumocócica.



CONSEJO INTERTERRITORIAL DEL SISTEMA NACIONAL DE SALUD

CALENDARIO COMÚN DE VACUNACIÓN A LO LARGO DE TODA LA VIDA

Calendario recomendado año 2019

VACUNACIÓN	EDAD													
	Pre-natal*	0 meses	2 meses	4 meses	11 meses	12 meses	15 meses	3-4 años	6 años	12 años	14 años	15-18 años	19-64 años	≥ 65 años
Poliomielitis			VPI	VPI	VPI				VPI[a]					
Difteria-Tétanos-Pertussis	dTpa		DTPa	DTPa	DTPa				DTPa[a]		Td	Td[b]	Td[b]	Td
Haemophilus influenzae b			Hib	Hib	Hib									
Sarampión-Rubéola-Parotiditis						TV		TV				TV[c]	TV[c]	
Hepatitis B[d]		HB[d]	HB	HB	HB							HB[e]		
Enfermedad meningocócica C				MenC[f]		MenC				MenC		MenC[g]		
Varicela							VVZ	VVZ		VVZ[h]		VVZ[h]	VVZ[h]	
Virus del Papiloma Humano										VPH[i]		VPH[i]		
Enfermedad neumocócica			VNC1	VNC2	VNC3									VN[k]
Gripe	gripe													gripe anual

*Se administrará una dosis de vacuna frente a tosferina en embarazadas entre las semanas 27 y 36 de gestación. En temporada de gripe se vacunará a embarazadas en cualquier trimestre de gestación.

[a] Se administrará la vacuna combinada DTPa/VPI a los menores vacunados con pauta 2+1 cuando alcancen la edad de 6 años. Los menores vacunados con pauta 3+1 recibirán dTpa.

[b] Vacunar o completar vacunación en caso de no tener administradas 5 dosis durante la infancia y adolescencia

[c] Vacunar con dos dosis si susceptible

[d] Pauta 0, 2, 4, 11 meses. Se administrará la pauta 2, 4 y 11 meses siempre que se asegure una alta cobertura de cribado prenatal de la embarazada y la vacunación de hijos/as de madres portadoras de AgHBs en las primeras 24 horas de vida junto con administración de inmunoglobulina HB.

[e] En personas no vacunadas con anterioridad se administrarán 3 dosis con pauta 0, 1 y 6 meses

[f] Según la vacuna utilizada puede ser necesaria la primovacunación con una dosis (4 meses) o dos dosis (2 y 4 meses de edad).

[g] Se administrará 1 dosis en las personas no vacunadas después de los 10 años de edad.

[h] Personas que refieran no haber pasado la enfermedad ni haber sido vacunadas con anterioridad. Pauta con 2 dosis.

[i] Vacunar solo a las niñas con 2 dosis.

[j] Vacunar solo a las mujeres no vacunadas con anterioridad, con pauta de 3 dosis.

[k] Vacunación frente a neumococo a los 65 años de edad.

Figura 1: Calendario de vacunación recomendado a lo largo de toda la vida. 2019. Fuente: Consejo Interterritorial del Sistema Nacional de Salud

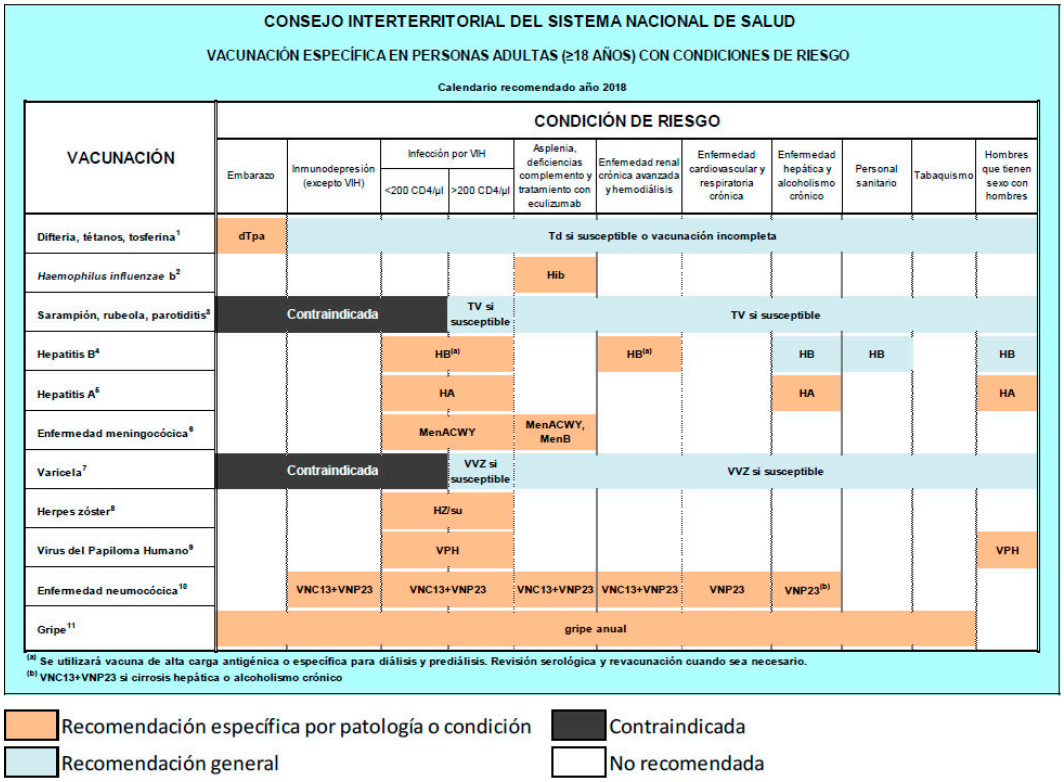


Figura 2: Calendario de vacunación específica en personas adultas con condición de riesgo. Fuente: Consejo Interterritorial del Sistema Nacional de Salud

1.6.2 Vacunas antineumocócicas conjugadas

Debido a la baja inmunogenicidad que presentaba la vacuna antineumocócica polisacárida en niños menores de dos años y a los buenos resultados obtenidos en la vacuna conjuda contra *Haemophilus influenzae* tipo b (Hib), se introdujo en el calendario de vacunación infantil de Estados Unidos en el año 2000 una vacuna antineumocócica conjugada 7-valente, que mostró buenos resultados en la reducción de la enfermedad en niños. Posteriormente se ampliaron los serotipos contenidos en las vacunas conjugadas a 10 (VNC10) y 13 (VNC13).[124] Las vacunas conjugadas producen una respuesta inmunitaria desde los primeros meses de vida.

La VNC13 era una vacuna indicada para prevenir la enfermedad neumocócica en niños, pero en 2015 se publicaron los resultados de un ensayo clínico aleatorizado en adultos de 65 años y más, en el que se mostraba que la VNC13 prevenía la neumonía adquirida en la comunidad causada por los serotipos incluidos en la

vacuna.[125] La publicación de estos resultados condujo a la ampliación en la indicación del uso de vacunas conjugadas en personas mayores.

Los primeros resultados sobre el efecto protector indirecto de la VNC en adultos no vacunados se informaron en los Estados Unidos unos años después de la introducción de la vacuna, [126,127] y estudios recientes en países con una alta cobertura de VNC refuerzan su papel para evitar los casos de ENI causados por los serotipos incluidos en la vacuna en adultos no vacunados y ancianos.[128–133]

En España, la introducción de la vacuna VNC13 en la población infantil ha sido paulatina y desde finales de 2016 todas las Comunidades Autónomas incluyen la vacuna en su calendario de vacunación infantil.

Guevara et al. compararon las tasas de incidencia de ENI antes y después de la introducción de la VNC13 en el calendario de vacunación infantil en Navarra y encontraron una disminución de los casos de ENI debida a serotipos contenidos en la VNC13 del 52% en el conjunto población.[134]

1.6.3 Pautas de vacunación recomendadas en ≥65 años

Actualmente, el programa de vacunación antineumocócica recomendado por la Advisory Committee on Immunization Practices (ACIP) para adultos de 65 años y más en los Estados Unidos es el siguiente:[119,135]

Si el paciente de 65 años es inmunocompetente y no ha recibido dosis previa de VNC13, recibirá 1 dosis de VNC13, seguido de 1 dosis de VNP23 con un año de diferencia como minino.

Si el paciente recibió ya una dosis de VNP23, pero no VNC13, recibirá 1 dosis de VNC13 al menos 1 año después de VNP23.

Cuando debido a la situación de riesgo del paciente se indiquen ambas vacunas (VNC13 y VNP23), se administrará primero la VNC13 y posteriormente la VNP23 con al menos 8 semanas de diferencia.

En España, la recomendación actual es la de vacunar con VNP23 a las personas de 65 años y más; y una dosis de recuerdo al menos 5 años después de la dosis anterior si recibió una dosis previa a los 65 años. Se recomienda la pauta secuencial de

administración de VNC13 y VNP23 separada por un intervalo óptimo de 12 meses y mínimo de al menos 8 semanas en personas que presenten inmunodepresión, asplenia, cirrosis, fístula de líquido céfalo raquídeo o implante coclear.[121,122]

2. Hipótesis

Los reingresos en personas de 65 años y más tras la hospitalización por NAC pueden estar asociadas a las decisiones terapéuticas adoptadas durante el episodio inicial.

El uso conjunto del índice de Barthel y el *Pneumonia Severity Index* pueden mejorar la capacidad de predecir el pronóstico de muerte por NAC.

La vacunación antineumococócica polisacárida 23-valente es efectiva para prevenir los ingresos hospitalarios por NAC en pacientes de 65 años y más.

La vacunación antineumococócica polisacárida 23-valente es efectiva para prevenir las formas graves de NAC en pacientes de 65 años y más.

La baja cobertura de la vacuna antineumocócica polisacarida 23 valente en personas de 65 años y más puede deberse a factores predisponentes y a recursos disponibles.

3. Objetivos

3.1 Objetivo general

Investigar las características de la presentación de la NAC y los factores que se asocian a su aparición, evolución y resolución en personas hospitalizadas de 65 años y más.

3.2 Objetivos específicos

1. Determinar los factores de riesgo asociados al reingreso hospitalario en los 30 días posteriores al alta por NAC en personas de 65 años y más.
2. Evaluar la capacidad predictiva de la mortalidad por NAC mediante la combinación del índice de Barthel y el índice de severidad de la neumonía en personas de 65 años y más hospitalizadas.
3. Determinar los factores asociados a la cobertura de vacuna antineumocócica polisacárida 23-valente en personas de 65 años y más hospitalizadas por causas no relacionadas con neumonía, enfermedad respiratoria aguda o síndrome gripal en España.
4. Estimar la efectividad de la vacunación antineumocócica polisacárida 23 valente para prevenir la hospitalización por NAC en sujetos hospitalizados de 65 años y más y estimar la efectividad de la vacunación antineumocócica polisacárida 23-valente para prevenir las formas graves de NAC (ingreso a UCI y muerte) en sujetos hospitalizados de 65 años y más.

4. Resultados

4.1 Artículo 1

Título:

Factors associated with 30-day readmission after hospitalisation for community-acquired pneumonia in older patients: a cross-sectional study in seven Spanish regions.

Autores:

Toledo D, Soldevila N, Torner N, Pérez-Lozano MJ, Espejo E, Navarro G, Egurrola M, Domínguez Á; On-behalf of the Project FIS PI12/02079 Working Group.

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Factors associated with 30-day readmission after hospitalisation for community-acquired pneumonia in older patients: a cross-sectional study in seven Spanish regions

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ABSTRACT

Objective Hospital readmission in patients admitted for community-acquired pneumonia (CAP) is frequent in the elderly and patients with multiple comorbidities, resulting in a clinical and economic burden. The aim of this study was to determine factors associated with 30-day readmission in patients with CAP.

Design A cross-sectional study.

Setting The study was conducted in patients admitted to 20 hospitals in seven Spanish regions during two influenza seasons (2013–2014 and 2014–2015).

Participants We included patients aged ≥65 years admitted through the emergency department with a diagnosis compatible with CAP. Patients who died during the initial hospitalisation and those hospitalised more than 30 days were excluded. Finally, 1756 CAP cases were included and of these, 200 (11.39%) were readmitted.

Main outcome measures 30-day readmission.

Results Factors associated with 30-day readmission were living with a person aged <15 years (adjusted OR (aOR) 2.10, 95% CI 1.01 to 4.41), >3 hospital visits during the 90 previous days (aOR 1.53, 95% CI 1.01 to 2.34), chronic respiratory failure (aOR 1.74, 95% CI 1.24 to 2.45), heart failure (aOR 1.69, 95% CI 1.21 to 2.35), chronic liver disease (aOR 2.27, 95% CI 1.20 to 4.31) and discharge to home with home healthcare (aOR 5.61, 95% CI 1.70 to 18.50). No associations were found with pneumococcal or seasonal influenza vaccination in any of the three previous seasons.

Conclusions This study shows that 11.39% of patients aged ≥65 years initially hospitalised for CAP were readmitted within 30 days after discharge. Rehospitalisation was associated with preventable and non-preventable factors.

Strengths and limitations of this study

- ► All the information on readmission was obtained from medical records.
- ► The study is part of a multicentre study carried out in seven autonomous communities representing 70% of the Spanish population.
- ► It was not possible to collect detailed information on the readmission episode.

INTRODUCTION

Community-acquired pneumonia (CAP) is a frequent, potentially serious disease in people aged ≥65 years and one of the leading causes of hospitalisation and mortality worldwide in this age group,[1–4] in whom recovery from an episode of CAP is predictive of increased mortality in subsequent years.[5]

The incidence of CAP differs between European countries due to variations in age distribution, the introduction of vaccination programmes and the clinical guidelines used. However, the incidence of cases and hospitalisations increases with age in all countries.[6 7] In Spain, CAP is not a reportable disease and therefore the incidence in the population is unknown, although 2013 data also show an increase in hospitalisation (394.04 per 100,000 in the 65–74 years age group and 2584.95 per 100,000 in the >85 years age group).[8]

In people aged ≥65 years, full recovery after hospitalisation due to CAP is usually slow and the probability of readmission during a period of time after discharge is greater.[9] Thirty-day readmission postdischarge is usually used as an indicator of vulnerability.[2 10–12]

Readmission in patients initially hospitalised due to CAP is relatively frequent (especially in the elderly and patients with multiple comorbidities), and is often associated with a worsening of a baseline disease or the appearance of a new pathology,[13] and this results in a significant clinical and economic burden for health systems.[2 14] Studies have explored

the factors associated with readmission following hospitalisation due to CAP, and have identified factors that improve the prognosis at discharge and are considered preventable, such as influenza and pneumococcal vaccination, the use of hospital care protocols, discharge planning and postdischarge follow-up. Adequate discharge planning, including patient stability and destination, has been associated with reduced readmission.[15–17] However, the effect of seasonal influenza and pneumococcal vaccination and the adequacy of hospital care (use of clinical guidelines and antibiotic plans) may be more controversial.[18–21] The initial severity of CAP, worsening of comorbidities and some individual patient characteristics have been described as non-preventable factors,[15 21–25] and factors such as age, sex, socioeconomic status, education and some comorbidities have been independently associated with a greater likelihood of readmission.[25 26]

The objective of this study was to determine the risk factors associated with 30-day readmission in people aged ≥65 years initially hospitalised due to CAP.

MATERIALS AND METHODS

Study design

This cross-sectional study was carried out as part of a multicentre study in 20 hospitals from seven Spanish regions (Andalusia, the Basque Country, Castile and Leon, Catalonia, Madrid, Navarre and Valencian Community). Patients aged ≥65 years hospitalised due to CAP in the participating hospitals during the 2013–2014 and 2014–2015 influenza seasons were recruited.

Study population

The Spanish health system assigns each citizen a primary healthcare centre and a referral hospital to be attended. The assignation of the population to each hospital is made according to geography. Consequently, if there is a readmission, it would be in the same hospital. However, in an emergency, the patient may be treated in any hospital.

Patients included were aged ≥65 years admitted through the emergency department to any of the participating hospitals for ≥24 hours with a chest X-ray showing pulmonary infiltrate compatible with pneumonia and ≥1 of the following symptoms or signs of acute lower respiratory tract infection: cough, pleural chest pain, dyspnoea, fever >38°C, hypothermia <35°C and abnormal auscultator respiratory sounds unexplained by other causes.

Patients who died during the initial hospitalisation and patients hospitalised for more than 30 days were not included. Institutionalised patients, patients with nosocomial pneumonia (onset ≥48 hours after hospital admission), patients whose main residence was not in any of the seven participating regions and those who did not provide signed informed consent were excluded.

Outcomes

The dependent variable was 30-day readmission, defined as 'hospitalisation for any reason within 30 days of discharge'. Information on readmission was collected by re-review of index hospital medical records up to 30 days after initial discharge.

All participating hospitals had a specifically trained team of health professionals who used a structured questionnaire to obtain sociodemographic information and lifestyle factors by patient interview and the review of patient's medical record to collect immunisation history, risk medical conditions and the CAP hospital care process.

Information collected included sociodemographic variables: age, sex, marital status, educational level, cohabitation; lifestyle factors: smoking status (current smoker, ex-smoker, non-smoker) and high alcohol consumption (>40 g/day in men, >20 g/day in women). The Barthel Index[27] was used to assess the functional capacity at hospital admission (ranging from 0 — complete dependence to 100 — complete independence). Patients were considered vaccinated against pneumococcal disease if they had received a dose of pneumococcal vaccine in the last 5 years and against seasonal influenza if they had received a dose of the influenza vaccination at least 14 days before symptom onset. Comorbidities considered at high or moderate risk (chronic respiratory failure, history of pneumonia during the last 2 years, solid or haematological neoplasm, diabetes mellitus, renal failure, chronic obstructive pulmonary disease (COPD), heart failure, disabling neurological disease, chronic liver disease and haemoglobinopathy or anaemia) were collected from the patient's medical record through chart review and were assessed using the Charlson Comorbidity Index,[28] which assigns a weight to each comorbid condition (0, no comorbidity; 1, low comorbidity and 2, high comorbidity). Number of primary care nurse visits, number of hospital visits in the last 90 days. Severity of illness quantified in five risk classes using the Pneumonia Severity Index (PSI) at admission,[29] length of stay (LOS) <8 and ≥8 days,[8] intensive care unit (ICU) admission, mechanical ventilation, adequacy of antibiotic treatment plan according to clinical guidelines (yes/no) and discharge disposition (home without services, home with home healthcare or social health centre) 6 were also colected

Statistical analysis

The Barthel Index, a continuous variable, was dichotomised into 0–89 (moderate-to-high degree of dependency) and ≥90 (little or no dependency).

A bivariate analysis was conducted to compare 30-day readmission and no readmission according to sociodemographic variables, lifestyle factors, the Barthel Index, immunisation history, risk medical conditions, prior medical utilisation and hospital care process. Independent variables were checked for collinearity using the variance inflation factor.[30]

As Spanish regions have varying degrees of autonomy in organising health services, persons living in the same region tend to have similar access to healthcare. Therefore, to estimate the crude OR and adjusted OR (aOR), we used multilevel regression models that considered

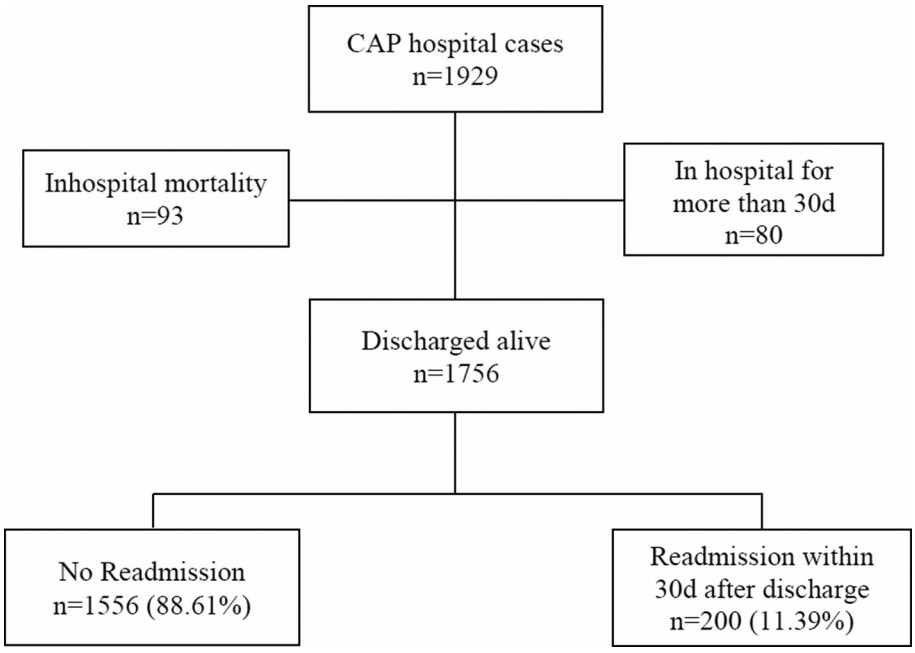

Figure 1 Flow chart of hospital readmissions. CAP, community-acquired pneumonia.

the outcome variable in people from the same region to obtain accurate statistical estimates of predictors of 30-day readmission.[30] Covariates were introduced into the model using a backward stepwise procedure, with a cut-off point of p<0.2.

The analysis was performed using the SPSS V.24 statistical package and R V.3.3.0 statistical software.

RESULTS

Overall, 1929 inpatients met all study eligibility criteria for CAP: 93 patients died during the initial hospitalisation and 80 were hospitalised for >30 days. Therefore, 1756 CAP cases were discharged within 30 days after the initial hospitalisation: of these, 200 (11.39%) were readmitted within 30 days after hospital discharge (figure 1).

The reasons for 30-day readmission were unrelated to pneumonia in 49.5% (99 cases), pneumonia-related in 44.5% (89 cases) and unknown diagnosis in 6% (12 cases).

The descriptive analysis and unadjusted associations of factors related to 30-day readmission are shown in table 1. No differences were observed according to lifestyle factors and immunisation history.

Factors independently associated with 30-day readmission in the multilevel analysis (table 2) were living with a person aged <15 years (aOR 2.10, 95% CI 1.01 to 4.41; p=0.04), more than three hospital visits during the 90 previous days (aOR 1.53, 95% CI 1.01 to 2.34; p=0.04) chronic respiratory failure (aOR 1.74, 95% CI 1.24 to 2.45; p=0.001), heart failure (aOR 1.69, 95% CI 1.21 to 2.35; p=0.002), chronic liver disease (aOR 2.27, 95% CI 1.21 to 4.31; p=0.01) and discharge to home with home healthcare (aOR 5.61, 95% CI 1.70 to 18.50; p=0.005).

A moderate-to-high degree of dependency was tentatively associated with readmission (aOR 1.39, 95% CI 0.99 to 1.95; p=0.05).

No associations were observed with age, sex, pneumococcal vaccination or seasonal influenza vaccination in any of the three previous seasons, the PSI or any variable related to the hospital care process.

DISCUSSION

The overall 30-day readmission rate in our study was 11.39%. Although all participating hospitals were referral centres, readmission rates ranged between regions from 2.5% to 14%. This might be due to the differences in the hospital healthcare burden of participating hospitals and in the protocols used.

In the Pneumonia Patient Outcomes Research Team cohort study, carried out in the USA and Canada, the readmission rate in adults was 10.1%.[31] Readmission rates at 30 days in people aged ≥65 years admitted for CAP vary between 8% and 27%, depending on the population and country studied.[11 19 21 25 32] In Spain, national data show 30-day readmissions increased from 11.5% in 2004 to 13.5% in 2013 in adults admitted for CAP.[8]

Our results show that non-preventable factors, specifically patient characteristics (living with a person aged <15 years, more than three hospital visits during the 90 previous days and some comorbidities) and one preventable factor (discharge disposition) were significantly associated with 30-day readmission. Factors such as cohabitation and the discharge dispostion have been little studied and their identification provides a new perspective on the risk factors involved in 30-day readmission of these patients.

Table 1 Distribution of 30-day readmission cases according to patient characteristics

	Readmission n=200	No readmission n=1556	Crude OR (95%CI)	P values
Sociodemographic				
Age median (range)	80 (65–101)	78 (64–100)	1.02 (0.99–1.04)	0.07
Age group				
65–74 years	56 (28.0%)	501 (32.2%)	1	
75–84 years	98 (49.0%)	729 (46.9%)	1.20 (0.85–1.70)	0.31
>84 years	46 (23.0%)	326 (20.5%)	1.26 (0.83–1.91)	0.27
Sex				
Female	64 (32.0%)	622 (40.0%)	1	
Male	136 (68.0%)	934 (60.0%)	1.44 (1.05–1.97)	0.02
Educational level				
No/primary education	153 (78.1%)	1118 (72.4%)	1	
Secondary or higher	43 (21.9%)	427 (27.6%)	0.75 (0.51–1.10)	0.14
Marital status				
Married/cohabiting	116 (58.0%)	912 (58.6%)	1	
Single	21 (10.5%)	107 (6.9%)	1.56 (0.94–2.59)	0.09
Widowed/divorced	63 (31.5%)	536 (34.4%)	0.93 (0.67–1.29)	0.66
Cohabitation				
Lives alone	31 (15.5%)	289 (18.6%)	1	
Lives with cohabitant aged >15 years	155 (77.5%)	1203 (77.4%)	1.20 (0.80–1.80)	0.39
Lives with cohabitant aged <15 years	14 (7.0%)	63 (4.1%)	2.03 (1.02–4.04)	0.04
Lifestyle factors				
Smoking status				
Non-smoker	79 (39.5%)	693 (44.5%)	1	
Smoker	16 (8.0%)	138 (8.9%)	1.04 (0.59–1.83)	0.90
Ex-smoker	105 (52.5%)	725 (46.6%)	1.28 (0.94–1.75)	0.11
High alcohol consumption				
No	197 (98.5%)	1524 (97.9%)	1	
Yes	3 (1.5%)	32 (2.1%)	1.38 (0.42–4.54)	0.60
Prior utilisation of resources				
No of nurse visits in last 90 days				
0–2	147 (73.5%)	1182 (76.4%)	1	
≥3	53 (26.5%)	365 (23.6%)	1.17 (0.82–1.65)	0.39
No of hospital visits in last 90 days				
0–2	164 (82.8%)	1355 (87.6%)	1	
≥3	34 (17.2%)	192 (12.4%)	1.53 (1.02–2.31)	0.04
Barthel Index				
Little or no dependency >90	108 (54.0%)	990 (63.6%)	1	
Moderate-to-high dependency ≤90	92 (46.0%)	566 (36.4%)	1.47 (1.08–2.01)	0.01
Immunisations				
Influenza vaccination in any of the three previous seasons				
No	54 (27.0%)	464 (29.8%)	1	
Yes	146 (73.0%)	1092 (70.2%)	1.16 (0.83–1.61)	0.39
Pneumococcal vaccination in five previous years				
No	161 (80.5%)	1281 (82.3%)	1	

Continued

Table 1 Continued

	Readmission n=200	No readmission n=1556	Crude OR (95%CI)	P values
Yes	39 (19.5%)	275 (17.7%)	1.11 (0.76–1.62)	0.58
Risk medical conditions				
Chronic respiratory failure				
No	136 (68.0%)	1269 (81.6%)	1	
Yes	64 (32.0%)	287 (18.4%)	2.08 (1.50–2.88)	<0.001
Pneumonia during the last 2 years				
No	146 (73.0%)	1267 (81.4%)	1	
Yes	54 (27.0%)	289 (18.6%)	1.65 (1.18–2.32)	0.004
Any malignancy				
No	161 (80.5%)	1271 (81.7%)	1	
Yes	39 (19.5%)	285 (18.3%)	1.08 (0.74–1.58)	0.67
Diabetes				
No	139 (69.5%)	1023 (65.7%)	1	
Yes	61 (30.5%)	533 (34.3%)	0.83 (0.60–1.14)	0.26
Renal failure				
No	151 (75.5%)	1263 (81.2%)	1	
Yes	49 (24.5%)	293 (18.8%)	1.38 (0.97–1.96)	0.07
Chronic obstructive pulmonary disease				
No	128 (64.0%)	1074 (69.0%)	1	
Yes	72 (36.0%)	482 (31.0%)	1.25 (0.92–1.70)	0.16
Heart failure				
No	128 (64.0%)	1168 (75.1%)	1	
Yes	72 (36.0%)	388 (24.9%)	1.69 (1.24–2.31)	0.001
Chronic liver disease				
No	186 (93.0%)	1504 (96.7%)	1	
Yes	14 (7.0%)	52 (3.3%)	2.13 (1.15–3.94)	0.01
Haemoglobinopathy or anaemia				
No	160 (80.0%)	1324 (85.1%)	1	
Yes	40 (20.0%)	232 (14.9%)	1.40 (0.96–2.04)	0.08
Disabling neurological disease				
No	179 (89.5%)	1416 (91.0%)	1	
Yes	21 (10.5%)	140 (9.0%)	1.17 (0.72–1.90)	0.52
Charlson Index				
No comorbidity (0)	18 (9.0%)	233 (15.0%)	1	
Low comorbidity (1)	54 (27.0%)	378 (24.3%)	1.83 (1.05–3.20)	0.03
High comorbidity (≥2)	128 (64.0%)	945 (60.7%)	1.71 (1.02–2.86)	0.04
Hospital care process				
Intensive care unit				
No	188 (94.5%)	1499 (96.9%)	1	
Yes	11 (5.5%)	48 (3.1%)	1.93 (0.97–3.81)	0.06
Mechanical ventilation				
No	157 (78.5%)	1317 (84.9%)	1	
Yes	43 (21.5%)	235 (15.1%)	1.50 (1.03–2.18)	0.03
Pneumonia Severity Index				

Continued

Table 1 Continued

	Readmission n=200	No readmission n=1556	Crude OR (95%CI)	P values
I–III	69 (34.7%)	645 (41.7%)	1	
IV–V	130 (65.3%)	902 (58.3%)	1.40 (1.02–1.92)	0.04
Length of hospital stay				
<8 days	80 (40.0%)	766 (49.2%)	1	
≥8 days	120 (60.0%)	790 (50.8%)	1.45 (1.05–2.02)	0.02
Antibiotic treatment				
No	97 (50.3%)	700 (46.6%)	1	
Yes	96 (49.7%)	802 (53.4%)	1.07 (0.76–1.50)	0.70
Discharge disposition				
Home without services	185 (92.5%)	1477 (94.9%)	1	
Home with home healthcare	9 (4.5%)	19 (1.2%)	5.05 (1.58–16.15)	0.01
Social health centre	6 (3.0%)	60 (3.9%)	1.23 (0.41–2.92)	0.63

Table 2 Multilevel regression analysis of factors associated with 30-day readmission

	Adjusted OR (95%CI)	P values
Age	1.02 (0.99–1.04)	0.13
Sex—male	1.39 (0.99–3.12)	0.06
Cohabitation		
Lives alone	1	
Lives with cohabitant aged >15 years	1.17 (0.71–1.95)	0.54
Lives with cohabitant aged <15 years	2.10 (1.01–4.41)	0.04
Marital status		
Married/cohabiting	1	
Single	1.73 (0.96–3.11)	0.07
Widowed/divorced	0.94 (0.61–1.44)	0.77
No of hospital visits ≥3	1.53 (1.01–2.34)	0.04
Barthel Index		
Moderate-to-high dependency ≤90	1.39 (0.99–1.95)	0.05
Pneumonia during the last 2 years	1.31 (0.91–1.88)	0.14
Chronic respiratory failure	1.74 (1.24–2.45)	0.001
Diabetes	0.74 (0.53–1.04)	0.08
Heart failure	1.69 (1.21–2.35)	0.002
Chronic liver disease	2.27 (1.20–4.31)	0.01
Mechanical ventilation	1.33 (0.90–1.97)	0.15
Discharge disposition		
Home without services	1	
Home with home healthcare	5.61 (1.70–18.50)	0.005
Social health centre	1.27 (0.53–3.05)	0.59

Calvillo-King *et al* in a thorough review of studies on readmission, underlined the importance of considering social factors (sociodemographic, socioeconomic and the social environment) as elements that could influence readmission after an episode of CAP.[22] Our study evaluated sociodemographic and socioeconomic factors and the social environment. Although the influence of sex varies between studies and may be closely related to other factors such as age, risk habits and some comorbidities, the association with male sex disappeared in the final model, in contrast to the results found by Neupane *et al,* and Bohannon and Maljanian.[19 33]

Patients living with children aged <15 years had a twofold higher probability of readmission than those living alone or with a partner. Although it is known that school children may be a source of infection of the elderly in some infectious diseases, we found no studies that investigated the type of cohabitation in this context, possibly because one factor usually associated with readmission in people aged ≥65 years is living in geriatric residences.[11] In Spain, the recommendation of vaccination of persons in contact with high-risk persons, including persons aged ≥65 years with risk factors has been maintained.[34] We also found no association with factors identified by other authors, such as the educational level or the history of smoking or alcohol use.[25 35]

In the studies by Neupane *et al* in two Canadian cities and Adamuz *et al* in a tertiary hospital in Barcelona, seasonal influenza and pneumococcal vaccination were included in the adjusted analysis of readmission due to CAP, but no association was found.[19 23] We investigated seasonal influenza and pneumococcal vaccination in the previous 5 years but found no association in the crude or adjusted models.

In our study, 49.5% of 30-day readmissions were due to causes unrelated to CAP and 91% of readmitted patients presented comorbidities. Patients with chronic liver disease, heart failure and respiratory failure had higher

30-day readmission rates, findings consistent with other studies showing that some cardiovascular and respiratory diseases play an important role in the risk of readmission in patients with CAP,[12 23–25 36] and that the reason for readmission generally differs from the initial diagnosis of CAP due, in most cases, to destabilisation of comorbidities[10 23–26 37 38]. Fine *et al*, in a cohort study, found that pneumonia often occurs in patients with underlying comorbidities and often results in a worsening of such underlying conditions.[31]

We found an association with prior hospital utilisation in the 90 days before admission for CAP, but no association with general practitioner and primary care nurse visits. Healthcare in Spain is free, which encourages patients to make multiple visits to primary care centres and/or hospitals, ensuring patient care and follow-up. Adamuz *et al* and Tang *et al* found an association between readmission and hospitalisation in the 90 days before admission for CAP.[11 23]

One preventable factor that influences CAP episodes in people aged ≥65 years is the quality of care received during hospitalisation, while discharge planning and follow-up until recovery influence patient recovery and, therefore, readmission.[16 21 23 24] We found, as did Dong *et al*,[16] an association with discharge to home with home healthcare. A possible explanation might be an inadequate evaluation of the patient's stability at discharge. Various authors have suggested the importance of the discharge dispostion in patients admitted due to other causes such as COPD or some specific interventions.[39–41] However, with respect to patients with CAP, only Dong *et al* and the present study have found an association between the discharge dispostion and readmission. Other variables related to the quality of care were studied to assess these aspects but no association with readmission was found.

Strengths and limitations

The main strength of the study is that all clinical information was obtained from patient medical records and, therefore, was unlikely to be biased. Another strength is the cross-sectional design, as it is part of a multicentre study carried out in seven regions representing 70% of the Spanish population.

A limitation is that it was not possible to collect patient characteristics at discharge, and therefore we cannot say whether there was instability at discharge that may have caused the readmission. Therefore, the variable 'discharge disposition' was considered as a proxy to define instability.

CONCLUSIONS

In conclusion, this study shows that 11.39% of patients aged ≥65 years hospitalised due to CAP are readmitted within 30 days after an episode of CAP and that this was associated with living with a cohabitant aged <15 years, more than three hospital visits during the 90 previous days, chronic respiratory failure, heart failure, chronic liver disease and discharge to home with home healthcare services.

Because social factors, in addition to postdischarge and prereadmission clinical information, may influence the prognosis, it is important that these factors continue to be considered in future research.

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4.2 Artículo 2

Título:

A Composite of Functional Status and Pneumonia Severity Index Improves the Prediction of Pneumonia Mortality in Older Patients.

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A Composite of Functional Status and Pneumonia Severity Index Improves the Prediction of Pneumonia Mortality in Older Patients

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BACKGROUND: The baseline health status may be a determinant of interest in the evolution of pneumonia.

OBJECTIVE: Our objective was to assess the predictive ability of community-acquired pneumonia (CAP) mortality by combining the Barthel Index (BI) and Pneumonia Severity Index (PSI) in patients aged ≥ 65 years.

DESIGN, PATIENTS AND MAIN MEASURES: In this prospective, observational, multicenter analysis of comorbidities, the clinical data, additional examinations and severity of CAP were measured by the PSI and functional status by the BI. Two multivariable models were generated: Model 1 including the PSI and BI and model 2 with PSI plus BI stratified categorically.

KEY RESULTS: The total population was 1919 patients, of whom 61% had severe pneumonia (PSI IV–V) and 40.4% had some degree of dependence (BI ≤ 90 points). Mortality in the PSI V–IV group was 12.5%. Some degree of dependence was associated with increased mortality in both the mild (7.2% vs. 3.2%; p = 0.016) and severe (14% vs. 3.3%; p < 0.001) pneumonia groups. The combination of PSI IV–V and BI ≤ 90 was the greatest risk factor for mortality (aOR 4.17; 95% CI 2.48 to 7.02) in our series.

CONCLUSIONS: The use of a bimodal model to assess CAP mortality (PSI + BI) provides more accurate prognostic information than the use of each index separately.

KEY WORDS: functional status; community-acquired pneumonia; severity assessment.

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INTRODUCTION

Community-acquired pneumonia (CAP) causes high mortality and morbidity worldwide. The incidence increases with age and is estimated at 3.1/1000 inhabitants/year in patients aged ≥ 65 years, with a mortality rate of 10–25%.[1,2] CAP in elderly patients is a destabilizing factor for baseline comorbidities and results in a slower recovery and major burden for caregivers as well as considerable economic costs.[3,4]

Scales that assess the severity of CAP [Pneumonia Severity Index (PSI), CURB-65] are of great utility for prognostic evaluations and determining the level and intensity of care required.[5,6] However, although these scales work well in clinical practice, there are other intrinsic factors in elderly patients that are determinants of the outcomes but are not included in the scales. The previous quality of life is a decisive prognostic factor, especially in institutionalized patients.[7] The functional status has been independently associated with the outcome of CAP and a worse prognosis.[8,9] The incidence of emergency room visits in the elderly due to CAP increases in tandem with a worse functional status.[10] In addition, CAP in the elderly may have some hidden clinical manifestations that can delay the diagnosis and the administration of antibiotic treatment, and it may have clearly unfavorable prognostic consequences.[11,12]

The baseline functional status is a determinant of immediate and long-term survival after CAP. It is estimated that 60% of patients with multiple dependency will die during the first 12 months and only 25% will survive for ≥ 2 years.[13]

Identification of the risk of complications or mortality is crucial since it involves specific prognostic and ethical implications such as the introduction or interruption of some therapeutic measures.[14] Moreover, the effectiveness of preventive measures against respiratory infections in the elderly can be influenced by the baseline status, with a decrease in the effectiveness of the influenza vaccine observed in patients with poor functional status.[15]

There is growing evidence that the functional status, measured by the Barthel Index (BI), is more important than age and comorbidity in predicting prognosis at 12 months in the elderly.[16] Even small changes in the BI are associated with clinically relevant outcomes.[16] In CAP, a worse BI is directly related to increased costs, hospital length of stay and mortality.[17] The BI showed a very good correlation between the degree of functional impairment and survival of elderly

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patients admitted to an acute geriatric unit.[18] A recent study has reported that, in patients of different ages diagnosed with CAP with a BI ≤ 80, mortality was four times greater than in the general population.[19]

Identification of severity and the risk of death in elderly patients with CAP is a challenge for clinicians because many patients have associated comorbidities and other situations that affect their baseline health and cannot be assessed by conventional pneumonia severity scales.[20] Therefore, accurate management of CAP in this population requires a holistic approach, taking the functional status into account in addition to the assessment of disease severity. The association between increased mortality in CAP patients with a worse functional status suggests that the addition of functional indexes to prognostic scales could improve the identification of adverse outcomes and provide data to improve clinical care.

The objective of this study was to assess the predictive power of a composite index combining the BI and PSI in assessing mortality in non-institutionalized patients with CAP aged ≥ 65 years.

MATERIAL AND METHODS

Study Design. Inclusion and Exclusion Criteria

We conducted an observational, prospective, multicenter study involving 20 hospitals from seven Spanish regions in 2013–2015. The enrollment was prospective. Patients admitted to the hospital for pneumonia were asked to participate in the study if they met the inclusion criteria.

Inclusion criteria were a diagnosis of CAP requiring hospitalization for ≥ 24 h in patients aged ≥ 65 years. Pneumonia was defined as an acute clinical picture with ≥ 1 of the following symptoms: fever, dyspnea, cough, sputum, chest pain and new onset of alveolar infiltration on chest x-ray.[21]

Patients aged ≤ 64 years, institutionalized patients and those with nosocomial pneumonia, defined as pneumonia occurring ≤ 48 h after hospital admission or within the first 14 days after discharge, were excluded.

Patients were consecutively approached for enrollment and were offered verbal and written information. Signed informed consent was required to be included in the study.

Variables Analyzed

Baseline variables were collected within the first 24 h after hospital admission. The following variables were collected: age, sex, smoking status, alcohol intake > 80 g/day and social support. Comorbidities analyzed included chronic obstructive pulmonary disease (COPD), defined as a current or past history of smoking (> 20 pack-years), clinical evaluation and lung function tests with an obstructive pattern (FEV1/FVC <70). Histories of renal failure, heart failure, cerebrovascular disease, dementia, diabetes mellitus, chronic liver diseases (viral, toxic liver or cirrhosis) and neoplasia were collected. Factors collected in association with immunosuppression included HIV infection, hematologic malignancy resulting in impairment of humoral or cellular immunity, chemotherapy during the 4 weeks before the diagnosis of CAP, prolonged corticosteroid therapy (> 20 mg prednisone/day for at least 3 weeks) and solid organ transplantation. Information on the vaccination status (pneumococcal and influenza) and the duration of symptoms before diagnosis was recorded.

Assessment of Functional Status

The BI is a clinical tool that evaluates the ability to perform basic activities of daily living and assigns a score depending on the degree of dependence.[22] Activities assessed include autonomy in feeding, moving, climbing stairs, dressing, using the toilet and continence. The score ranges from 0 (total dependence) to 100 (complete autonomy). The Barthel Index (BI) was used to assess the functional status 4 weeks prior to admission for pneumonia. Since this was a multicenter study all researchers had the same version of the BI test. When the patient had cognitive deterioration or confusion, then information was obtained from the main carer, family or nursing staff. A cutoff of BI ≤ 90 was used to define some degree of dependency.

Assessment of Severity

The severity of CAP was assessed using the PSI, which is based on demographics, comorbidities, physical examination and radiologic and laboratory data at the diagnosis of pneumonia.[5] According to the risk of death at 30 days, patients were classified as low or moderate risk (PSI I–III) or high or severe risk (PSI IV–V).

Composite Index

To evaluate the prognostic value, we constructed an index that dichotomously combined the presence of severe pneumonia (PSI IV–V) and the existence of some degree of dependency: PSI IV–V + BI ≤ 90.

Outcomes

The primary outcome was 30-day mortality after the diagnosis of CAP.

Other adverse outcomes, such as prolonged length of stay (defined as a stay above the 75th percentile of days of stay in the series), readmission in the first 30 days after discharge, intensive care unit (ICU) admission, the use of vasopressors, requirement for invasive or non-invasive ventilation (IMV/NIV) and the development of pleural empyema, were assessed.

Ethical Aspects

Data were treated confidentially by strictly applying Spanish and European legislation. Written informed consent was

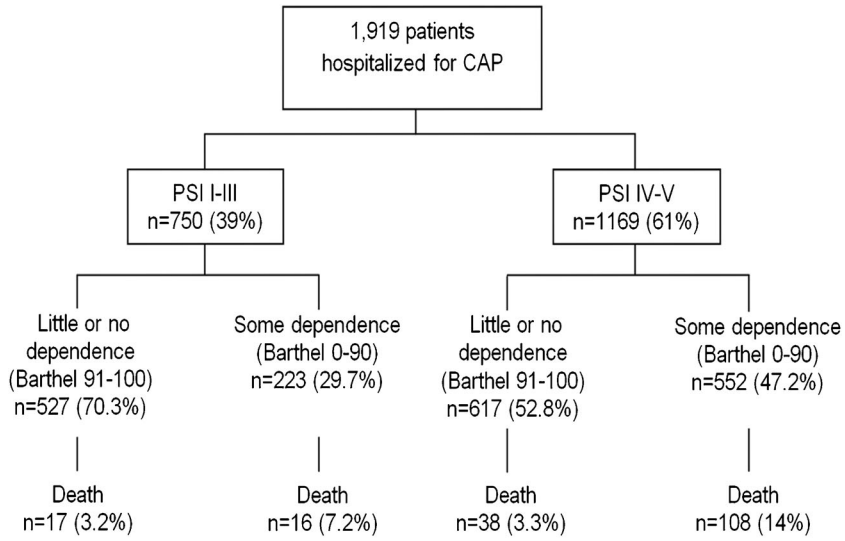

Figure 1 Patient distribution according to pneumonia severity (Pneumonia Severity Index) and level of dependence (Barthel Index).

obtained from all participants. The study was approved by the ethics committees of all participating hospitals (Hospital Clínic of Barcelona Clinical Research Ethics Committee; University Hospital Mutua de Terrassa Clinical Research Ethics Committee; Health Corporacion Parc Taulí of Sabadell Clinical Research Ethics Committee; Clinical Research Ethics Committee of the Hospital of Mataró, Maresme Consorci Sanitari; Clinical Research Ethics Committee of the Catalan Fundació Unio Hospitals, University Hospital of Barcelona Vall d'Hebrón Clinical Research Ethics Committee, Clinical Research Ethics Committee of the Basque Country; Clinical Health Area of Burgos and Soria Clinical Research Ethics

Table 1 Patient Characteristics According to Degree of Dependence

	Barthel>90 (n = 1144)	Barthel≤90 (n = 775)	Unadjusted OR 95% CI	p value
Demographics				
Mean age	76.5 (SD: 6.8)	81.9 (SD: 7.1)	–	< 0.001
Males	772 (67.5)	395 (51)	0.50 (0.42–0.60)	< 0.001
Social support (lives alone)	243 (21.2)	101 (13)	0.56 (0.43–0.72)	< 0.001
Comorbid conditions				
Smoking	127 (11.1)	41 (5.3)	0.45 (0.31–0.64)	< 0.001
Alcohol abuse	276 (24.1)	97 (12.5)	0.45 (0.35–0.58)	< 0.001
COPD	377 (33)	211 (27.2)	0.76 (0.62–0.93)	0.008
Diabetes mellitus	358 (31.3)	287 (37)	1.29 (1.07–1.57)	0.009
Chronic renal failure	184 (16.1)	211 (27.2)	1.95 (1.56–2.44)	< 0.001
Malignancy	204 (17.8)	133 (17.2)	1.05 (0.82–1.33)	0.705
Chronic liver disease	52 (4.59	23 (3)	0.64 (0.39–1.06)	0.080
Cerebrovascular disease	39 (3.4)	119 (15.4)	5.14 (3.54–7.47)	< 0.001
Dementia	46 (4)	183 (23.6)	7.34 (5.26–10.35)	< 0.001
Chronic heart disease	254 (22.2)	277 (35.7)	1.95 (1.59–2.39)	< 0.001
Immunosuppression	99 (8.7)	76 (9.8)	1.15 (0.84–1.57)	0.389
Influenza vaccination	543 (47.5)	262 (46.7)	1.03 (0.86–1.24)	0.745
Pneumococcal vaccination	550 (48.1)	378 (48.8)	1.03 (0.86–1.23)	0.764
Clinical data				
Duration of symptoms	5.9 (SD: 11.1)	5.4 (SD: 7.2)	–	0.175
PSI IV–V	617 (53.9)	552 (71.2)	2.11 (1.74–2.57)	< 0.001
Microbiology				
Etiologil diagnosis	285 (24.9)	188 (24.3)	0.97 (0.78–1.19)	0.744
Pneumococcal etiology	187 (20.8)	111 (20.1)	0.96 (0.74–1.24)	0.739
Bacteremia	60 (9.9)	53 (13.7)	1.44 (0.97–2.13)	0.069
Evolution				
Length of stay	9.7 (SD: 9.5)	11.8 (SD: 10)	–	< 0.001
Prolonged LOS (LOS > 75thP)	223 (19.5)	237 (30.5)	1.72 (1.39–2.13)	< 0.001
Readmission (30 days)	143 (12.5)	121 (15.6)	1.29 (0.99–1.68)	0.052
ICU admission	56 (4.9)	25 (3.2)	0.65 (0.40–1.05)	0.074
Vasopressors use	58 (5.2)	82 (10.7)	2.22 (1.56–3.14)	< 0.001
NIV/IMV	169 (14.7)	147 (18.9)	1.74 (0.58–2.20)	0.317
Empyema	28 (2.4)	20 (2.6)	0.95 (0.59–1.70)	0.868
Mortality	38 (3.3)	108 (14)	4.71 (3.22–6.91)	< 0.001

COPD: chronic obstructive pulmonary disease. LOS: length of stay. ICU: intensive care unit. IMV: invasive mechanical ventilation. NIV: non-invasive ventilation. 75thP: 75th percentile

Table 2 Characteristics of Patients with Severe Pneumonia (PSI IV–V) by Degree of Dependence

	PSI IV–V and Barthel > 90 (n = 617)	PSI IV–V and Barthel ≤ 90 (n = 552)	Unadjusted OR 95% CI	p value
Demographics				
Mean age	77.8 (SD: 6.9)	82.8 (SD: 7)	–	< 0.001
Males	450 (72.9)	302 (54.7)	0.45 (0.35–0.57)	< 0.001
Social support (lives alone)	134 (21.7)	74 (13.4)	0.56 (0.41–0.76)	< 0.001
Comorbid conditions				
Smoking	68 (11)	24 (4.3)	0.37 (0.23–0.59)	< 0.001
Alcohol abuse	149 (24.1)	70 (12.7)	0.46 (0.33–0.62)	< 0.001
COPD	217 (35.2)	156 (28.3)	1.37 (1.07–1.76)	0.011
Diabetes mellitus	189 (30.6)	203 (36.8)	1.32 (1.03–1.68)	0.026
Chronic renal failure	123 (19.9)	163 (29.5)	1.68 (1.29–2.20)	< 0.001
Malignancy	149 (24.1)	103 (18.7)	1.38 (1.05–1.84)	0.023
Chronic liver disease	32 (5.2)	21 (3.8)	0.72 (0.41–1.27)	0.257
Cerebrovascular disease	24 (3.9)	91 (16.5)	4.88 (3.06–7.78)	< 0.001
Dementia	26 (4.2)	137 (24.8)	7.50 (4.84–11.62)	< 0.001
Chronic heart disease	156 (25.3)	219 (39.7)	1.94 (1.51–2.49)	< 0.001
Immunosuppression	60 (9.7)	57 (10.3)	1.07 (0.73–1.57)	0.732
Influenza vaccination	313 (50.7)	264 (47.8)	1.12 (0.89–1.41)	0.322
Pneumococcal vaccination	315 (51.1)	277 (50.2)	1.04 (0.82–1.30)	0.766
Clinical data				
Duration of symptoms	6 (SD: 13.4)	5.3 (SD: 7.2)	–	0.280
Microbiology				
Etiologic diagnosis	175 (28.4)	140 (25.4)	0.86 (0.66–1.11)	0.248
Pneumococcal etiology	118 (24.2)	85 (21.7)	0.87 (0.63–1.199	0.382
Bacteremia	43 (13.2)	46 (16)	1.25 (0.79–1.97)	0.328
Evolution				
Length of stay	10.3 (SD: 8.6)	12.9 (SD: 0.9)	–	< 0.001
Prolonged LOS (LOS > 75thP)	142 (23)	190 (34.4)	1.75 (1.36–2.27)	< 0.001
Readmission (30 days)	83 (13.5)	94 (17)	1.32 (0.96–1.82)	0.089
ICU admission	41 (6.7)	24 (4.4)	1.56 (00.93–2.62)	0.089
Vasopressors use	39 (6.5)	70 (13)	2.15 (1.43–3.24)	< 0.001
NIV/IMV	114 (18.5)	122 (22.1)	0.79 (0.59–1.06)	0.119
Empyema	23 (3.7)	17 (3)	1.22 (0.65–2.34)	0.534
Mortality	21 (3.4)	92 (16.7)	5.68 (3.48–9.26)	< 0.001

COPD: chronic obstructive pulmonary disease. ICU: intensive care unit. IMV: invasive mechanical ventilation. LOS: length of stay. NIV: non-invasive ventilation. PSI: Pneumonia Severity Index. 75thP: 75th percentile

Committee; Leon Health Area Clinical Research Ethics Committee, Ethics Committee for Clinical Research Area Health Valladolid-East Health Area Clinical Research Ethics Coordinating Committee of Andalusia; Clinic Ramon y Cajal, Madrid Clinical Research Ethics Committee and General Hospital University of Valencia Consortium Clinical Research Ethics Committee).

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Statistical Analysis

The demographic and clinical characteristics, comorbidities and outcomes of patients with PSI IV–V with and without a BI ≤ 90 were compared. A bivariate analysis was made of patient characteristics according to 30-day survival.

The results are expressed as absolute numbers and percentages for categorical variables and as mean and standard deviation for continuous variables. A bivariate analysis was made to identify patient characteristics associated with PSI IV–V in patients with and without BI ≤ 90 and factors associated with mortality. Categorical variables were analysed using the chi² test, while continuous variables were analyzed using the Student's t test. The results were expressed as odds ratios (OR) and 95% confidence intervals (95% CI). Unadjusted odds ratios in the univariate analysis were calculated. Then, an adjusted OR (aOR) was calculated using multivariate analysis (stepwise forward) to assess the association between mortality (dependent variable) and independent variables with a value of $p < 0.10$ in the univariate analysis.

Two multivariable models were constructed: Model 1 independently included the PSI and the BI, and model 2 included the PSI + BI stratified categorically.

Kaplan-Meier survival curves were constructed to compare mortality in patients with PSI IV–V with or without BI ≤ 90 and statistical significance was assessed using the Mantel-Cox log rank test.

RESULTS

The total study population was 1919 patients, of whom 61% had PSI IV–V and 40.4% (775 cases) had a BI ≤ 90: the mean BI was 82.3 (27.3). Figure 1 shows the distribution of patients according to the PSI and BI.

Older age and comorbidities were significantly associated with a worse BI (Table 1). A worse BI was significantly associated with a poor CAP outcome.

Table 2 compares the characteristics of patients with PSI IV–V with and without BI ≤ 90. Patients with PSI IV–V and

Table 3 Patient Characteristics According to Survival

	Survivors (n = 1773)	Death (n = 146)	Unadjusted OR 95% CI	P value
Demographics				
Mean age	78.6 (SD: 7.3)	82.4 (SD: 7.8)	–	< 0.001
Males	1070 (6.9)	88 (60.3)	0.98 (0.69–1.34)	0.890
Social support (lives alone)	323 (18.2)	21 (14.4)	0.75 (0.47–1.22)	0.246
Comorbid conditions				
Smoking	153 (8.6)	15 (10.3)	1.21 (0.69–2.12)	0.499
Alcohol abuse	352 (19.9)	21 (14.4)	0.68 (0.42–1.09)	0.108
COPD	554 (31.2)	34 (23.3)	0.67 (0.45–0.99)	0.045
Diabetes mellitus	596 (33.6)	49 (33.6)	0.99 (0.69–1.43)	0.989
Chronic renal failure	353 (19.9)	42 (28.8)	1.62 (1.12–2.37)	0.011
Malignancy	297 (16.8)	40 (27.4)	1.87 (1.28–2.76)	0.001
Chronic liver disease	66 (3.7)	9 (6.29	1.69 (0.83–3.48)	0.143
Cerebrovascular disease	135 (7.6)	23 (15.8)	2.27 (1.41–3.67)	0.001
Dementia	188 (10.6)	41 (28.1)	3.29 (2.23–4.87)	< 0.001
Chronic heart disease	476 (26.8)	55 (37.7)	1.65 (1.16–2.34)	0.005
Immunosuppression	159 (9)	16 (11)	1.25 (0.73–2.15)	0.422
Influenza vaccination	931 (52.5)	83 (56.8)	1.19 (0.85–1.68)	0.313
Pneumococcal vaccination	929 (52.4)	62 (42.5)	1.49 (1.06–2.09)	0.021
Clinical data				
Duration of symptoms	5.7 (SD: 9.9)	5.4 (SD: 6.3)	–	0.680
PSI IV–V	1056 (59.6)	133 (77.4)	2.32 (1.56–3.47)	< 0.001
Barthel ≤ 90	667 (37.6)	108 (74)	4.71 (3.22–6.91)	< 0.001
PSI IV–V + BI ≤ 90	444 (25)	108 (73.9)	4.71 (3.22–6.91)	< 0.001
Microbiology				
Etiologic diagnosis	442 (24.9)	31 (21.2)	0.81 (0.54–1.22)	0.319
Pneumococcal etiology	285 (21.1)	13 (13.1)	0.57 (0.31–1.03)	0.059
Bacteremia	101 (11.2)	12 (13.2)	1.20 (0.63–2.28)	0.574
Evolution				
Length of stay	10.5 (SD: 9.9)	11.3 (SD: 7)	–	0.348
Prolonged LOS (LOS > 75thP)	421 (23.7)	49 (33.6)	1.62 (1.13–2.33)	0.008
Readmission (30 days)	238 (13.4)	26 (17.8)	1.39 (0.90–2.18)	0.139
ICU admission	67 (3.8)	14 (9.6)	2.70 (1.48–4.93)	0.001
Vasopressors use	117 (6.6)	23 (15.8)	2.65 (1.63–4.29)	< 0.001
NIV/IMV	282 (15.9)	34 (23.2)	0.78 (0.17–3.62)	0.754
Empyema	44 (2.5)	4 (2.7)	0.89 (0.32–2.51)	0.825

BI: Barthel Index. COPD: chronic obstructive pulmonary disease.ICU: intensive care unit. IMV: invasive mechanical ventilation. LOS: length of stay. NIV: non-invasive ventilation. PSI: Pneumonia Severity Index. 75thP: 75th percentile

BI ≤ 90 were older, had significantly more comorbidities and had a more unfavorable evolution with more complications and greater mortality.

Evolution

The 75th percentile of mean stay was 12 days, and 264 (13.8%) patients were readmitted within 30 days. In 140 (7.3%) patients, vasopressors were required, and 81 patients (4.6%) required ICU admission, while 23 (1.2%) and 15 (0.8%) patients required invasive and non-invasive mechanical ventilation, respectively. Forty-eight (2.5%) patients developed pleural empyema.

Patients with BI ≤ 90 with or without PSI IV–V had a significantly longer mean hospital stay and more frequent requirement for vasopressors than patients without BI ≤ 90 (Tables 1 and 2).

Overall mortality was 7.6% (146 patients). Factors significantly associated with increased mortality were a history of chronic renal failure, malignancy, cerebrovascular disease, dementia, chronic heart disease, PSI IV-V, BI ≤ 90 and the combination of the latter two factors. ICU admission and the use of vasopressors were associated with a worse outcome (Table 3).

Evolution According to PSI and BI

Thirty-three (4.4%) patients with PSI I–III died compared with 12.5% (146 patients) with PSI IV–V (Fig. 1). BI ≤ 90 was significantly associated with increased mortality in patients with PSI I–III (7.2% vs. 3.2%; OR 2.32, 95% CI 1.15–4.68; p = 0.016) and PSI IV–V (14% vs. 3.3 %, OR 4.71, 95% CI 3.22–6.91; p = <0.001), respectively. Figure 2 compares mortality in patients with PSI IV–V with and without BI ≤ 90 (Mantel-Cox log rank 34.733; p < 0.001).

Multivariable Analysis

The results of the two multivariable models are shown in Table 4. BI ≤ 90 was an important risk factor for mortality (aOR 3.32; 95% CI 2.19–5.03). On the other hand, the composite index of BI ≤ 90 and PSI IV–V was the greatest risk factor for mortality (aOR 4.17; 95% CI 2.48–7.02). Age, dementia and neoplasia were also independently associated with mortality in both models.

DISCUSSION

The results of this study show that, in a cohort of non-institutionalized patients aged ≥ 65 years hospitalized for

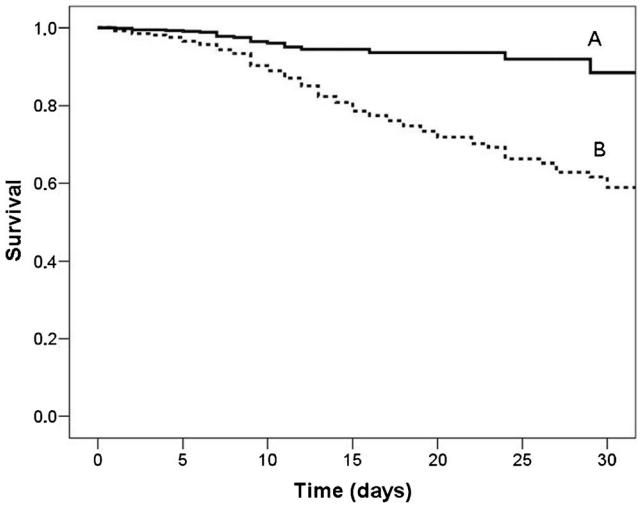

Figure 2 Kaplan-Meier survival curves by severity and functional status in patients with severe pneumonia: (A) severe pneumonia (PSI IV–V) and Barthel Index > 90 points; (B) severe pneumonia (PSI IV–V) and Barthel Index ≤ 90 points (p < 0.001).

CAP, the combination of the BI and PSI improved the prediction of mortality. Other factors independently associated with mortality were older age, active neoplasm and dementia.

Accurate recognition of severity is essential for the management of pneumonia since therapeutic decision-making with the introduction of more or less intensive support measures or their interruption depends on it.[23] However, the exclusive use of pneumonia severity scales results in a loss of prognostic information as it does not take into account the baseline functional status, which has been shown to be a determinant of mortality, especially in the elderly.

Assessment of the functional status using the BI has been shown to be an independent predictor of mortality in several studies with heterogeneous populations. In patients attending the ER for fever with different infectious foci, a worse baseline BI was associated with greater mortality.[24] Studies of primarily institutionalized patients have reported that a low BI is associated not only with increased risk of nursing home-acquired pneumonia, but also with increased mortality.[25] A prospective observational study of factors other than the PSI associated with pneumonia mortality found a BI < 80 was more important than other factors, such as age or comorbidities, and as important as the PSI in predicting the prognosis of elderly patients with pneumonia.[19] This is particularly relevant in the case of institutionalized patients, in whom a low BI is a major determinant of the need for hospitalization.[26] Furthermore, in patients aged > 75 years with CAP, a high level of autonomy determined by the BI has been reported as a protective factor against mortality.[27,28]

Table 4 Multivariate Analysis of Factors Associated with Mortality

	aOR 95% CI	p
Model 1a: Including Barthel Index ≤ 90		
Barthel ≤ 90	3.32 (2.19–5.03)	< 0.001
Malignancy	2.17 (1.45–3.24)	< 0.001
Dementia	1.94 (1.28–2.95)	0.002
Age	1.05 (1.02–1.07)	0.001
Model 1b: Including Pneumonia Severity Index (PSI) grade IV–V		
Dementia	2.64 (1.75–3.98)	< 0.001
Malignancy	2.03 (1.36–3.03)	0.001
Chronic heart disease	1.45 (1.01–2.08)	0.044
PSI IV–V	1.56 (1.03–1.08)	< 0.001
Age	1.06 (1.03–2.38)	0.038
Model 2: Pneumonia Severity Index (PSI) grade IV–V plus Barthel Index ≤ 90		
PSI IV–V + Barthel ≤ 90	4.17 (2.48–7.02)	< 0.001
Dementia	1.99 (1.25–3.18)	0.004
Malignancy	1.77 (1.09–2.85)	0.020
Age	1.04 (1.01–1.07)	0.007

An interesting point of our study is that, as shown in Fig. 2, the difference in mortality appeared to be largely after the 15th day. This is probably more related to the destabilization of comorbidities and the functional basal status rather than to the initial infectious process, in which mortality occurs earlier. The BI may be able to detect this better than the PSI. This increased mortality after 15 days may be due to the short- and long-term cardiovascular mortality previously described in relation to pneumonia.[29,30]

A prospective, multicenter study by Marrie et al. analyzed factors associated with mortality in patients hospitalized for pneumonia and found that a worse functional status evaluated by autonomy of movement was independently associated with reduced survival.[31]

Therefore, the question arises as to whether combining these indices would increase the predictive ability of pneumonia mortality in the elderly.

Despite the evidence on the influence of the functional status in the prognosis of pneumonia, there are few reports on the combined use of scales measuring functional status and the prognosis of pneumonia. Yeon et al. proposed the combined use of pneumonia risk scales (PSI, CURB-65) and the ECOG scale (Eastern Cooperative Oncology Group), which evaluates the quality of life and autonomy, and found the combination of indices improved predictions of mortality in patients with pneumonia.[32,33] However, these studies have some limitations: several reports were based on very elderly patients (> 75 years) or patients living in nursing homes or long-term care facilities and with little baseline autonomy.[28,34] The assessment of the functional status was made using scales designed for other patients (e.g., cancer patients) or only assessed the degree of mobility.

A strength of our study is that we collected data prospectively from a large number of patients, thus minimizing information bias. We used the BI, which is widely validated for the assessment of the functional status, unlike other studies that applied scales designed for cancer patients.[33] Furthermore, use of a strict cutoff value of 90 points for BI to define some dependence allows us to demonstrate how slight changes in functional basal status can have an impact on the prognosis of pneumonia at the same initial level of severity measured by PSI, and a wider cutoff point could further increase the predictive capacity of the combined model.

The study had some limitations. We did not include institutionalized elderly patients and therefore the results may not

be applicable to this population, nor can the results be generalized to patients aged ≤ 64 years, who were excluded. Another potential limitation of our study is that we found significantly more dementia (23.6%) and cerebrovascular disease (15.4%) in the BI ≤ 90 group. Both entities are potentially associated with aspiration pneumonia, which was not assessed in our study. We recognize that the realization of BI at the time of acute illness could be affected by possible recall bias. However, we believe that recall bias would be higher for lower scores, which is why we chose to use a cutoff of 90 points.

Despite the limitations of dichotomizing quantitative scales such as the PSI and BI, this approach gives to the clinician a simple and easy tool with important prognostic information.

A potential limitation may be the time to perform BI. However, this essay takes about 5 min to complete, and there are several helpful computer tools that may be used to perform the BI.

We propose that the first assessment to be performed in a patient over 65 years of age diagnosed with community pneumonia is BI and second PSI to establish a holistic and more accurate severity assessment, which should alert the clinician to potential unfavorable outcomes and complications.

In conclusion, a combined assessment using the pneumonia severity scale and Barthel Index more accurately predicted mortality than the application of each tool separately. Future studies are needed to validate our data in different populations.

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4.3 Artículo 3

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Factors associated with pneumococcal polysaccharide vaccination of the elderly in Spain: A cross-sectional study.

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RESEARCH PAPER

Factors associated with pneumococcal polysaccharide vaccination of the elderly in Spain: A cross-sectional study

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ABSTRACT

Vaccination of the elderly is an important factor in limiting the impact of pneumonia in the community. The aim of this study was to investigate the factors associated with pneumococcal polysaccharide vaccination in patients aged ≥ 65 years hospitalized for causes unrelated to pneumonia, acute respiratory disease, or influenza-like illness in Spain. We made a cross-sectional study during 2013-2014. A bivariate analysis was performed comparing vaccinated and unvaccinated patients, taking into account sociodemographic variables and risk medical conditions. A multivariate analysis was performed using multilevel regression models. 921 patients were included; 403 (43.8%) had received the pneumococcal vaccine (394 received the polysaccharide vaccine). Visiting the general practitioner ≥ 3 times during the last year (OR = 1.79; 95% CI 1.25-2.57); having received the influenza vaccination in the 2013-14 season (OR = 2.57; 95% CI 1.72-3.84) or in any of the 3 previous seasons (OR = 11.70; 95% CI 7.42-18.45) were associated with receiving the pneumococcal polysaccharide vaccine. Pneumococcal vaccination coverage of hospitalized elderly people is low. The elderly need to be targeted about pneumococcal vaccination and activities that encourage healthcare workers to proactively propose vaccination might be useful. Educational campaigns aimed at the elderly could also help to increase vaccination coverages and reduce the burden of pneumococcal disease in the community.

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Introduction

Streptococcus pneumoniae, an asymptomatic colonizer of the nasopharynx, is a major cause of infections including pneumonia, meningitis, bacteremia, sinusitis, and otitis media. Most studies of the etiology of hospitalized community-acquired pneumonia in adults rank *S. pneumoniae* first among all known causes.

Despite advances in antimicrobial therapy, early mortality due to pneumococcal bacteremia has remained constant at 5% to 10% over the last century.[1]

Adults aged ≥65 years comprise about 15% of the population but have a high case-fatality rate (≥15%). In this age group, most invasive cases result from the complications of pneumonia, but 5–10 times as many older adults have pneumococcal pneumonia without bacteremia. Mortality increases substantially with age and is 2-to- 5-fold higher in adults with underlying diseases than in healthier older adults.[2]

Recognition of continued morbidity and mortality from pneumococcal infections despite the use of appropriate antibiotics led to increased interest in disease prevention by vaccination and, since 1983, a 23-valent pneumococcal polysaccharide vaccine (PPSV) containing antigens against 23 of the 94 serotypes has been available.[1] Post-licensure studies show the vaccine is protective against invasive pneumococcal disease (IPD) in immunocompetent older adults.[3-5] Evidence supporting a beneficial effect of PPSV in preventing pneumococcal pneumonia is more limited, but some studies have shown benefits.[6-9] The median hospital stay in hospitalized adults with community-acquired pneumococcal pneumonia has been shown to be shorter in vaccinated patients[10] and it has been reported that, in elderly people with chronic illness, the PPSV may reduce hospitalization during the influenza season,[6] while, in people vaccinated with both the PPSV and the influenza vaccine, the benefit against hospitalization was greater than in those receiving only the influenza vaccine.[11,12] The World Health Organization states that the PPSV has demonstrated a protective effect against IPD and all-cause pneumonia among healthy young adults and, to a lesser extent, against IPD in elderly people who are not severely immunosuppressed.[13] Cost-effectiveness studies support the recommendation of

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pneumococcal vaccination of the elderly, especially when the expected increase in the population aged ≥ 65 y in forthcoming years is taken into account.[14,15]

PPSV vaccination is recommended in the United States for all persons aged ≥65 years and for adults aged <65 years at increased risk of invasive pneumococcal disease (cigarette smoking, chronic lung disease including asthma, chronic cardiovascular disease, diabetes mellitus, chronic liver disease, cirrhosis, chronic alcoholism, functional or anatomic asplenia, immunocompromising conditions including HIV infection, and diseases associated with treatment with immunosuppressive drugs or radiation therapy, cochlear implants and cerebrospinal fluid leaks).[16] Similar recommendations are in place in most European Union countries, although in some countries vaccination is recommended only for adults with high risk conditions and not for healthy adults aged ≥65 years.[17]

A 13-valent conjugate pneumococcal vaccine (PCV13) has become available for adults, and the United States recommends that this new vaccine should be administered following by one dose of PPSV at least 8 weeks later in people aged ≥65 years.[18] A recent randomized clinical trial among adults aged ≥ 65 y found that the PCV13 is effective against vaccine-type invasive and non-invasive community-acquired pneumonia in the elderly.[19] In addition, the PCV has a clear effect against pneumococcal disease in the unvaccinated population (children and adults) that is not observed with the PPSV.[20]

In Spain, free universal PPSV vaccination of people aged ≥65 years is recommended and is administered in primary care centers or hospitals throughout the year with no requirement for an order from the attending physician. However, most pneumococcal vaccination takes place during seasonal influenza vaccination campaigns.[21] Although it was planned that all regions would introduce the pneumococcal conjugate vaccine (PCV) in pediatric vaccination calendars by the end of 2016, except for the Madrid Region during 2006-2012 and Galicia since 2011, no pneumococcal conjugate vaccine has been included in the pediatric vaccination calendar. However, it is recommended by the Spanish Association of Pediatrics and many private and public pediatricians recommend the vaccine, which is paid for the parents, in contrast with all routine vaccines included in the pediatric vaccination calendar, which are administered free of charge. The recommended schedule is 3 doses at 2, 4 and 6 months with a fourth dose between 12 and 18 months.[22] The vaccine has been offered free of charge only for children with risk medical conditions for IPD. Pediatric PCV coverage, excluding Madrid and Galicia, is estimated at around 50%.[23]

This coverage has been sufficient to originate some changes in the distribution of serotypes both in children and adults.[24] Studies carried out Catalan hospitals reported a progressive decline in rates of IPD in adults, mainly in PCV7 and PCV13 serotypes.[25,26] Guevara et al.[27] compared incidence rates of IPD before and after the introduction of the pediatric PCV13 in Navarra and found a decline of 81% in cases of IPD due to PCV13 serotypes in children aged <5 years and a 52% decline in the whole population.

The indirect protective effects (herd protection) of PCV in unvaccinated adults were reported in the United States a few years after the introduction of the vaccine.[28] Recent studies in countries with a high PCV coverage reinforce its role in avoiding cases of IPD caused by PCV serotypes in unvaccinated adults and the elderly.[29-36] Data on pneumococcal surveillance in the elderly must be assessed to decide the type of pneumococcal vaccine most appropriate to protect them against IPD. A population-based study by Ochoa et al.[37] in Tarragona found that the proportion of cases of IPD caused by PCV13 serotypes during 2006-2009 was 62.5% in people aged ≥ 65 y. Similar proportions (59.3% and 62.6%) were found in Spanish studies carried out in 2007-2009 [38] and 2009.[39]

The aim of this study was to investigate the factors associated with PPSV coverage in people aged ≥65 years hospitalized for causes unrelated to pneumonia, acute respiratory disease, or influenza-like illness in Spain.

Results

Of the 921 patients included in the study, 403 (43.8%) were vaccinated with pneumococcal vaccine: 394 had received the PPSV, 4 the PPSV and the PCV13 and 5 only the PCV13. Because the recommended schedule when conjugate vaccine is used is to administer PCV13 followed by PPSV at least 8 weeks later, the 5 patients who had received only the PCV13 were excluded from the analysis.

The distribution of the study variables (predisposing characteristics, enabling resources, and risk medical conditions) in vaccinated and unvaccinated patients is shown in Table 1. No differences were observed according to age and sex. Secondary or higher education level was more frequent in unvaccinated (61.1%) than in vaccinated patients (38.9%). Influenza vaccination in the 2013-14 season was more frequent in vaccinated (60.9%) than in unvaccinated patients (39.1%). A history of influenza vaccination in any of the 3 previous seasons was more frequent in vaccinated (59.4%) than in unvaccinated patients (40.6%). Patients who visited the general practitioner (GP) ≥3 times during the previous year had a higher vaccination rate than those who had not (51.1% and 28.8%, respectively). Patients making ≥3 hospital visits during the previous year had higher vaccination rates than those who did not (46.9% and 41.3%, respectively). Patients with a high level of dependence (Barthel index < 40) had a lower rate of vaccination than those with a low level of dependence (27.0% and 45.8%, respectively). Patients with low and high comorbidity had a higher vaccination rate than those without comorbidities (48.3%, 42.2%, and 40.4%, respectively). Table 2 shows the distribution of risk medical conditions in vaccinated and unvaccinated patients. Patients with chronic obstructive pulmonary disease (COPD) and chronic respiratory failure had a higher vaccination uptake ($p < 0.01$).

The results of the multilevel regression model are shown in Table 3. Variables related to enabling resources (model 1) significantly associated with vaccine uptake were ≥3 GP visits during the previous year (OR=2.02; 95% CI 1.44-2.83) and a Barthel index < 40 (OR=0.48; 95% CI 0.29-0.78).

When predisposing characteristics were added (model 2), influenza vaccination in the 2013-14 season (OR=2.58; 95% CI 1.73-3.85) and influenza vaccination in any of the 3 previous seasons (OR=11.60; 95% CI 7.38-18.24) were associated with receiving the pneumococcal vaccination. Three or more GP

Table 1. Distribution of vaccinated and non-vaccinated hospitalized patients according to sociodemographic characteristics, comorbidities, and history vaccination between September 2013 and September 2014 from 7 Spanish regions.

	Vaccinated patients (N = 398)	Unvaccinated patients (N = 518)	Crude OR	p value
Predisposing characteristics				
Age group				
65-75	142 (44.9%)	174 (55.1%)	1	
>75	256 (42.7%)	344 (57.3%)	1.05 (0.77 – 1.43)	0.77
Sex				
Male	250 (44.9%)	307 (55.1%)	1	
Female	148 (41.2%)	211 (58.8%)	0.84 (0.62 – 1.13)	0.25
Educational level				
No education	183 (45.8%)	217 (54.2%)	1	
Primary	122 (44.9%)	150 (55.1%)	0.86 (0.60 – 1.22)	0.40
Secondary or higher	93 (38.9%)	146 (61.1%)	0.66 (0.44 – 0.98)	0.04
Smoking status				
Smoker or ex-smoker	202 (44.4%)	253 (55.6%)	1.04 (0.77 – 1.40)	0.79
Alcohol intake				
Yes	10 (43.5%)	13 (56.5%)	0.68 (0.27 – 1.73)	0.42
Influenza vaccine in season 2013-14	240 (60.9%)	154 (39.1%)	5.52 (3.91 – 7.81)	<0.001
Influenza vaccine in season 2010-11	288 (61.8%)	178 (38.2%)	10.25 (6.98 – 15.06)	<0.001
Influenza vaccine in season 2011-12	297 (61.2%)	188 (38.8%)	10.12 (6.92 – 14.81)	<0.001
Influenza vaccine in season 2012-13	291 (61.3%)	184 (38.7%)	8.26 (5.75 – 11.87)	<0.001
Influenza vaccine in any of the 3 previous seasons	348 (59.4%)	238 (40.6%)	15.57 (10.29 – 23.54)	<0.001
Enabling resources				
Marital status				
Married/Cohabiting	235 (44.1%)	298 (55.9%)	1	
Single	29 (43.9%)	37 (56.1%)	0.83 (0.46 – 1.51)	0.54
Widowed	126 (41.9%)	175 (58.1%)	0.97 (0.70 – 1.35)	0.87
Separated/Divorced	6 (60.0%)	4 (40.0%)	1.98 (0.47 – 8.26)	0.35
No. of GP visits				
0-2	86 (28.8%)	213 (71.2%)	1	
≥3	310 (51.1%)	297 (48.9%)	2.04 (1.46 – 2.85)	<0.001
No. of hospital visits				
0-2	219 (41.3%)	311 (58.7%)	1	
≥3	177 (46.9%)	200 (53.1%)	1.39 (1.02 – 1.89)	0.03
Household size				
Live alone	70 (40.0%)	105 (60.0%)	1	
Lives with cohabitant	328 (44.4%)	410 (55.6%)	1.16 (0.79 – 1.70)	0.45
Barthel index				
≥40	367 (45.8%)	434 (54.2%)	1	
<40	31 (27.0%)	84 (73.0%)	0.55 (0.34 – 0.89)	0.01
Charlson comorbidity index*				
0	69 (40.4%)	102 (59.6%)	1	
1	115 (48.3%)	123 (51.7%)	1.81 (1.16 – 2.84)	0.01
≥2	214 (42.2%)	293 (57.8%)	1.58 (1.07 – 2.35)	0.02

*0: no comorbidity, 1: low comorbidity, ≥2: high comorbidity

Table 2. Distribution of vaccinated and non-vaccinated hospitalized patients according to risk medical conditions between September 2013 and September 2014 from 7 Spanish regions.

	Vaccinated patients n (%), N = 398	Unvaccinated patients n (%), N = 518	Crude OR	p value
Chronic obstructive pulmonary disease	89 (57.8%)	65 (42.2%)	2.40 (1.59 – 3.62)	<0.001
Chronic respiratory failure	65 (52.0%)	60 (48.0%)	1.98 (1.25 – 3.14)	0.004
Asthma	48 (55.2%)	39 (44.8%)	1.15 (0.69 – 1.92)	0.59
Pneumonia during the last 2 years	22 (43.1%)	29 (56.9%)	1.08 (0.57 – 2.06)	0.80
Neoplasia	86 (43.7%)	111 (56.3%)	0.85 (0.60 – 1.22)	0.39
Transplantation	3 (60.0%)	2 (40.0%)	3.31 (0.47 – 23.49)	0.23
Immunosuppressive treatment	17 (37.0%)	29 (63.0%)	0.65 (0.32 – 1.29)	0.21
Asplenia	2 (66.7%)	1 (33.3%)	9.04 (0.53 – 153.65)	0.13
Diabetes	125 (39.4%)	192 (60.6%)	0.99 (0.72 – 1.36)	0.96
Renal failure	84 (42.9%)	112 (57.1%)	1.30 (0.90 – 1.88)	0.16
Nephrotic syndrome	4 (57.1%)	3 (42.9%)	1.51 (0.29 – 7.79)	0.62
Congestive heart disease	110 (42.8%)	147 (57.2%)	1.57 (1.09 – 2.25)	0.01
Disabling neurological disease	21 (32.8%)	43 (67.2%)	0.82 (0.45 – 1.51)	0.52
Obesity	96 (49.0%)	100 (51.0%)	1.38 (0.94 – 2.00)	0.10
Chronic liver disease	21 (50.0%)	21 (50.0%)	1.33 (0.65 – 2.72)	0.43
Hemoglobinopathy or anemia	61 (39.9%)	92 (60.1%)	1.00 (0.67 – 1.48)	0.98
Cognitive dysfunction	39 (35.8%)	70 (64.2%)	1.07 (0.66 – 1.72)	0.78
Convulsions	5 (38.5%)	8 (61.5%)	1.04 (0.28 – 3.83)	0.95
Neuromuscular disease	13 (52.0%)	12 (48.0%)	0.89 (0.38 – 2.11)	0.79

No vaccinated or unvaccinated patients presented AIDS or asymptomatic HIV infection.

Table 3. Factors associated with 23-valent pneumococcal vaccination in hospitalized patients between September 2013 and September 2014 from 7 Spanish regions. Results of multilevel regression analysis.

	Model 1 (*Enabling resources*) Adjusted OR (95%CI)	p value	Model 2 (*Model 1 + Predisposing characteristics*) Adjusted OR (95%CI)	p value	Model 3 (*Model 2 + Risk medical conditions*) Adjusted OR (95%CI)	p value
Enabling resources						
No. of GP visits						
0-2	1		1		1	
≥3	2.02 (1.44 – 2.83)	<0.001	1.82 (1.27 – 2.62)	0.001	1.79 (1.25 – 2.57)	0.001
No. of hospital visits						
0-2	1		1		1	
≥3	1.37 (0.99 – 1.89)	0.05	1.42 (1.01 – 1.99)	0.04	1.37 (0.97 – 1.93)	0.07
Barthel index						
≥40	1		1		1	
<40	0.48 (0.29 – 0.78)	0.004	0.35 (0.19 – 0.63)	<0.001	0.33 (0.18 – 0.60)	<0.001
Predisposing characteristics						
Influenza vaccine in season 2013/14			2.58 (1.73 – 3.85)	<0.001	2.57 (1.72 – 3.84)	<0.001
Influenza vaccine in any of the 3 previous seasons			11.60 (7.38 – 18.24)	<0.001	11.70 (7.42 – 18.45)	<0.001
Charlson comorbidity index						
0					1	
1					1.56 (0.96 – 2.55)	0.07
≥2					1.43 (0.92 – 2.24)	0.11

*0: no comorbidity, 1: low comorbidity, ≥2: high comorbidity.

visits and the Barthel index score were also associated with influenza vaccination.

When the Charlson index was added (model 3), the significant variables were the same as in model 2, with only slight decreases in the values of the odds ratio for ≥3 GP visits (OR=1.79; 95% CI 1.25-2.57); Barthel index < 40 (OR=0.33; 95% CI 0.18-0.60); influenza vaccination in the 2013-14 season (OR=2.57; 95% CI 1.72-3.84); and influenza vaccination in any of the 3 previous seasons (OR=11.70; 95% CI 7.42-18.45).

Discussion

This study found that pneumococcal vaccination coverage in the elderly in Spain is low (43.8%). Some Spanish studies have found a higher coverage. In Catalonia, where vaccination of the elderly was initiated at the end of 1999, rates slightly above 50% were reported in 2003 by Vila Córcoles et al.[21] In the United States, achieving a 90% coverage of pneumococcal vaccination in non-institutionalized adults aged ≥65 years is a Healthy 2020 objective,[40] but the coverage is lower, even though vaccination is widely offered free to the elderly.[41] In a nationally representative sample of non-institutionalized adults aged ≥65 years, PPSV coverage was 59.5% in 2013.[42] In Ontario (Canada), the coverage in people aged ≥65 y in 2006 was 39% in healthy people and 49% in people with underlying diseases.[43] In the same country, Sabapathy et al.[44] found a PPSV coverage of 49.8% in 2009 and Schneeberg et al.[45] a coverage of 58% in a 2012 cross-sectional survey. In Israel, Schwartz et al.[46] reported a coverage of 72.7% during 2008-2009 in elderly members of a healthcare organization. In Australia, the coverage was 62.9% in 2006 in patients aged ≥ 60 y hospitalized in a large tertiary referral hospital,[47] and 67.6% in 2008 in people aged ≥65 years with chronic diseases (asthma, diabetes and cardiovascular disease).[48] The coverage found in patients admitted to a Korean university hospital in 2013 was 21.8%.[49]

In patients aged ≥75 years admitted to a French geriatric unit during 2009-2010, PVC coverage was 17.2% but increased to 84.5% after an intervention that reminded physicians about whether pneumococcal vaccination was indicated or not.[50] In the same country, a coverage of 48% was found in 2013 in a large cohort of patients with secondary immune deficiency.[51]

ATurkish study by Arslam et al.[52] found a PPSV coverage of 0.9% in elderly people in 2008 which increased to 19.1% after an intervention where families were asked whether their grandparents were vaccinated. In another Turkish study[53] carried out in 2009 in diabetic patients with a mean age of 57 y PPSV coverage was 9.8%, clearly lower that that found in the present study in diabetic patients (39.4%), but reached 40.7% after a physician training program.

In the present study, patients with COPD, asthma, and chronic respiratory failure had vaccination coverages of 57.8%, 55.2%, and 52.0%, respectively. Although not statistically significant, the coverage in patients with asthma was higher than in the whole population studied, but lower than that obtained by Dower et al.[48] Neither smokers nor patients with alcohol intake had a higher vaccination coverage.

In the bivariate analysis, we found an association between a higher Charlson index and PPSV uptake, but this disappeared in the final model.

Other variables that were associated with the PPSV coverage in the final model were having visited the GP ≥3 times during the last year, the Barthel index and having a history of influenza vaccination. Other authors[43,54] have also found that patients who had visited the physician more times during the last year are more likely to be vaccinated, but the study by Loubet et al.[51] in immunocompromised patients did not find such an association. In our study, patients with a lower Barthel index (a higher level of dependence) had a lower rate of vaccination, probably because physicians do not believe that age alone is a good

reason for recommending pneumococcal vaccination, independently of the functional status and limitations in activity. In a European survey of primary care physicians and specialists to determine pneumococcal disease awareness and attitudes, the patient's health condition was a key factor influencing a physician's decision to prescribe pneumococcal vaccination.[55]

In contrast to the findings of Al-Sukhni et al.[43] a history of influenza vaccination in any of the 3 previous seasons was closely associated with pneumococcal vaccination in the final model (OR: 11.7; 95% CI 7.4-18.5), suggesting that, in Spain, patients who follow annual recommendations on influenza vaccination are more predisposed to accept other vaccine recommendations or that physicians who provide the influenza vaccination also provide pneumococcal vaccination. Liu et al.[56] in China and Loubet et al.[51] in France found similar results to ours. We cannot say whether this may be due to the role of healthcare professionals or to patient attitudes as this was not an objective of the study. However, experience with the influenza vaccination[57] suggests that physicians' attitudes to pneumococcal vaccination might play an important role.

Studies[45,46,54] show that age is associated with vaccination, but we found no such association. Neither was gender associated with vaccination and the of other studies are heterogeneous: some found an association with male gender[44,46,58] and others with female gender.[45,54,59]

Socioeconomic status is an important factor possibly associated with PPSV coverage in the elderly, but it is difficult to assess. We used the educational level as a proxy of socioeconomic status, and although higher coverages were found in patients with a lower educational level in the bivariate analysis, no association was shown in the final model. Scheenberg et al.[45] found lower coverages in people with a higher educational level and in people with higher incomes in the crude analysis but, in the adjusted analysis, the association disappeared. Sabapathy et al.[44] found a non-significant association between higher income and lower coverages in hospitalized elderly people. Other studies have found that a lower educational level[54] or lower income[46] are significantly associated with a low rate of vaccination in adjusted models.

The strategy and action plan for healthy aging in Europe states that a goal for vaccination of older people and infectious disease prevention is to reduce the health risks for older people that are due to gaps in vaccination against infectious diseases.[60] In order to reduce these gaps it is necessary to assess different possible strategies.

The results of a European physician survey found that risk medical conditions were a key factor in recommending the PPSV.[55] However, taking into account the expected increase in the population aged ≥65 years in forthcoming years and the frequency of risk medical conditions in age group, age-based policies should be potentiated. Some authors suggest that interventions such as physicians' independent initiation of standing orders, advertising, provider and patient mailing, reminder calls, easy access to patients' vaccination history, and patient and staff education might increase vaccination coverages.[50,61-63]

The strategy followed in Spain of pneumococcal vaccination of the elderly without the need for an order from the attending physician, in order to vaccinate all persons aged ≥ 65 years, has been recommended by some authors[54,64] and we believe this strategy should not be changed in Spain. However, despite standing orders, physicians' opinions are a key factor in patients receiving the vaccine [61,65] and staff education seems especially important in improving pneumococcal vaccination coverage in the elderly.

The role of physicians in promoting pneumococcal vaccination in the elderly has been widely recognized. A Spanish study by Picazo et al.[66] found that only 14% of people aged >60 years knew about the pneumococcal vaccine and 46% of unvaccinated elderly people stated the reason for not vaccinating was because the physician did not recommend it. In the survey by Lode et al.[55] the main driver for pneumococcal vaccination was recommendation from a healthcare professional. Therefore, the promotion of pneumococcal vaccination in primary care physicians and specialists by improving their knowledge of the burden of pneumococcal disease and their attitudes to pneumococcal vaccination might have a beneficial effect on vaccination coverages.

Strengths and limitations

Like any observational study, this work has strengths and limitations. The main strength of the study is that the vaccination status was obtained from written documents (hospital medical records, vaccination cards, or primary healthcare registers) and, therefore, it is unlikely that this information was biased. The differences found between the self-reported status and the true vaccination status might act as confounders of the main conclusions.[43,51] A possible limitation of the study is that it was made in hospitalized patients who are not representative of the total elderly population in Spain. However, these patients were non-institutionalized and were hospitalized for causes unrelated to pneumonia, acute respiratory disease, or influenza-like illness. Therefore, it may be suggested that there are no large differences with respect to the general elderly population. Another possible limitation is that no standard definitions of predisposing characteristics or enabling resources are available. We have followed criteria proposed by other authors[67,68] to examine whether the likelihood of vaccine uptake among the studied population is influenced by different factors. Finally, because this is a cross-sectional study, no causal relationship can be established. However, we identified some variables that are clearly associated with pneumococcal vaccination coverage and this may aid to improve vaccination strategies for the elderly.

Conclusion

The results of this study show that pneumococcal vaccination coverage of elderly people hospitalized for reasons other than pneumonia, acute respiratory disease or influenza-like illness is low in Spain and that some predisposing characteristics and enabling resources influence vaccination rates. The elderly should be a target for pneumococcal vaccination and healthcare workers should be encouraged to proactively propose vaccination. Educational campaigns aimed at the elderly could also

help to increase the vaccination coverage and reduce the burden of pneumococcal disease in the community.

Methods

Study design

We carried out a cross-sectional study in hospitalized patients aged ≥65 years. 921 hospitalized patients from 19 hospitals located in the main cities of 7 Spanish regions (Andalusia, the Basque Country, Catalonia, Castile and Leon, Madrid, Navarre and Valencia Community) with unplanned hospital admission due to causes other than pneumonia, acute respiratory disease, or influenza-like illness were recruited between September 2013 and September 2014.

Patients included in the study were sought from patients admitted to the internal medicine service through the emergency department, and from patients admitted to the general surgery, otorhinolaryngology, ophthalmology, dermatology, and traumatology services. Patients referred from nursing homes and those who did not provide written consent were excluded.

Measures

Patients were considered vaccinated with the pneumococcal vaccine if they had received a dose of the vaccine at any time before data collection. Information on the vaccination status was obtained from vaccination registers, hospital medical records, vaccination cards or primary healthcare records.

Specifically-trained health professionals used a structured questionnaire to collect information by patient interview and review of medical records about predisposing characteristics, enabling resources and risk medical conditions. Social determinants of utilization are shown to affect the individual determinants both directly and through the health system. Various types of individual determinants then influence the health services used by the individual, determine influence the health services used by the individual.[67-69]

The following predisposing characteristics were recorded: age, sex, educational level, smoking and alcohol intake, influenza vaccination status in the 2013-2014 season and influenza vaccination history in the 3 previous influenza seasons. Variables related to social support were collected to measure enabling resources: marital status, number of GP and hospital visits during the last year, whether the patient lived alone or at home with cohabitants, and the Barthel index, which has a total score ranging from 0 (complete dependence) to 100 (complete independence), as a measurement of limitations in activity in patients.[70] The Barthel index was used to assess the functional capacity at hospital admission. Risk medical conditions included were: COPD, chronic respiratory failure, history of pneumonia during the last 2 years, neoplasia, transplantation, immunosuppressive treatment, asplenia, diabetes, renal failure, nephrotic syndrome, autoimmune disease, AIDS, asymptomatic HIV infection, congestive heart disease, disabling neurological disease, obesity, chronic liver disease, hemoglobinopathy or anemia, cognitive dysfunction, convulsions and neuromuscular disease. Comorbidities were assessed using the Charlson comorbidity index, which assigns a weight to each comorbid condition.[71]

Statistical analyses

A bivariate analysis was made to compare vaccinated and unvaccinated patients taking into account the sociodemographic variables and risk medical conditions. As each Spanish region may introduce specific vaccination programs for specific population groups and because regions have some degree of autonomy in organizing health services, persons living in the same region tend to experience similar access to health care. Therefore, to estimate the crude and adjusted odds ratio (OR) we used multilevel regression models to consider the connection between the outcome variable in people from the same region, in order to obtain accurate statistical estimates of vaccine predictors. Covariates were introduced into the model using a backward stepwise procedure, with a cut-off point of $p < 0.2$.

Model 1 included only variables related to enabling resources; model 2 also included predisposing variables and model 3 included enabling resources, predisposing variables, and risk medical conditions.

The analysis was performed using the SPSS v.18 statistical package and the R v3.1.2 statistical software (http://cran.r-project.org).

Ethical considerations

All data collected were treated as confidential, in strict observance of legislation on observational studies. The study was approved by the Ethics Committees of the hospitals involved (Comité Ético de Investigación Clínica del Hospital Clínic de Barcelona; Comité Ético de Investigación Clínica del Hospital Universitari Mutua de Terrassa; Comité Ético de Investigación Clínica de la Corporació Sanitaria Parc Taulí de Sabadell; Comité Ético de Investigación Clínica del Hospital de Mataró, Consorci Sanitari del Maresme; Comité Ètic d'Investigació Clínica de la Fundació Unio Catalana Hospitals; Comité Ético de Investigación Clínica Área de Euskadi; Comité Ético de Investigación Clínica Área de Salud de Burgos y Soria; Comité Ético de Investigación Clínica Área de Salud de León; Comité Ético de Investigación Clínica Área de Salud Valladolid– Este; Comité Coordinador de Ética de la Investigación Biomédica de Andalucía; Comité Ético de Investigación Clínica del Hospital Ramón y Cajal, Madrid and Comité Ético de Investigación Clínica del Consorcio Hospital General Universitario de Valencia). Written informed consent was obtained from all the patients included in the study.

Abbreviations

CI	confidence interval
COPD	chronic obstructive pulmonary disease
GP	general practitioner
IPD	invasive pneumococcal disease
OR	odds ratio
PCV	pneumococcal conjugate vaccine
PCV7	7-valent conjugate pneumococcal vaccine

PCV13 13-valent conjugate pneumococcal vaccine
PPSV 23-valent pneumococcal polysaccharide vaccine

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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4.4 Artículo 4

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Effectiveness of 23-valent pneumococcal polysaccharide vaccination in preventing community-acquired pneumonia hospitalization and severe outcomes in the elderly in Spain.

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RESEARCH ARTICLE

Effectiveness of 23-valent pneumococcal polysaccharide vaccination in preventing community-acquired pneumonia hospitalization and severe outcomes in the elderly in Spain

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Abstract

Pneumococcal pneumonia is a serious cause of morbidity and mortality in the elderly, but investigation of the etiological agent of community-acquired pneumonia (CAP) is not possible in most hospitalized patients. The aim of this study was to estimate the effect of pneumococcal polysaccharide vaccination (PPSV23) in preventing CAP hospitalization and reducing the risk of intensive care unit admission (ICU) and fatal outcomes in hospitalized people aged ≥65 years. We made a multicenter case-control study in 20 Spanish hospitals during 2013–2014 and 2014–2015. We selected patients aged ≥65 years hospitalized with a diagnosis of pneumonia and controls matched by sex, age and date of hospitalization. Multivariate analysis was performed using conditional logistic regression to estimate vaccine effectiveness and unconditional logistic regression to evaluate the reduction in the risk of severe and fatal outcomes. 1895 cases and 1895 controls were included; 13.7% of cases and 14.4% of controls had received PPSV23 in the last five years. The effectiveness of PPSV23 in preventing CAP hospitalization was 15.2% (95% CI -3.1–30.3). The benefit of PPSV23 in avoiding ICU admission or death was 28.1% (95% CI -14.3–56.9) in all patients, 30.9% (95% CI -32.2–67.4) in immunocompetent patients and 26.9% (95% CI -38.6–64.8) in immunocompromised patients. In conclusion, PPSV23 showed a modest trend to avoidance of hospitalizations due to CAP and to the prevention of death or ICU admission in elderly patients hospitalized with a diagnosis of CAP.

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Introduction

Streptococcus pneumoniae is a leading cause of serious illness, along with bacteremia, meningitis and pneumonia. In adults aged ≥65 years, most invasive cases result from the complications of pneumonia [1]. Pneumococcal disease causes a substantial burden among older adults [2], and up to one third of patients require intensive care unit (ICU) admission and nearly 20% die during hospitalization or in the first month after discharge [3].

Recognition of continued morbidity and mortality due to pneumococcal infections despite the use of appropriate antibiotics led to increased interest in disease prevention by vaccination and, since 1983, a 23-valent pneumococcal polysaccharide vaccine (PPSV23) containing antigens against 23 of the 94 serotypes has been available [4]. Post-licensure studies showed the vaccine is protective against invasive disease in immunocompetent older adults [5–7]. Evidence in support of a beneficial effect of PPSV23 in preventing pneumococcal pneumonia is more limited.

Until the 13-valent conjugate pneumococcal vaccination (PCV13) for adults recently became available, PPSV23 vaccination was recommended in the United States for all persons aged ≥65 years and for adults aged <65 years at increased risk of invasive pneumococcal disease [8]. Similar recommendations are in place in most European Union countries, although in France, the Netherlands, and Sweden vaccination is recommended only for adults with high risk conditions and not for healthy adults aged ≥65 years [9]. Currently, the recommended pneumococcal vaccination schedule for adults aged ≥65 years in the United States and other countries is the administration of PCV13 followed by PPSV23 at least 1 year after PCV13 if the subject has not received any previous pneumococcal vaccine and a dose of PCV13 if they have previously received a PPSV23 dose (1 year after PPSV23) [10,11]. In adults aged ≥65 years with immunocompromising conditions, functional or anatomic asplenia, cerebrospinal fluid leaks or cochlear implants, the recommended interval between PCV13 followed by PPSV23 is ≥8 weeks [12]. In contrast, in Spain as in other countries, the current recommendation is to maintain PPSV23 vaccination in persons aged ≥ 65 years [13,14]. By the end of 2016, all Spanish regions included the PCV13 vaccine in the pediatric vaccination calendar; previously, only two regions had included it.

Because samples for the investigation of the etiological agent are not always collected, pathogens are detected in only one third of all cases of community-acquired pneumonia (CAP) [15] and, due to limitations in the sensitivity and specificity of the available diagnostic test, the cause of pneumonia cannot be identified in most hospitalized patients [16]. Therefore, CAP is an outcome of public health relevance that does not depend on the etiologic diagnosis, and thus the study of PPSV23 vaccine effectiveness (VE) against hospitalized cases of CAP may be considered a proxy of VE against pneumococcal pneumonia.

In Spain, CAP remains a major health problem in older adults [17] and free, universal PPSV23 vaccination of people aged ≥65 years has progressively been included in the vaccination schedule of some regions from 1999 onwards [18], although the coverage at any time before data collection has remained < 50% [19]. According to the standing order strategy [20], PPSV23 is administered in primary care centers or hospitals without requiring a specific order from the attending physician [21].

Because *S. pneumoniae* infection in the elderly may result not only in CAP but also death [22], it may be of interest to assess the benefit of pneumococcal vaccination in protecting against the worst CAP outcomes, such as ICU admission and death.

The objective of this study was to estimate the effect of pneumococcal polysaccharide vaccination in preventing CAP hospitalization in hospitalized subjects aged ≥65 years and reducing the risk of severe and fatal outcomes in CAP hospitalized subjects aged ≥65 years.

Methods

Study design

We carried out a multicenter case-control study in 20 hospitals from seven Spanish regions (Andalusia, Castile and Leon, Catalonia, Madrid, Navarra, the Basque Country and Valencia Community). Cases and corresponding controls admitted to participating hospitals between September 2013 and June 2015 were recruited.

Selection of cases and controls

We selected patients aged ≥65 years hospitalized for at least 24h with a diagnosis of CAP. The diagnosis of pneumonia was based on the finding of a new infiltrate typical of pneumonia on chest radiography, fever and any symptoms of lower respiratory tract infection. Pneumonia was considered as nosocomial, and therefore excluded, if the onset of symptoms occurred more than 48h after hospital admission [23].

One matched control was selected for each case from among patients with unplanned hospital admission due to causes other than pneumonia or acute respiratory disease. Controls were matched according to sex, age (±3 years) and date of hospitalization (preferentially ±10 days but ±30 days if no appropriate control was found using the ±10 day interval) and were selected from patients admitted to the internal medicine service, general surgery, otorhinolaryngology, ophthalmology, dermatology, or traumatology services. When there was more than one possible control for a case, the patient with a date of hospitalization ±10 days and with the age closest to the case was chosen. Patients referred from nursing homes and those who did not provide written informed consent were excluded.

Data collection

The following demographic variables and pre-existing medical conditions were recorded: age, sex, marital status, educational level, smoking status, high alcohol consumption (>40gr/day for men and >24gr/day for women), number of hospital visits during the last year, whether the patient lived alone or with cohabitants, the Barthel index as a measurement of limitations in activity (ranging from 0 -complete dependence- to 100 -complete independence), chronic obstructive pulmonary disease (COPD), chronic respiratory failure, other lung diseases, neoplasia, transplantation, immunosuppressive treatment, asplenia, diabetes, renal failure, nephrotic syndrome, autoimmune disease, AIDS, HIV infection, congestive heart disease, disabling neurological disease, chronic liver disease, hemoglobinopathy or anemia, and cognitive dysfunction. A severe outcome was defined as ICU admission or death. Information on influenza vaccination in the current season and pneumococcal vaccination was collected by review of the hospital medical record and, if this information was not contained in the hospital medical record, the primary care medical.

Given that antibody concentrations and effectiveness of the vaccine decline after 5–10 years in elderly persons [24,25], the main analysis was made considering as vaccinated with the pneumococcal vaccine cases and controls who had received a dose of PPVS23 ≥14 days and in the 5 years before symptom onset (cases) or before symptom onset of the matched case (controls). All other subjects were considered unvaccinated.

Cases were considered vaccinated with the current seasonal influenza vaccine if they had received a dose of the vaccine ≥14 days before symptom onset. Controls were considered vaccinated if they had received a dose of the vaccine at least 14 days before the onset of symptoms of the matched case.

Sample size calculation

The minimum sample size required, calculated using Schlesselman's criteria [26], assuming a PPSV23 rate among controls of 27.5%, a vaccination effectiveness of 24%, a statistical power of 80% and a confidence level of 95% according to previous studies [27], was 1118 cases and 1118 controls.

Statistical analysis

A bivariate comparison for matched data of demographic variables and medical conditions between cases and controls was made using McNemar's test. A two-tailed distribution was assumed for all p-values.

To control for the possible influence of influenza viruses on CAP hospitalization, we considered two periods in each season: an epidemic period including the weeks when influenza viruses circulated in Spain and a non-epidemic period including the remaining weeks. According to the reports of the Spanish network for epidemiological surveillance [28,29], epidemic weeks were 25 November to 20 April in the 2013–2014 season and 24 November to 19 April in the 2014–2015 season.

The interaction between PPSV23 and the other variables was analyzed.

Vaccine effectiveness (VE) was calculated using the formula: VE = (1 –OR) x 100.

A univariate conditional logistic regression model was used to estimate the crude VE in preventing CAP hospitalization. Propensity score (PS) analysis was used to evaluate the adjusted vaccine effectiveness. The PS was created using a logistic regression model with PPSV23 vaccination status as the outcome and demographic variables, Barthel index, smoking and alcohol intake, number of hospital visits, comorbidities, epidemic period and influenza vaccination as independent variables. The PS was used as a covariate in the final conditional logistic regression model.

To assess the benefit of PPSV23 in avoiding severe outcomes in hospitalized patients we compared the characteristics of hospitalized patients with CAP who died or were admitted to the ICU with those of other hospitalized patients with CAP using unconditional logistic regression. We created a PS using a logistic regression model with PPSV23 vaccination status as the outcome and demographic variables, Barthel index, smoking and alcohol intake, number of hospital visits, comorbidities, epidemic period and influenza vaccination as independent variables. The PS was used as a covariate in the final unconditional logistic regression model.

The analysis was performed using the SPSS v.23 statistical package and the R v3.3.0 statistical software (http://cran.r-project.org).

Ethical considerations

All data collected were treated as confidential, in strict observance of legislation on observational studies. The study was approved by the Ethics Committees of the participating hospitals (Comité Ético de Investigación Clínica del Hospital Clínic de Barcelona; Comité Ético de Investigación Clínica del Hospital Universitari Mutua de Terrassa; Comité Ético de Investigación Clínica de la Corporació Sanitaria Parc Taulí de Sabadell; Comité Ético de Investigación Clínica del Hospital de Mataró, Consorci Sanitari del Maresme; Comité Ètic d'Investigació Clínica de la Fundació Unio Catalana Hospitals; Comité Ético de Investigación Clínica Área de Euskadi; Comité Ético de Investigación Clínica Área de Salud de Burgos y Soria; Comité Ético de Investigación Clínica Área de Salud de León; Comité Ético de Investigación Clínica Área de Salud Valladolid-Este; Comité Coordinador de Ética de la Investigación Biomédica de Andalucía; Comité Ético de Investigación Clínica del Hospital Ramón y Cajal, Madrid and

Comité Ético de Investigación Clínica del Consorcio Hospital General Universitario de Valencia). Written informed consent was obtained from all patients included in the study.

Results

A total of 1895 cases and 1895 controls were included in the study. The distribution of cases and controls according to demographic variables, medical conditions and vaccination history is shown in Table 1.

A total of 1003 cases (52.0%) and 923 controls (47.8%) had received pneumococcal vaccination and most (973 cases and 896 controls) had received PPSV23; only 5 cases and 5 controls had received PCV13 alone and 16 cases and 8 controls had received both vaccines; 259 cases and 272 controls had received PPSV23 in the previous 5 years. All patients who had received PCV13 were excluded from the study of VE.

Of the 1895 cases with CAP, the etiological agent was determined in 469 (24.7%) and, of these, *S. pneumoniae* was detected in 324 (69.1%).

Most patients hospitalized due to CAP (89.8%) and controls (86.5%) presented one or more comorbidities, whose distribution is shown in Table 2.

Of the 1895 cases, 130 died within 30 days of admission and 81 were admitted to the ICU, of whom 14 died.

No interaction between PPSV23 and comorbidities (p = 0.32) or age (p = 0.24) was observed32).

The adjusted effectiveness of PPSV23 against CAP hospitalization is shown in Table 3 and the benefit of PPSV23 in avoiding ICU admission or death in cases is shown in Table 4. The effectiveness of PPSV23 in preventing CAP hospitalization was 15.2% (95% CI -3.1–30.3) in all cases, which was not significant. The effectiveness of PPSV23 in preventing severe outcomes in cases was 28.1% (95% CI -14.3–56.9) in all patients, 30.9% (95% CI -32.2–67.4) in immunocompetent patients and 26.9% (95% CI -38.6–64.8) in immunocompromised patients.

S1 and S2 Tables show the VE excluding cases and controls vaccinated more than 5 years previously. The VE against hospitalization was lower (6.1%; -21.8 to 27.6), but was significantly higher (40.9%; 2.9–65.6; p = 0.04) in preventing ICU admission or death.

Discussion

The results of this study show that PPSV23 vaccination resulted in a non-significant trend to protection against hospitalization due to CAP in the elderly and in preventing severe outcomes when persons vaccinated ≥5 years previously were considered unvaccinated, but offered significant protection against severe outcomes when cases and controls vaccinated ≥ 5 years previously were excluded from the analysis (VE: 40.9%; 2.9–65.6).

Comparison of our results with other studies of CAP hospitalization in the elderly that considered patients vaccinated if they had received PPSV23 in the previous 5 years shows some similarities. A case-control study in Japan in people aged ≥65 years found no association between vaccination in the previous 5 years and CAP [30]. In a Spanish cohort study in individuals aged ≥60 years, vaccination within the last 5 years was not associated with a reduced risk of all-cause CAP, but after exclusion of subjects who had received PPSV23 more than 5 years ago, vaccination was associated with a reduced risk for all-cause CAP hospitalization (25%; 2–42) [31]. In a case-control study carried out in three Spanish regions five years after the introduction of PPSV23, VE against CAP hospitalization was 23.6% (0.9–41) [27].

A meta-analysis of the last Cochrane review found a pooled estimate of vaccine efficacy of 28% (7–44) for all-cause pneumonia, but there was substantial variability in the effect estimate

Table 1. Distribution of cases and controls according to demographic variables, medical conditions and vaccination history.

Characteristics	Cases (N = 1895)	Controls (N = 1895)	Crude OR (95% CI)	p-value
Age group				
65–74 years	592 (31.2%)	603 (31.8%)	1	
75–84 years	879 (46.4%)	897 (47.3%)	1.17 (0.84–1.64)	0.36
≥85 years	424 (22.4%)	395 (20.8%)	1.69 (1.07–2.68)	0.03
Sex				
Female	746 (39.4%)	746 (39.4%)	-	
Male	1149 (60.6%)	1149 (60.6%)	-	
Marital status				
Married/Cohabiting	1099 (58.0%)	1108 (58.7%)	1	
Single	140 (7.4%)	147 (7.8%)	0.96 (0.75–1.24)	0.77
Widowed	611 (32.3%)	607 (32.1%)	1.02 (0.87–1.20)	0.82
Separated/Divorced	44 (2.3%)	27 (1.4%)	1.66 (1.01–2.70)	0.04
Educational level				
Without or primary	1378 (73.5%)	1308 (70.3%)	1	
Secondary or higher	498 (26.5%)	553 (29.7%)	0.81 (0.69–0.95)	0.01
Household size				
Live alone	339 (17.9%)	363 (19.2%)	1	
Live with cohabitant	1555 (82.1%)	1526 (80.8%)	1.09 (0.93–1.29)	0.29
Barthel index				
0–90	766 (40.4%)	773 (40.8%)	0.98 (0.85–1.13)	0.80
>90	1129 (59.6%)	1122 (59.2%)	1	
Smoking status				
Non smoker	838 (44.2%)	983 (51.9%)	1	
Smoker	165 (8.7%)	145 (7.7%)	1.73 (1.31–2.27)	<0.01
Ex-smoker	892 (47.1%)	767 (40.5%)	1.78 (1.48–2.14)	<0.01
High alcohol consumption				
Yes	71 (3.7%)	54 (2.8%)	1.34 (0.93–1.93)	0.12
No	1824 (96.3%)	1841 (97.2%)	1	
No. of hospital visits				
0–2	922 (48.9%)	897 (47.8%)	1	
≥3	962 (51.1%)	978 (52.2%)	0.95 (0.82–1.10)	0.50
Risk medical conditions				
No	193 (10.2%)	255 (13.5%)	1	
Yes	1702 (89.8%)	1640 (86.5%)	1.38 (1.13–1.69)	0.002
Epidemiologic week				
Yes	1302 (68.7%)	1266 (66.8%)	1.92 (1.31–2.83)	0.001
No	593 (31.3%)	629 (33.2%)	1	
Influenza vaccine				
Yes	891 (47.0%)	855 (45.1%)	1.10 (0.95–1.27)	0.19
No	1004 (53.0%)	1040 (54.9%)	1	
Pneumococcal polysaccharide vaccine in 5 previous years				
Yes	259 (13.7%)	272 (14.4%)	0.94 (0.78–1.14)	0.53
No	1636 (86.3%)	1623 (85.6%)	1	

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due to heterogeneity, and the effectiveness of vaccination in preventing all-cause pneumonia in adults could not be demonstrated [32]. In another meta-analysis, the pooled effect estimate for preventing CAP was 7% (-19 to 28) among individuals who were vaccinated in the previous five years [33].

Table 2. Distribution of cases and controls according to comorbidities.

Characteristics	Cases (N = 1895)	Controls (N = 1895)	Crude OR (95% CI)	p-value
Immunocompetent				
Chronic respiratory failure	381 (20.1%)	210 (11.1%)	2.22 (1.82–2.71)	<0.001
Diabetes with complications	112 (5.9%)	134 (7.1%)	0.83 (0.64–1.07)	0.15
Diabetes without complications	534 (28.2%)	554 (29.2%)	0.95 (0.82–1.09)	0.47
Renal failure without hemodialysis	344 (18.2%)	369 (19.5%)	0.91 (0.77–1.08)	0.28
Autoimmune disease	89 (4.7%)	89 (4.7%)	1.00 (0.73–1.37)	1.00
Chronic obstructive pulmonary disease	570 (30.1%)	289 (15.3%)	2.60 (2.18–3.09)	<0.001
Congestive heart disease	528 (27.9%)	563 (29.7%)	0.90 (0.77–1.05)	0.17
Neurological disease	155 (8.2%)	121 (6.4%)	1.30 (1.02–1.66)	0.04
Chronic liver disease	72 (3.8%)	106 (5.6%)	0.66 (0.48–0.90)	0.01
Cognitive dysfunction	229 (12.1%)	220 (11.6%)	1.05 (0.85–1.29)	0.63
Immunocompromised				
Solid organ neoplasia	330 (17.4%)	398 (21.0%)	0.79 (0.67–0.93)	0.01
Hematologic neoplasia	47 (2.5%)	45 (2.4%)	1.04 (0.69–1.58)	0.83
Transplantation	20 (1.1%)	13 (0.7%)	1.54 (0.76–3.09)	0.23
Immunosuppressive treatment	73 (3.9%)	88 (4.6%)	0.82 (0.59–1.13)	0.22
Oral corticosteroid therapy	100 (5.3%)	61 (3.2%)	1.71 (1.22–2.38)	0.002
Asplenia	5 (0.3%)	4 (0.2%)	1.25 (0.34–4.65)	0.74
Renal failure with hemodialysis	31 (1.6%)	41 (2.2%)	0.75 (0.47–1.20)	0.23
Nephrotic syndrome	25 (1.3%)	9 (0.5%)	3.00 (1.35–6.68)	0.01
AIDS	3 (0.2%)	1 (0.1%)	3.00 (0.31–28.84)	0.34
HIV infection	3 (0.2%)	2 (0.1%)	1.50 (0.25–8.98)	0.66
Hemoglobinopathy or anemia	299 (15.8%)	328 (17.3%)	0.89 (0.74–1.06)	0.19

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In a large case-control study in Connecticut, vaccination was effective against invasive pneumococcal disease, but no VE was found in subjects aged ≥65 years vaccinated more than 5 years ago [34]. A retrospective case-control study in Israel in subjects aged ≥65 years found that PPSV23 administered in the 5 previous years was effective against invasive pneumococcal disease, but no protective effect against hospital-treated pneumonia was found (aOR: 1.01; 0.97–1.04) [35]. In Australia, using the screening method, VE against invasive pneumococcal

Table 3. Crude and adjusted effectiveness of PPSV23 against hospitalization due to community-acquired pneumonia.

	Cases vaccinated[a]/N (%)	Controls vaccinated[a]/N (%)	Crude vaccine effectiveness (95% CI)	p-value	Adjusted vaccine effectiveness (95% CI)	p-value
All	259/1895 (13.7%)	272/1895 (14.4%)	5.8% (-13.7–21.9)	0.53	15.2% (-3.1–30.3)	0.10[b]
65–74 years	116/592 (19.6%)	133/592 (22.5%)	16.2% (-11.3–36.9)	0.22	23.6% (-3.0–43.3)	0.08[c]
75–84 years	94/879 (10.7%)	95/879 (10.8%)	1.2% (-34.5–27.5%)	0.94	11.5% (-22.1–35.9)	0.46[d]
≥85 years	49/424 (11.6%)	44/424 (10.4%)	-12.8% (-73.6–26.7)	0.58	0.3% (-57.7–36.9)	0.99[e]

[a] In the 5 previous years. Adjusted for the propensity score.

Statistical power:

[b] 41%,

[c]46%,

[d]12%,

[e]3%

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Table 4. Effectiveness of the PPSV23 in avoiding intensive care unit admission or death in hospitalized patients with community-acquired pneumonia.

	Severe outcomes vaccinated[a]/N (%)	Non severe outcomes vaccinated[a]/N (%)	Crude vaccine effectiveness (95% CI)	p-value	Adjusted vaccine effectiveness (95% CI)	p-value
All	21/211 (10.0%)	238/1684 (14.1%)	32.9% (-5.2–59.2)	0.09	28.1% (-14.3–56.9)	0.18[b]
Immunocompetent	10/97 (10.3%)	147/974 (15.1%)	35.3% (-21.6–69.1)	0.21	30.9% (-32.2–67.4)	0.30[c]
Immunocompromised	11/114 (9.6%)	91/710 (12.8%)	27.4% (-35.0–64.4)	0.34	26.9% (-38.6–64.8)	0.36[d]

[a] In the 5 previous years. Adjusted for the propensity score.

Statistical power:

[b]29%,

[c]20%,

[d]15%

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disease in subjects aged ≥65 years in which those who received the vaccine in the previous 5 years was 71% (54–82) [36]. An indirect cohort study in Spain found that PPSV23 in the previous 5 years prevented 44% (24–60) of all invasive pneumococcal disease serotypes included in the vaccine [37]. The estimate of these authors was clearly higher than ours, but this seems logical because they investigated prevention against *S. pneumoniae* disease in which VE is expected to be higher than against all CAP.

A possible explanation for the differences found in PPSV23 effectiveness against CAP hospitalization might lie in the influence of the circulation of influenza viruses and other environmental factors on bacterial complications [30,38–41]. To avoid the possible influence of these factors, we defined the weeks when the influenza virus was circulating in Spain in each season and introduced this variable in the estimate of PPSV23 effectiveness; however, this was not done in the studies with negative results, making comparisons difficult.

No conclusions can be drawn on our estimates of VE in different age groups due to a lack of statistical power, as also suggested in the study by Vila-Córcoles et al. [42].

In the present study, the effectiveness of PPSV23 in preventing ICU admission or death was 28.1% (95% CI -14.3–56.9) for all patients and 40.9% when subjects vaccinated more than 5 years previously were excluded (S2 Table). In a Spanish cohort study, vaccination within the last 5 years was not associated with a reduced risk of death from CAP (1.04; 0.64–1.69) [31]. Other studies of subjects vaccinated at any time found that the protective effect of the PPSV23 against death was higher in immunocompetent than in immunocompromised patients [5,43,44]. However, although effectiveness is attenuated in immunocompromised patients, these are precisely the patients who have the most to gain by immunization as the risk of death is higher [45].

In a recent randomized, placebo-controlled trial, the VE of the PCV13 against CAP in the elderly was 45.6% (21.8–62.5) [46] and the benefit of the conjugate vaccine versus the polysaccharide vaccine in avoiding deaths has also been reported [47]. Therefore, it may be questioned whether the use of PCV13 would be more useful in preventing CAP in the elderly. The results of several impact studies suggest that routine immunization with pneumococcal conjugate vaccines in children reduces the incidence of disease due to conjugate vaccine serotypes in the elderly [48–51]. However, the epidemiology of specific serotypes evolves [52] and the duration of immunity and the need for revaccination is not currently clear [53]. On the other hand, the effect of herd immunity due to the direct effect of adult PCV13 vaccination remains unclear [54]. In fact, the CDC states that routine PCV13 vaccination in adults aged ≥65 years will be reevaluated in 2018 [10].

A cost-effectiveness study carried out in the UK show that the incidence of vaccine-type disease will probably be very low due to the wider benefits of childhood PCV13 vaccination and that a specific PCV13 vaccination program targeting the immunocompetent elderly would not be cost-effective [55]. A Dutch study found that PCV13 vaccination of immunocompetent persons aged 65–74 years was not cost-effective, although vaccination of high-risk individuals aged 65–74 years was cost-saving [56].

The results of the present and above-mentioned studies, together with the fact that PPSV23 includes eleven serotypes not found in PCV13, support the current indication for PPSV23 vaccination in the elderly and the interest in maintaining continuous surveillance of disease-causing serotypes in the elderly in order to evaluate the potential benefit and cost-effectiveness of expanding PCV13 vaccination to all elderly persons.

One limitation of the present study is that the main analysis was carried out considering persons not vaccinated in the previous five years as unvaccinated, which could have led to an underestimate of the VE. Another possible limitation is that interviewers knew whether interviewees were cases or controls, influencing information gathering. The same protocol was followed in cases and controls and information on the vaccination history was collected from information collected in medical records, vaccination cards or registers before the study began. Therefore, it is unlikely that the results were affected by this possible information bias.

Most potential confounding factors described in the literature, including influenza vaccination and comorbidities, were taken into account and their possible effect limited by adjustment [45]. Thus, although some residual confounding cannot be ruled out, this is unlikely to have invalidated the results.

Cases were older and had more medical risk conditions than controls, and therefore were more likely to receive the vaccine, but since a propensity score was used for the adjustment it seems unlikely that this would invalidate the results.

Finally, because the number of *Streptococcus pneumoniae* cases found was very limited, it was not possible to estimate VE in cases of *S. pneumoniae* CAP due to lack of statistical power.

In conclusion, the results of this study indicate that PPSV23 vaccination showed a modest trend to avoidance of hospitalization due to CAP in elderly subjects and in preventing death or ICU admission in elderly patients hospitalized with a diagnosis of CAP. The current indication for PPSV23 vaccination in the elderly should be maintained but continuous surveillance of disease-causing serotypes in this population is required.

Supporting information

S1 Table. Crude and adjusted effectiveness of PPSV23 against hospitalization due to community-acquired pneumonia.
(DOCX)

S2 Table. Effectiveness of the PPSV23 in avoiding intensive care unit admission or death in hospitalized patients with community-acquired pneumonia.
(DOCX)

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5. Discusión

Los estudios que hemos realizado muestran que los factores sociodemográficos, de tratamiento y de prevención influyen en los episodios de NAC que requieren hospitalización en las personas de 65 años y más.

En el primer estudio se analizaron los factores de riesgo asociados al reingreso hospitalario en los 30 días posteriores al alta por NAC en personas de 65 años y más. El reingreso en los 30 días tras el alta suele emplearse como un indicador de vulnerabilidad. En nuestro estudio definimos el reingreso como la "hospitalización por cualquier motivo en los 30 días posteriores al alta", la información se obtuvo mediante la revisión de la historia clínica (HC) del paciente 30 días después del alta inicial.

La tasa de reingreso a los 30 días fue de 11,39%, si bien entre los 20 hospitales participantes se observaron valores que oscilaron entre el 2,5% y el 20,5%. Esta diferencia podría explicarse por las diferencias en la carga asistencial de los hospitales participantes y por los protocolos utilizados en cada centro. Nuestros resultados son coincidentes con los obtenidos en estudios realizados en Estados Unidos y Canadá, donde la tasa de reingreso en los 30 días posteriores al alta en personas de 65 años y más varía entre 8% y 27%.[51,136–139]

Además de considerar en nuestro estudio los factores sociales como elementos que podrían influir en el reingreso tras un episodio de NAC,[54] también se han considerado factores poco conocidos como el tipo de convivencia o el destino del paciente al alta, por lo que su identificación en nuestro estudio proporciona una nueva perspectiva en relación a los factores de riesgo asociados con el reingreso durante los 30 días posteriores al alta.

A pesar que la influencia del sexo como factor asociado al reingreso varía de unos estudios a otros, en nuestro estudio no se observó asociación del reingreso con el sexo, a diferencia de lo encontrado por Neupane et al. y Bohannon et al.[136,140] Además, a diferencia de Jasti et al. y El Sohl et al. tampoco se observó asociación con el nivel educativo, los hábitos de tabaquismo o el consumo de riesgo de alcohol.[138,141]

Aunque se sabe que los niños en edad escolar pueden actuar como fuente de infección de algunas enfermedades infecciosas para las personas de edad avanzada,

no se encontraron estudios que investigaran la asociación entre el tipo de conviviente y el reingreso, debido posiblemente a que un factor usualmente asociado con el reingreso en personas de 65 años y más es vivir en residencias geriátricas. Sin embargo, en nuestro estudio se observó que los pacientes que conviven con niños menores de 15 años presentaron una probabilidad de reingreso dos veces superior a la de los que viven solos o con una persona.

Coincidiendo con el estudio de Neupane et al. en Canadá y con el de Adamuz et al. en Barcelona, en nuestro estudio no hemos observado asociación entre los antecedentes de vacunación antigripal y de vacunación antineumocócica en los últimos 5 años y el reingreso en los 30 días tras el alta.[136,142]

Nuestros resultados muestran que los pacientes con enfermedad hepática crónica, insuficiencia cardíaca e insuficiencia respiratoria presentaron tasas más altas de reingreso en los 30 días tras el alta, al igual que se ha observado en estudios realizados por Jenks et al., Tang et al. y Jasti et al. en Estados Unidos, y Adamuz et al. y Capelastegui et al. en España, que muestran que algunas enfermedades cardiovasculares y respiratorias desempeñan un papel importante en el riesgo de reingreso en pacientes dados de alta previamente por un episodio de NAC.[52,138,142–144] Si bien, el 49,5% de los pacientes que reingresaron en nuestro estudio fue por razones relacionadas con el episodio de NAC, el 91% de los pacientes que reingresaron presentaban una o más comorbilidades activas. La razón del reingreso generalmente difiere del diagnóstico inicial debido, en la mayoría de los casos, a la desestabilización de las comorbilidades que presentan, variando desde un 32,67% presentado por Dharmarajan et al. a un 74% presentado por Jasti et al.[50,138,142–144]

La calidad de la atención que recibe el paciente de 65 años y más durante la hospitalización por NAC y la adecuada planificación del alta y el seguimiento hasta su recuperación son factores que influyen en el reingreso.[137,142,143,145] A pesar que se estudiaron otras variables relacionadas con la calidad de la atención para evaluar estos aspectos, no se observó asociación entre ellas. Sin embargo, coincidiendo con Dong et al. observamos que la elección de hospitalización domiciliaria como destino al alta influye en el reingreso del paciente.[145] Esto podría deberse a una evaluación inadecuada de la estabilidad del paciente en el momento del alta. Estudios realizados en pacientes con EPOC o en pacientes de cirugía destacan la

importancia de la selección del destino del alta.[146–148] Respecto a pacientes con NAC, solo los resultados del estudio de Dong et al. y los nuestros han encontrado una asociación entre el destino al alta y el reingreso en los 30 días posteriores al alta.

En el segundo estudio se evaluó la capacidad predictiva de la mortalidad por NAC mediante la combinación del IB y el PSI en personas de 65 años y más hospitalizadas. Se utilizó un límite de ≤ 90 para definir algún grado de dependencia en el IB; y según el PSI se clasificaron a los pacientes en dos categorias: de riesgo bajo o moderado (PSI I-III) y de riesgo alto o grave (PSI IV-V). Para evaluar el valor pronóstico de ambos índices para la mortalidad, se construyó un índice que combinó la presencia de neumonía grave (PSI IV-V) y la existencia de cierto grado de dependencia (PSI IV-V y IB ≤90).

Nuestros resultados muestran que la utilización de forma combinada del IB y del PSI mejora la predicción de mortalidad en las personas de 65 años y más hospitalizadas por NAC. También se observó que la edad avanzada, las neoplasias activas y la demencia se asocian de forma independiente a la mortalidad.

Es importante conocer el estado de gravedad del paciente con NAC debido a que la toma de decisiones terapéuticas (introducción y/o interrupción de medidas de soporte), dependerá en gran medida de la puntuación obtenida en las escalas de gravedad.[149] Sin embargo, el uso exclusivo de las escalas de gravedad de neumonía produce una pérdida de información sobre el pronóstico debido a que no considera el estado funcional inicial del paciente que se ha demostrado, especialmente en los ancianos, que es un factor determinante de la mortalidad.

Diversos estudios realizados en poblaciones heterogéneas coinciden en que la evaluación del estado funcional mediante IB se convierte en un predictor independiente de mortalidad. Yalçinli et al. en un hospital en Turquía, observaron que en un grupo de pacientes mayores que acudieron a urgencias por fiebre debido a diferentes focos infecciosos, los que presentaban un IB basal menor tenían una mayor mortalidad.[150]

Murcia et al. en un estudio realizado en un hospital de Alicante en el que valoraban el IB y factores no incluidos en el PSI, observaron que un IB <80 se asociaba con

una mayor mortalidad en pacientes con NAC.[102] Torres et al. y Calle et al. observaron que un alto nivel de autonomía en pacientes con NAC se comporta como un factor protector de la mortalidad.[151,152]

En nuestro estudio se observa que la diferencia en la mortalidad entre los pacientes que presentan un PSI IV-V y un IB >90, respecto a los que presentan PSI IV-V y un IB ≤90 es mayor después del día 15 del ingreso. Probablemente, este hecho esté relacionado con la desestabilización de las comorbilidades y con el estado funcional basal y no con el proceso infeccioso inicial. El IB puede ser capaz de detectar mejor la fragilidad del paciente que el PSI. Marrie et al. analizaron en un estudio multicéntrico los factores asociados con la mortalidad en pacientes hospitalizados por neumonía y observaron que un peor estado funcional se asocia de forma independiente con una reducción de la supervivencia.[153]

A pesar de la evidencia disponible sobre la influencia del estado funcional en el pronóstico de la neumonía, hay pocos informes sobre el uso combinado de escalas que midan el estado funcional y el pronóstico de la neumonía. Yeon et al. plantearon el uso combinado de escalas de gravedad de neumonía, PSI y CURB-65, junto a la escala Eastern Cooperative Oncology Group (ECOG), escala que evalúa la calidad de vida y la autonomía del paciente, observando que a pesar de utilizar una escala diseñada para pacientes con cáncer la combinación de escalas mejoraba la predicción de mortalidad en pacientes con neumonía.[103]

Por todo ello consideramos que la primera evaluación que se realiza en un paciente mayor de 65 años diagnosticado con NAC debe ser el IB y la segunda el PSI.

De este modo se tendrá una evaluación de gravedad holística y más precisa, que debería alertar al médico sobre posibles resultados y complicaciones desfavorables.

En el tercer artículo buscamos determinar los factores que se asocian a la cobertura deVNP23 en personas de 65 años y más hospitalizadas por causas no relacionadas con neumonía, enfermedad respiratoria aguda o síndrome gripal en España, considerados como controles en el estudio multicentrico. Los pacientes se consideraron vacunados con la VNP23 si recibieron una dosis en cualquier momento antes del ingreso hospitalario y la información sobre el estado de

vacunación se obtuvo de los registros médicos del hospital o registros de atención primaria.

Nuestro estudio encontró una cobertura de vacunación del 43,8% en los controles, una cobertura baja, a pesar del interés de las autoridades sanitarias en incrementar las coberturas en este grupo de edad mediante su inclusión en el calendario de vacunación recomendado por el Consejo Interterritorial del Sistema Nacional de Salud. La cobertura registrada fue inferior a la encontrada en 2003 por Vila Córcoles et al. en Cataluña cuatro años después de la introducción de la vacunación en personas de 65 años y más.[115]

Fuera del territorio español, las coberturas varían dependiendo del ámbito en el que se estudian. Así, entre adultos mayores no institucionalizados ni hospitalizados las coberturas varían entre un 39% en 2006 en Canadá y un 63,6% en 2015 en EUA,[154–157] mientras que en la población de 65 años y más que presenta inmunosupresión la cobertura fue de 48% en 2013 en Francia. Entre personas con alguna comorbilidad (asma, diabetes, enfermedad respiratoria o cardiovascular) la cobertura varía del 49,8% en 2006 en Canadá al 67,6% en 2008 en Australia.[154,158] Coberturas ligeramente más elevadas se observan entre la población que mantienen una relación continua con su centro asistencial alcanzando coberturas del 50,2% en Canadá y del 72,8% en 2013 en Australia,[157,159,160] y coberturas ligeramente más bajas en personas de mayor edad hospitalizadas por otras causas, variando entre un 21,8% en 2013 en Korea y 50,3% en 2006 en Australia.[161,162]

Las coberturas de vacunación con VPN23 en personas con enfermedades crónicas suelen ser superiores que las de la población sin comorbilidades. Los resultados del presente estudio muestran coberturas superiores en los pacientes con enfermedades crónicas como EPOC (57,8%) o insuficiencia respiratoria crónica (52,0%). A pesar que no se encontró asociación, la cobertura en pacientes con asma fue mayor (55,2%) que la registrada en el conjunto de la población estudiada (43,8%), pero menor que la obtenida por Dower et al. (61,4% vs 67,6%).[158] En nuestro estudio, los pacientes con algún hábito de riesgo como tabaquismo (44,4%) o consumo de alcohol (43,5%) también presentaron bajas coberturas.

Los resultados obtenidos señalan también que la cobertura de VPN23 se asoció con haber realizado más de 3 visitas al médico de cabecera en el último año, al índice de Barthel y haber recibido la vacuna antigripal. Al-Sukhni et al. en un estudio en Canadá y Lu et al. en EUA también encontraron que los pacientes que visitaron más veces al médico durante el último año tenían más probabilidades de ser vacunados.[154,163] Sin embargo, en un estudio en pacientes inmunocoprometidos no se encontró tal asociación.[164]

En nuestro estudio, los pacientes con un mayor nivel de dependencia registrado con un IB<40 presentaron una cobertura de vacunación más baja (27%). Una posible explicación sería que los médicos no consideran que la edad, por sí sola, sea un factor para recomendar la vacunación antineumocócica, independientemente del estado funcional y las limitaciones en la actividad diaria que presente el paciente, pero no hemos investigado sobre este hecho y es algo que se debería estudiar en el futuro.

Haber recibido la vacuna antigripal en cualquiera de las 3 temporadas previas se asoció estrechamente con el antecedente de vacunación antineumocócica, coincidiendo con Liu et al. en China y Loubet et al. en Francia.[164,165] Nuestros resultados sugieren que en España los pacientes que siguen las recomendaciones anuales sobre la vacunación antigripal tendrían una mayor predisposición a aceptar la recomendación sobre otras vacunas o bien que los profesionales sanitarios que recomiendan la vacunación antigripal también recomiendan la vacuna antineumocócica.

Lode et al. en una encuesta llevada a cabo en 13 países europeos sobre el nivel de concienciación y conocimiento sobre la infección neumocócica entre los médicos y especialistas de atención primaria, observaron que el estado de salud del paciente era un factor clave que influía en la decisión del profesional para prescribir la vacunación antineumocócica.[166]

A pesar que no fue un objetivo del estudio analizar la posición de los profesionales de la salud respecto a la vacunación antineumocócica, los resultados obtenidos en un estudio sobre la vacunación antigripal[167] sugieren que la actitud del médico

respecto a la vacunación antineumocócica podría desempeñar un papel importante en la vacunación de sus pacientes.

Nuestros resultados no mostraron asociación entre la vacunación antineumocócica y la edad, a diferencia de lo encontrado por Schneeberg et al. en Canadá, Schwartz et al. en Israel y Lu et al. en EUA.[156,159,163] Tampoco encontramos asociación con el sexo del paciente, a pesar de que se muestra un factor asociado a la vacunación según algunos autores.[168,169]

En nuestro estudio se utilizó el nivel educativo como variable para estudiar el nivel socioeconómico del paciente, pero no se encontró asociación con la vacunación antineumocócica en el modelo final. Sin embargo, en el análisis crudo se encontró una mayor cobertura en pacientes con un nivel educativo más bajo (45,8% vs 38,9%). Esto coincide con los resultados del estudio de Scheenberg et al. que muestran coberturas más bajas en las personas con un nivel educativo más alto y en las personas con mayores ingresos en el análisis crudo, si bien en el análisis ajustado dicha asociación desaparece.[156] En el estudio de Sabapathy et al. observaron una asociación no significativa entre tener mayores ingresos y una menor cobertura.[157] Por el contrario, Schwarts et al. y Lu et al. encontraron que unos ingresos bajos o un nivel educativo inferior se asocia significativamente a una cobertura de vacunación más baja.[159,163]

Uno de los objetivos del Plan de Acción y Estrategia para un envejecimiento saludable en Europa, 2012-2020 es disminuir los riesgos para la salud de las personas mayores, reduciendo la morbilidad y mortalidad ocasionada por las brechas en la vacunación contra enfermedades infecciosas comunes.[170] Para reducir estas brechas es necesario considerar diferentes posibles estrategias.

Algunos autores sugieren que intervenciones como la vacunación sin necesidad de tener una orden explicita del médico, la publicidad, el envío de correos al paciente y al médico, las llamadas de recordatorio, el fácil acceso al historial de vacunación del paciente y la promoción de la vacunación mediante campañas de educación al paciente y a los profesionales sanitarios podrían incrementar las coberturas de vacunación.[171–173]

La estrategia de vacunación antineumocócica seguida en España no requiere la orden explícita del médico y es gratuita con el fin de alcanzar a toda la población de 65 años y más, por lo que consideramos que esta estrategia no debe cambiarse.

El último estudio muestra los resultados sobre la efectividad (EV) de la VNP23 en la prevención de la hospitalización por NAC y de las formas más graves de NAC (ingreso en UCI y muerte) en personas hospitalizadas de 65 años y más. Para ello se realizó un estudio de casos y controles apareados (1:1). Debido a que las concentraciones de anticuerpos y la protección de la vacuna disminuyen después de 5-10 años en personas de edad avanzada,[174,175] se consideraron vacunados con VNP23 los casos y los controles que habrían recibido una dosis de VNP23 entre los 14 días y los 5 años previos al inicio de síntomas del caso.

Los resultados del estudio de efectividad de la vacunación con VNP23 muestra cierta la protección frente la hospitalización por NAC (EV:15,2%; -3,1-30,3) y una protección muy superior para evitar los resultados más graves de la NAC (UCI y muerte) cuando se excluyeron del análisis los pacientes con vacunación de más de 5 años (EV:40,9%; 2,9-65,6).

Acorde con nuestros resultados, el estudio realizado por Washio et al. en Japón tampoco encontraron asociación entre haber sido vacunado en los últimos 5 años y la NAC.[176] Por el contrario, Ochoa-Gondar et al. en Tarragona no observaron asociación entre la vacunación en los últimos 5 años y la reducción de riesgo por NAC; pero al excluir a los que recibieron la vacuna VNP23 más de 5 años antes del episodio de NAC la vacunación se asoció a un menor riesgo de hospitalización de NAC por todas las causas (25%; 2,0-42,0).[177] En el estudio de casos y controles realizado por Domínguez et al. en tres comunidades autónomas de nuestro país entre 2005 y 2007, posterior a la introducción de la VPN23 en España, se observó una efectividad del 23,6% (0,9-41,0) frente a la hospitalización por NAC.[123]

La revisión sistemática Cochrane de 2013 refiere una estimación de la eficacia de la vacuna del 28% (7-44) para la neumonía por todas las causas, pero hubo una variabilidad importante en los estudios considerados, por lo que se concluyó que no se podía demostrar la efectividad de la vacunación en la prevención de la neumonía por todas las causas en adultos.[178] Un metaanálisis realizado en 2015 encontró una

estimación de efectividad para prevenir la NAC del 7% (-19 a 28) entre las personas que fueron vacunadas en los últimos cinco años.[179] En otro metaanálisis publicado en 2016 la estimación de la efectividad fue 48% (25-63) para prevenir la enfermedad neumocócica invasiva.[180]

Autores como Andrews et al. en Australia (EV: 71%; 54-82) y Gutierrez et al. en España (EV: 44%; 24-66) encontraron efectividad vacunal frente a la enfermedad neumocócica invasiva en personas de 65 años y más vacunadas en los últimos 5 años.[181,182] La estimación de estos autores fue claramente superior a la nuestra, pero esto parece lógico porque investigaron especificamente la prevención contra la enfermedad por *S. pneumoniae* en la que cabe esperar que la efectividad vacunal sea mayor frente a la NAC por todas las causas.

Una posible explicación de las diferencias observadas en la efectividad de VNP23 frente a la hospitalización con NAC en diferentes estudios podría estar relacionada con la circulación de los virus de la gripe y otros factores ambientales como la temperatura o la humedad relativa de determinadas épocas que predisponen a sobreinfecciones bacterianas.[183–186] En nuestro estudio, para evitar la posible influencia de estos factores, se definió y consideró en la estimación de la efectividad de VNP23 las semanas en que el virus de la gripe circulaba en España durante las temporadas de estudio.

Desafortunadamente, debido a la falta de poder estadístico derivadas del escaso número de casos y controles no pudimos sacar conclusiones sobre la efectividad de la vacunación en diferentes subgrupos de edad.

Nuestros resultados muestran una efectividad de VNP23 frente a la prevención del ingreso en UCI o la muerte del 28,1% (-14,3 a 56,9) para todos los pacientes y del 40,9% (2,9-65,6) cuando los sujetos vacunados por más de 5 años en el momento del ingreso por NAC fueron excluidos. En estudios en los que no se consideró el tiempo transcurrido desde la vacunación del paciente realizados en EUA por Jackson et al., en Suecia por Hedlund et al. y en Canadá por Johnstone et al. se ha observado un mayor efecto protector de la VNP23 frente a la muerte en pacientes inmunocompetentes.[187–189] Sin embargo, High et al en EUA observaron cierta

efectividad en pacientes inmunocomprometidos, pacientes diana para ser vacunados debido a que tiene un mayor riesgo de muerte.[190]

En una metaanálisis realizado por Falkenhorst et al. en Alemania se observó que la efectividad de la VNP23 frente a la ENI y la neumonía neumocócica era significativa en las personas de edad avanzada, siendo los niveles de efectividad observados comparables a los de la efectividad obtenida con la VNC13.[180]

En nuestro estudio sólo 5 de los participantes refirieron haber recibido la VNC13, por lo que no pudimos estudiar la efectividad de la VNC13 sola o como parte de la pauta secuencial junto a la VNP23.

Actualmente los CDC recomiendan la pauta secuencial VNC13+VNP23 separado por un intervalo óptimo de 12 meses y un mínimo de 8 semanas a las personas de 65 años y más.[119] Sin embargo, en España se recomienda solo la VNP23 a las personas de 65 años y más si no presentan alguna condición de riesgo que indique la vacunación secuencial.

Los resultados del presente estudio junto a los de otros autores mencionados anteriormente, y al hecho de que la VPN23 incluye once serotipos frente a los que la VNC13 no protege, respaldan la indicación actual de la vacunación con VNP23 en personas de 65 años y más. Es necesario mantener destacar la importancia de mantener la vigilancia continua de los serotipos causantes de enfermedad en este grupo de edad para evaluar el potencial beneficio que podría suponer incorporar a las recomendaciones de vacunación actuales la VNC13.

6. Conclusiones

1. En pacientes de 65 años y más hospitalizados por NAC la tasa de reingreso en los 30 días posteriores al alta fue moderada, asociándose a factores predisponentes relacionados con el tipo de atención al paciente.

2. La evaluación combinada del *Pneumonia Severity Index* y el índice de Barthel predice con mayor precisión la mortalidad que la aplicación de cada escala por separado.

3. La utilización de un punto de corte de 90 puntos en el índice de Barthel para definir alguna dependencia indica que cambios leves en el estado basal funcional pueden tener un impacto en el pronóstico de la neumonía similar al obtenido por el *Pneumonia Severity Index*; un punto de corte >90 aumentaría la capacidad predictiva del modelo combinado.

4. La cobertura de vacunación antineumocócica en las personas de 65 años y más hospitalizadas por motivos distintos a la neumonía, enfermedad respiratoria aguda o enfermedad gripal es baja (43,8%). Deberían establecerse estrategias para aumentar dicha cobertura

5. Las coberturas de vacunación antineumocócica en las personas de 65 años y más que presentaban EPOC (57,7%) o insuficiencia respiratoria crónica (52,0%) fueron superiores a los del conjunto de pacientes estudiados.

6. La vacunación con VNP23 mostró una efectividad modesta para evitar la hospitalización por NAC en las personas de 65 años y más (15,2%: IC95%; -3,1-30,3) y del 40,9% (IC95%; 2,9-65,6) para prevenir ingreso a UCI o muerte.

7. Para valorar la conveniencia de posibles cambios en las recomendaciones de vacunación de las personas de 65 años y más es fundamental mantener una vigilancia continua de los serotipos causantes de la enfermedad neumocócica en esta población.

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8. Publicaciones relacionadas con el tema de la tesis que no forman parte de la misma

1. Torner N, Izquierdo C, Soldevila N, **Toledo D**, Chamorro J, Espejo E, Fernández-Sierra A, Domínguez A; Project PI12/02079 Working Group. Factors associated with 30-day mortality in elderly inpatients with community acquired pneumonia during 2 influenza seasons. Hum Vaccin Immunother. 2017;13:450-455.

2. Fernandez-Sierra MA, Rueda-Domingo MT, Rodriguez-Del-Aguila MM, Perez-Lozano MJ, Force L, Fernandez-Villa T, Astray J, Egurrola M, Castilla J, Sanz F, **Toledo D,** Dominguez A; Workgroup Project PI12/02079. Adaptation of antibiotic treatment to clinical practice guidelines in patients aged ⩾65 years hospitalised due to community-acquired pneumonia. Epidemiol Infect. 2018;146:1870-1877.