eman ta zabal zazu

Universidad del País Vasco

Euskal Herriko Unibertsitatea

PhD Thesis

Long-term mortality in hospitalized patients with community-acquired pneumonia.

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2016

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Nire bizitzari zentzua ematen dion pertsonari, Xarles.
Ezagutu nizun momentu horretan maite izan nizulako, gaur maite zaitudalako eta beti maite izango zaitudalako.

“La alegría está en la lucha, en el esfuerzo, en el sufrimiento que supone la lucha y no en la victoria”

Mahatma Gandhi

ACKNOWLEDGMENT

Me gustaría agradecer en primer lugar al Dr. Alberto Capelastegui, al que considero mi mentor en medicina, por enseñarme, entenderme e inspirarme cada día, lo que sin duda motiva mi admiración por su persona y por lo que siempre me sentiré en deuda con él.

Mi más sincero agradecimiento al Dr. Jose María Quintana por su tiempo, dedicación y rigor académico. A él le debo mi desarrollo y formación como profesional investigador. A Urko Aguirre he de agradecer y reconocer su empeño, tiempo y esfuerzo en este trabajo.

A mis compañeros de trabajo del Hospital de Galdakao-Usansolo, a todo ellos, por su colaboración y trabajo en equipo. Me gustaría hacer una mención especial al Dr. España, por sus contribuciones, dedicación y por adentrarme en el mundo de las infecciones.

A Isabel Urrutia y Silvia Pascual, por ser como sois, estar ahí y formar parte de mi vida.

To Louisville team, for guiding me in my research. Your ideas, help and encouragement have been absolutely invaluable.

A Xarles, por inflar globos conmigo cada día. Por todo el tiempo que esta tesis nos ha robado y el que nos queda por compartir.

A toda mi familia, la peña txoko, por haberme apoyado siempre. A mi padre, por consolarme en los malos momentos y exigirme en los buenos. A mi madre, por preocuparse, sufrir y disfrutar con mis logros. A mis hermanas, amigas a las que quiero, admiro y adoro. A tia Bego y Emilio, por ser parte de nuestra pequeña familia.

A mi *kuadri*, por hacerme reír y haberme enseñado el sentido de la amistad. A mis amigas del alemán, por quererme pase lo que pase y por todas esas conversaciones interminables.

ABBREVIATIONS

AC	Alcohol consumption
ATS/IDSA	American Thoracic Society and Infections Diseases Society of America
AUC	Area under the curve
BT	Body temperature
BUN	Blood urea nitrogen
CAP	Community-acquired pneumonia
CAD	Coronary artery disease
CHF	Congestive heart failure
CI	Confidence intervals
COPD	Chronic pulmonary obstructive disease
CPR	Clinical prediction rules
CRP	C-reactive protein
CURB-65	Confusion, urea, respiratory rate, blood pressure and age ≥ 65
CVD	Cerebrovascular disease
DBP	Diastolic blood pressure
HCAP	Healthcare associated pneumonia
HR	Heart rate
HR	Hazard ratio
ICU	Intensive care unit
IRCU	Intermediate Respiratory Care Unit
OR	Odds ratio
PCT	Procalcitonin
ProADM	Proadrenomedullin
PSI	Pneumonia severity index
RR	Respiratory rate
SCAP	Severe community-acquired pneumonia index
SEPAR	Spanish Pulmonology and Thoracic Surgery Society
SBP	Systolic blood pressure

CONTENTS

1. ABSTRACT

Community-acquired pneumonia (CAP) is a major problem of public health with high morbimortality. The annual incidence ranges between two and eight cases per thousand inhabitants. Together with influenza, it was the seventh cause of mortality in the United States in 2008. Short-term mortality rates are high in patients admitted for CAP. It is even higher in those admitted to intensive care units, and up to 50% if there is a need for vasopressors. On the other hand, long-term mortality rates remain high, with 8%, 21%, and 36% within 90 days, one year, and five years, respectively.

Several authors have created severity scores in order to predict short-term mortality. Fifteen-day mortality after diagnosis has been related to acute episodes. However, the relationship between pneumonia and long-term mortality is controversial. Patients admitted for pneumonia have exhibited higher long-term mortality rates than those admitted for other reasons. In addition, various studies have tried to identify predictive factors for long-term mortality. To date, severity scores for predicting one-year mortality in these patients have not been created. The main goal of this thesis was to assess one-year mortality in patients admitted for CAP. To that end, three studies were conducted with three different cohorts, and one-year mortality was the common independent variable in all those cases.

Firstly, a cohort of patients aged over 18 years admitted for CAP to the Galdakao-Usansolo Hospital was assessed from January 2001 to July 2009. One-year mortality after diagnosis was assessed using the computer support of the Public Health System of the Basque country. In this sense, since it was long-term mortality and, in order to alleviate the impact of the factors associated with short-term mortality, patients who had died up to 15 days after diagnosis were excluded from the study.

A total of 2,351 patients were included and divided into two cohorts, a derivation cohort with 1,208 patients and a validation cohort with 1,143 patients. After one year, 250 (10.63%) patients had died. Clinically relevant variables that could be related to one-year mortality were assessed, and those that were statistically significant in the univariate analysis were included in the multivariate analysis.

Age >80 years, heart failure, dementia, respiratory rate ≥30 breaths per minute, and blood urea nitrogen (BUN) >30 mg/dL were significantly related to one-year mortality.

A predictive model was created with a weighted score (one-year CAPSI) including five variables in order to predict one-year mortality. Patients aged over 80 years received four points, heart failure two points, dementia six points, respiratory rate ≥30breaths per minute two points, and BUN >30 mg/dL three points. Considering one-year CAPSI as a continuous variable, the C-index was 0.76 in the derivation cohort and 0.77 in the validation cohort. Thus, for each increase of one unit on the score, patients exhibited a hazard ratio of 1.24 for one-year mortality. When the score was categorized into three classes, patients of the derivation cohort that had between four and five points exhibited a hazard ratio for one-year mortality of 3.19, whereas those with more than five points exhibited a hazard ratio of 9.91. The existing scores for short-term mortality risk were compared with the new one-year CAPSI model for the prediction of one-year mortality. This new model showed better predictive ability than CURB65 and SCAP score.

In the second section of the present study, the role of some biomarkers for prediction of one-year mortality were assessed. In addition, the values of serial measurement of biomarkers for this prediction were assessed. Systemic inflammation in pneumonia has been discussed in recent years and the role of biomarkers has been crucial in these studies. It seems clear that patients with severe pneumonia exhibit higher levels of biomarkers at the time of diagnosis. These biomarkers can be used to identify those patients with high probability of developing complications or even dying. However, some biomarkers go beyond and are useful to even identify long-term mortality.

231 patients admitted for CAP between June 2008 and July 2009 were included and blood tests were obtained to study the biomarkers at the time of diagnosis and after 3-5 days when possible. The biomarkers assessed were C-reactive protein, procalcitonin, and proadrenomedullin (proADM). In the same way as in the previous study, those patients who had died within 15 days after diagnosis were excluded from the study (one-year mortality rate of 10.39%). High proADM levels at the time of diagnosis were significantly related to severity of the disease measured by means of the different prediction scores. Risk scores showed a high predictive accuracy for one-year mortality. However, biomarkers showed poor predictive accuracy for one-year

mortality and were not able to improve the prediction ability of risk scores for one-year mortality when added to the scores.

In a subanalysis carried out including all deaths up to one year, proADM showed the best predictive ability for one-year mortality (C-index 0.71) and, when added to the one-year CAPSI, the prediction ability of the score was significantly improved. On the other hand, the role of changes in proADM values from admission to 3-5 days was assessed. Once it was adjusted by proADM value at baseline, a decrease in proADM from the first 24 hours to 3-5 days was associated with a significantly reduced risk of death at one year. However, once it was also adjusted by severity of disease and proADM baseline value, only when all deaths within one year were analyzed was associated with a significantly reduced risk of death at one year, meaning that, based on our sample, its predictive ability is mainly for short-term mortality.

Finally, one-year mortality was assessed in an external cohort of patients with pneumonia. To that end, I spent three months in a center of international reference for pneumonia in the "Division of Infectious Diseases at the University of Louisville School of Medicine". There, I assessed retrospectively one-year mortality from a cohort of patients admitted for CAP at the “Louisville Veterans Affairs Medical Center” from June 2001 to November 2006. Since this cohort of patients consisted of war veterans with very particular characteristics, it was not possible to apply the score used in the first study and I carried out a specific analysis in this cohort.

455 patients admitted for CAP at the Louisville Veterans Affairs Medical Center were included in the analysis and the clinically relevant variables and their relationship with one-year mortality was assessed. A genetic algorithm was used to identify the best predictive model for one-and five-year mortality. It was found that 121 (27%) patients had died within one year, whereas 265 (58%) had died after five years. A model with the inclusion of the variables age greater than 75 years, cancer, heart failure, albumin below 3.5 mg/dL, <100,000/L or >400,000/L platelets, and dementia exhibited a predictive power of 0.77 (AUC) for one-year mortality. However, that same model showed little predictive power for five-year mortality.

In summary, short-term mortality in hospitalized patients with CAP has been widely assessed while less is known about long-term prognosis. The aim of this thesis was to assess one-year mortality in hospitalized patients with CAP. An easy-to-use risk score (one-year CAPSI) for one-year mortality was created based on the presence of five variables with a high predictive accuracy. On the other hand, proADM was useful, based on our sample, for the prediction of one-year mortality; though mainly explain by short-term mortality. In addition, a decrease in proADM from the first 24 hours to 3-5 days, adjusted by proADM value at baseline, was associated with a significantly reduced risk of death at one year. Finally, a specific score for one-year mortality was created for a cohort of patients admitted for CAP at the Louisville Veterans Affairs Medical Center. Future research should focus on the impact of inflammation on CAP prognosis at long-term follow-up.

1.1 LABURPENA

Komunitatean hartutako pneumonia (KHP) erikortasun eta hilkortasun handiko osasun publiko arazo garrantzitsua da. Urteko inzidentzia bi eta zortzi 1000 biztanlekoa da. Estatu Batuetan, gripearekin batera, zazpigarren heriotza kausa izan zen 2008an. Epe laburreko hilkortasuna KHP daukaten paziente ospitaleratuetan altua da eta are gehiago zainketa intentsiboko unitate batean ospitaleratzean, droga basoaktiboen beharra dagoenean hilkortasun tasa %50 igotzen delarik. Epe luzeko hilkortasuna ere, altua izaten jarraitzen du %8, %21 eta %36a, 90 egun ondoren, urte batera eta bost urtetara, hurrenez hurren.

Hainbat autorek larritasun eskalak garatu dituzte epe laburreko hilkortasunerako. Zentzu berean, lehengo 15 egunetan ematen diren heriotzak prosezu akutuarekin erlazionatu dira. Hala ere, pneumonia eta epe luzeko hilkortasunaren arteko erlazioa ez dako batere argi. Badirudi, pneumoniagatik ospitaleratutako pazienteek, hilkortasun tasa handiagoa dutela beste arazoengatik ospitaleratutakoak baino. Badira egile batzuk, epe luzeko hilkortasun aurresaleak identifikatzen saitu direnak. Hala ere, urtebeteko hilkortasuna aurreikusteko eskala espezifikoak ez dira garatu orain arte. Tesi honen helburu nagusia KHP daukaten paziente ospitaleratuetan urtebeteko hilkortasuna aztertzea izan zen. Horretarako, hiru azterketa desberdin garatu ziren, hiruretan urtebeteko hilkortasuna aldagai independientea izanik.

Lehenengo eta behin, 18 urte baino gehiagoko KHP zuten paziente ospitaleratuak urtarrileko 2001tik uztaileko 2009ra aztertu ziren. Urtebeteko hilkortasuna zehaztu zen ordenagailu bidezko euskal sistemaren bidez. Prozesu akutuak hilkortasunaren gain duen eragina ekiditziko, lehenego 15 egunetan eman ziren heriotza guztiak baztertu egin ziren.

2.351 paziente sartu ziren eta lagina bitan zatitu zen, 1.208 paziente deribazio laginean eta 1.143 paziente balidazio laginean hain zuzen ere. 250 (10.63%) paziente urtebeteko epean hil ziren. Klinikoki urtebeteko hilkortasunarekin garrantzia zuten aldagaiak aztertu ziren eta estadistikoki signifikatiboak izan zirenak, analisi multibariantean sartu ziren.

Adina > 80 urte, bihotz-gutxiegitasuna, dementzia, arnas tasa ≥ 30 arnas minutuko eta BUN > 30 mg/dL urtebeteko hilkortasunarekin estadistikoki erlazionatu zen. Bost

aldagaietan oinarritutako urtebeteko hilkortasunerako eredu iragarpen bat garatu zen (one-year CAPSI). 80 urte baino gehiago zutenek lau puntu jasotzen zituzten, bihotz-gutxiegitasuna zutenek puntu bi, dementzia zutenek 6, arnas tasa ≥ 30 arnas minutuko zuetenek bi puntu eta BUN > 30 mg/dL zutenek berriz, hiru puntu. One-year CAPSI, etengabeko aldagaia bezela hartuta, C-indexa 0.76 izan zen deribazio laginean eta 0.77 balidazioan. Eskala puntu gehikuntza bakoitzeko, urtebeteko hilkortasun arriskua 1.24 (HR) zen. Eskala hiru zatitan banatzerakoan, hiru eta bost puntu arteko puntuazioa jasotzen zuten pazienteen urtebeteko hilkortasun arriskua 3.19 (HR) zen, bost puntu baino gehiago jasotzen zutenenen arriskua berriz, 9.91(HR) zen. One-year CAPSI, egungo eskalekin konparatu egin zen eta CURB65 eta SCAP eskalak baino iragarpen ahalmen handiagoa erakutsi zuen urtebeteko hilkortasunerako.

Bigarren atal honetan, biomarkadore batzuk aztertu ziren urtebeteko iragarpenean. Azkenengo boladan, pneumonian ematen den inflamazioa asko neurtu da eta biomarkadoreak garrantzi handikoak bilakatzen ari dira arlo honetan. Biomarkadoreen erabilera gaixotasunaren larritasuna neurtzeko eta epe laburreko konplikazioak iragartzeko argi dago. Gainera, badira biomarkadoreak epe luzeko pronostikoan ere erabilgarriak direnak.

Ekainaren 2008tik uztailaren 2009ra odol laginak lortu ahal izan ziren eta KHP zuten 231 paziente ospitaleratuak aztertu ziren. Odol laginak diagnostikoaren momentuan lortzen ziren eta hirugarren eta bostgarren egunen artean ere ahal izanez gero. Aztertutako biomarkadoreak proteina C erreaktiboa, prokaltzitonina eta proadrenomedulian (proADM) izan ziren. Lehenengo estudioan bezala, lehenengo 15 egunetako heriotzak analisitik kanpo geratu ziren (10.39%).

ProADM balio altuak gaixotasunaren larritasunarekin, larritasun eskalen bidez neurtua erlazionatu zen. Larritasun eskalak urtebaterako iragarpen balio handia erakutsi zuten. Biomarkadoreak, aldiz, iragarpen baxua izan zuten urtebeterako, gauza bera gertatzen zelarik behin biomarkadoreak eskalei gehituta. Aldi berean, beste analisi bat egin zen diagnostiko momentutik urtebeterarte heriotza guztiak barne hartuta. ProADM urtebeterako iragarpen altua izan zuen C-index 0.71rekin eta are gehiago,

one-year CAPSIri gehitzean, eskalaren iragarpen balioa handitu egin zen. Beste alde batetik, proADMren aldaketak aztertu ziren diagnostiko momentutik hiru-bostgarren egunera. Behin ProADM lehendabiziko balioagatik egokituta, proADM murrizketa diagnostikoko momentutik hirugarren-bostgarren egunera, urtebeteko hilkortasunaren murrizketarekin estadistikoki erlazionatu zen. Hala ere, lehendabiziko balioagatik aparte gaixotasunaren larritasunagatik egokitzerakoan, urtebeteko hilkortasunaren murrizketa heriotza guztiak barne zituen analisian bakarrik frogatu ahal izan zen. Ondorioz, behintzat gure paziente laginean, proADMak urtebeteko iragarpen balioa dauka baina batez ere, epe laburreko hilkortasuna dela-eta.

Azkenik, KHP zuten ospitaleratutako pazienteen urtebeteko hilkortasuna kanpoko lagin batean aztertu zen. Horretarako, hiru hile egon nintzen pneumonia arloan internazionalki ezaguna den zentru batean, Division of Infectious Diseases at the University of Louisville School of Medicine. Han nengoela, erretrospektiboki aztertu genituen 2001eko ekainatik 2006ko azarorarte KHPgatik ospitaleratutako pazienteak Louisvilleko *Veterans Affairs Medical Center*eko ospitalean. One-year CAPSI lagin honetan erabilia izan zenean, huts egin zuen urtebeteko iragarpenean, batez ere, laginen arteko desberdintasunengatik. Izan ere, guda zibilean izandako pertsonentzako ospitalea da eta horrek, ezaugarri espezifikoak izatea eragiten bait du. KHP rekin Kentuckyn, Louisvilleko *Veterans Affairs Medical Center*ean ospitaleratutako 455 paziente aztertu ziren. Algoritmo genetiko bat erabili zen urtebeteko eta bost urteko hilkortasunerako eredu iragarpen onenak zehazteko. 121 (%27) eta 265 (%58) paziente hil ziren urtebetera eta bost urtetara, hurrenez hurren. Adina > 75 urte, minbizia, bihotz-gutxiegitasuna, dementzia, albumina <3.5 mg/dL eta plaketak <100,000/L o >400,000/L kontuan hartutako ereduak, iragarpen balio handia izan zuen, 0.77 (AUC). Hala ere, eredu berak huts egin zuen bost urteko hilkortasuna iragartzeko erabilia izan zenean.

Laburbilduz, epe laburreko hilkortasuna luze eta zabal ikertu da, epe luzeko hilkortasunari buruz, berriz, gutxiago dakigu. Tesi honen helburu nagusia KHPgatik opstaleratutako pazienteetan urtebeteko hilkortasuna aztertzea izan zen. Horretarako, errez erabiltzeko eta bost aldagietan oinarritutako potentzia handiko iragarpen eredu bat garatu zen. Beste alde batetik, proADM erabilgarria izan zen urtebeteko hilkortasuneko iragarpenean, batez ere, epe laburreko hilkortasunagatik azalduta.

ProADM murrizketa diagnostikoaren momentutik hirugarren-bostgarren egunera, behin proADM hasierako balioagatik egokituta, urtebeteko hilkortasunaren murrizketarekin erlazionatu zen. Bukatzeko, urtebeterako iragarpen eredu espezifikoa garatu zen Kentucky, Louisvilleko *Veterans Affairs Medical Center*ean. Etorkizuneko ikerketek inflamazioaren eragina pneumoniaren epe luzeko pronostikoarengan aztertu behar zuketeen.

1.2 RESUMEN

La neumonía adquirida en la comunidad (NAC) es un importante problema de salud pública con una elevada morbi-mortalidad. La incidencia anual oscila entre dos y ocho por cada 1000 habitantes. En Estados Unidos, junto con la gripe, fue la séptima causa de mortalidad en 2008. La mortalidad a corto plazo de los pacientes ingresados por NAC es elevada siendo aún mayor en aquellos pacientes que requieren un ingreso en una unidad de cuidados intensivos y de hasta un 50 % en los que necesitan drogas vasoactivas. Más allá, la mortalidad a largo plazo persiste siendo elevado a los 90 días, al cabo de uno y cinco años con tasas del 8%, 21% y 36%, respectivamente.

Diversos autores han elaborado escalas de gravedad para mortalidad a corto plazo. En este sentido, la mortalidad a 15 días tras el diagnóstico se ha relacionado con el episodio agudo. Sin embargo, la relación entre la neumonía y la mortalidad a largo plazo no está del todo esclarecida. Los pacientes ingresados por neumonía padecen una mortalidad a largo plazo mayor que aquellos ingresados por otros motivos. Algunos autores han tratado de identificar los factores predictores de mortalidad a largo plazo. Sin embargo, hasta la fecha, no se han elaborado escalas de predicción específicas para la mortalidad a un año en estos pacientes. El principal objetivo de esta tesis fue evaluar la mortalidad a un año en pacientes ingresados por NAC. Para ello, se llevaron a cabo tres estudios en tres diferentes cohortes siendo la mortalidad a un año la variable independiente en todos los casos.

En primer lugar, se evaluó una muestra de pacientes mayores de 18 años ingresados por NAC desde enero de 2001 hasta julio de 2009. Se determinó la mortalidad a un año mediante el soporte informático del sistema vasco de salud. Al tratarse de mortalidad a largo plazo y tratando de evitar el impacto del episodio de agudo sobre la mortalidad, se excluyeron los muertos de los 15 primeros días desde el diagnóstico.
Se incluyeron un total de 2.351 pacientes dividiéndose la muestra en dos, una muestra derivación con 1.208 paciente y otra validación con 1.143. 250 (10.63%) pacientes fallecieron al cabo de un año. Se evaluaron las variables clínicamente relevantes que pudieran estar asociadas con la mortalidad a un año y aquellas que resultaron estadísticamente significativas en el análisis univariante se incluyeron en el análisis multivariante.

La edad >80 años, la insuficiencia cardíaca, la demencia, la frecuencia respiratoria ≥30 respiraciones por minuto y el BUN>30 mg/dL se relacionaron de forma significativa con la mortalidad a un año. Se elaboró un modelo de predicción para la mortalidad a un año mediante una escala ponderada (one-year CAPSI) basada en cinco variables. Aquellos pacientes mayores de 80 años obtenían cuatro puntos, la insuficiencia cardíaca dos puntos, la demencia seis puntos, la la frecuencia respiratoria ≥30 respiraciones por minuto dos puntos y el BUN>30 mg/dL tres puntos. Considerando one-year CAPSI en su forma continua, presentó un C-index de 0.76 en la muestra derivación y de 0.77 en la muestra validación. Por cada incremento en un punto en la escala, los pacientes presentaban un *hazard ratio* de 1.24 para la mortalidad a un año. Al categorizar la escala en tres clases, aquellos pacientes de la muestra derivación que obtenían entre tres y cinco puntos, presentaban un una probabilidad 3.19 (HR) veces mayor de muerte al cabo de un año, mientras que en aquellos con más de cinco puntos era 9.91(HR) veces mayor. Se comparó one-year CAPSI con las escalas existentes en la actualidad en su poder predictivo para la mortalidad a un año, siendo one-year CAPSI superior que las escalas CURB65 y SCAP.

En la segunda parte de este trabajo, se evaluó el papel de algunos biomarcadores para la predicción de mortalidad a un año. Además, se pudo evaluar el valor de los biomarcadores obtenidos en el seguimiento para la mortalidad a un año. Recientemente, se ha estudiado la inflamación sistémica en la neumonía con un papel primordial de los biomarcadores. Parece claro que niveles elevados de ciertos biomarcadores se relacionan con una mayor gravedad de la neumonía y de ahí su utilidad para la detección de complicaciones o la muerte. Sin embargo, algunos biomarcadores van más allá pudiendo incluso predecir la mortalidad a largo plazo.

Se analizaron 231 pacientes con diagnóstico de NAC entre junio de 2008 y julio de 2009 en los que se pudo obtener muestras sanguíneas para el análisis de biomarcadores en el momento del diagnóstico y a los tres cinco días en algunos de ellos. Los biomarcadores analizados fueron la proteína C reactiva, la procalcitonina y al proadrenomedulina (proADM). De la misma manera que en el primer estudio, se

excluyeron los pacientes fallecidos en los 15 primeros días desde el diagnóstico (10.39%).

Niveles elevados de proADM se relacionaron de forma significativa con la gravedad en el momento del diagnostico medido por las escalas de gravedad. Las escalas de gravedad mostraron una elevada capacidad predictiva para la mortalidad a un año. Sin embargo, los biomarcadores presentaron un escaso poder predictiva para la mortalidad a un año y tras añadir la proADM a las escalas, la capacidad predictiva no mejoró. En un subanálisis realizado incluyendo todos los muertes desde el diagnóstico hasta el año, la proADM fue el biomarcador que mejor predijo la mortalidad a un año con un C-index de 0.71. Asimismo, al añadirlo a one-year CAPSI la capacidad predictiva mejoró significativamente. Por otro lado, se evaluó el papel del cambio de los niveles de proDAM desde el momento del diagnóstico a los 3-5 días. Tras ajustar por el valor de proADM en el momento del diagnóstico, una reducción de los niveles de proADM desde el diagnóstico a los 3-5 días se asoció de forma significativa con una reducción de la mortalidad a un año. Sin embargo, tras ajustar por gravedad de la enfermedad además de por el valor basal de proADM, únicamente cuando todos los muertos fueron incluidos se asoció con una disminución de la mortalidad a un año. Por lo tanto, basándose en nuestra muestra, la capacidad predictiva de mortalidad de la proADM consiste principalmente en la predicción a corto plazo.

Por último, se evaluó la mortalidad a un año en una muestra externa de pacientes con NAC. Para ello, realicé una estancia de tres meses en un centro de referencia internacional en neumonías, Division of Infectious Diseases at the University of Louisville School of Medicine. Una vez allí, evalué de forma retrospectiva la mortalidad a un año de una muestra de pacientes ingresados por NAC desde junio de 2001 a noviembre de 2006, en el hospital “Veterans Affairs Medical Center of Louisville”, en Louisville, Kentucky. Se trató de replicar one-year CAPSI en dicha muestra sin éxito por tratarse de una muestra muy peculiar con pacientes veteranos de guerra con características sociodemográficas y clínicas muy específicas.

Se analizaron 455 pacientes ingresados por NAC en Veterans Affairs Medical Center de Louisville, Kentucky, y se evaluaron las variables clínicamente relevantes con la

mortalidad a un año. Se utilizó un algoritmo genético para determinar el mejor modelo predictivo de mortalidad a uno y cinco años. 121 (27%) pacientes fallecieron a un año y 265 (58%) a los cinco años. Un modelo incluyendo la edad mayor de 75 años, el cáncer, la insuficiencia cardiaca, demencia, albumina <3.5 mg/dL y plaquetas <100,000/L o >400,000/L presentaron una capacidad predictiva de 0.77 (AUC). Sin embargo, el mismo modelo presentó una débil capacidad predictiva para la mortalidad a los cinco años.

En resumen, la mortalidad a corto plazo en pacientes ingresados por NAC ha sido ampliamente estudiada mientras que el pronóstico a largo plazo no está del todo establecido. El objetivo de esta tesis fue evaluar la mortalidad a un año en pacientes ingresados por NAC. Para ello, se elaboró una escala de fácil implementación basada en cinco variables con un elevado poder predictivo. Por otro lado, a proADM fue de utilidad para la predicción de mortalidad a un año aunque principalmente explicado por la mortalidad a corto plazo. Asimismo, un descenso de los niveles de proADM desde el momento del diagnóstico a los 3-5 días, ajustado pro el valor basal de la proADM, se asoció con una reducción de la mortalidad a un año. Finalmente, se elaboró una escala específica para la mortalidad a un año en una muestra de pacientes ingresados por NAC en Veterans Affairs Medical Center de Louisville, Kentucky. Las investigaciones futuras deberían centrar sus esfuerzos en el impacto de la inflamación en el pronóstico a largo plazo de la NAC.

2. INTRODUCTION

2.1 Definition

The term “infection” comes from the vernacular language of the Romans: "*in-fec*" = enter, mix; and "*tion(em)*" = action. Derived from the verb "*inficere*" (stain, corrupt), its pathological value was used for the first time in medieval Latin. The word “pneumonia” is a medieval term and comes from the Greek *pneumonia* or *pleumonia*. This term was not used by the Greek physicians but by Plutarch in the second century AD, and subsequently used in English in 1603.

Pneumonia is defined as an infection of the pulmonary parenchyma associated with infiltrates on chest radiograph, which did not exist previously, and the presence of two or more breathing symptoms, such as fever, cough, expectoration, dyspnea, and pleuritic pain (1). Pneumonia can be caused by different microorganisms giving place to entities with different physiopathology, clinical picture, and prognosis, which in addition require specific treatments. Because of the disparity between the different forms, there are multiple classifications which give rise to a more global view and a better understanding of the disease (2).

Pneumonia can be classified according to the type of host and can affect immunocompetent or immunocompromised patients. On the one hand, the underlying etiologic agent is completely different and factors such as the type of immunosuppression or its intensity help in the etiologic diagnosis of presumed pneumonia. Each entity requires a different management with specific therapeutic attitudes and different prognosis.

When the disease affects the general population, it is called community-acquired pneumonia (CAP) and differs from that found in patients admitted to hospitals who, in the majority of cases, have a worse prognosis. The latter is defined as one that develops in patients hospitalized for more than 48 hours and that was not incubating at the time of admission. The American guidelines for nosocomial pneumonia incorporated the term healthcare-associated-pneumonia (HCAP) (3). Risk factors of this type of pneumonia include pathogens which are multidrug-resistant due a prior contact with healthcare and that may occur inside or outside hospitals. These risk factors include patients admitted in the last 90 days, those admitted to nursing homes

or other centers for chronic disease care, those receiving intravenous treatment at home, patients on chronic dialysis, and patients in contact with a family member with a multidrug-resistant pathogen. However, drug resistant pathogens can arise either in CAP or HCAP and it can be predicted by taking into account the cumulative number of the risk factors (4).

Another factor to take into account is anatomical involvement, which can be characterized by lobar pneumonia, bronchopneumonia, necrotizing pneumonia, lung abscess, or interstitial pneumonia. On the other hand, pneumonia can be classified by the causal agent. However, in the great majority of cases, the pathogen is not known at the time of diagnosis, what makes this classification little feasible in the clinical practice.

Finally, CAP has been classically catalogued as typical or atypical pneumonia according to the clinical picture and radiological findings. The atypical form usually emerges in a subtle manner, with little fever, non-productive cough. and with segmental and interstitial patchy infiltrates. The typical CAP is characterized by the presence of fever, involvement of the general state, and symptoms attributable to the respiratory system, such as cough, expectoration, dyspnea, and pleuritic chest pain.

In the same way, bacteria have been defined as typical and atypical. Among others, *Streptococcus pneumoniae*, *Haemophilus influenza*, and *Moraxella catarrhalis* were included in the first group. On the other hand, *Legionella pneumophila*, *Mycoplasma pneumonia*, and *Chlamydia pneumoniae* were included in the atypical group, even though this classification is in disuse. In addition, most of the time, it is not possible to identify the etiologic agent. Despite the microbiological definition of CAP, it is usually a syndromic diagnosis with the presence of a compatible clinical picture and a pulmonary infiltrate observed on the chest radiograph.

Under normal conditions, there is a balance between the host-microorganism interaction and, when it is disrupted, the infection occurs with the consequent activation of defense mechanisms, whose main function is to reduce the damage and restore homeostasis. Recently, new definitions have been published by "The Third International Consensus Definitions for Sepsis and Septic Shock", understanding the

concept of sepsis as the dysfunction of an organ that threatens life as a result of an aberrant or unregulated host response to the infection (5). In clinical practice, organ dysfunction can be measured through the Sequential Organ Failure Assessment with excess mortality greater than 10% in those patients with scoring over 2 points. When sepsis is combined with vasopressor requirement to maintain a mean arterial pressure of 65 mmHg or greater and a serum lactate level greater than 2 mmol/L (>18 mg/dL) in the absence of hypovolemia, it is called septic shock, and the combination of both conditions is associated with in-hospital mortality greater than 40%.

The severity of these patients has been discussed in the last decade. When CAP is severe, there is a critical situation characterized by a high short-term mortality rate, which, in addition, persists with a high long-term mortality rate (5). The early identification of severe patients with high probability of suffering complications, even in the long term, is fundamental for the implementation of strategies to improve their prognosis.

2.2 Epidemiology

The incidence ranges between two and eight cases per 1,000 inhabitants a year, although its real estimate is difficult due to the variability of the information obtained from studies (7). This incidence increases at the end of life of individuals with comorbidities and is slightly higher in men (8).

In the United States, the annual incidence in adult patients admitted for CAP was 248 cases for 100,000 inhabitants between 2010 and 2012. This incidence increased with age, i.e., 630 cases per 100,000 inhabitants (65-79 years) and 1,640 cases per 100,000 inhabitants (≥80 years) (9). A retrospective study conducted in Spain between 2003 and 2007 with hospitalized patients aged 50 years or older, and information retrieved from the Minimum Basic Dataset showed an annual incidence of 627 cases per 100,000 inhabitants (10).

CAP is responsible for 5 to 12% of respiratory infections and represents the first infectious cause that explains hospital admission. At the same time, it is an issue of

great relevance due to the high direct and indirect costs that it generates (8,10). Admission rates varies by country, study period time and study design. A study conducted in Biscay, in the reference area of the Galdakao-Usansolo hospital covering 300,000 inhabitants, estimated a CAP incidence of 3.1 per 1,000 adults per year, whereas 43.5% of patients attending the Emergency Department required hospital admission (11).

Recently, Huang et al. (12) published the cost and use of health resources in the United States. The study was conducted between 2004 and 2005 and assessed data of pneumococcal disease in both hospitalized patients and outpatients. The authors observed four million cases of pneumococcal disease with a direct cost of 2.5 billion dollars. The greatest severity and, accordingly, the highest cost were observed in patients aged over 65 years. However, when the authors assessed the loss of work days and productivity (indirect cost) among patients aged 18 to 50 years, the cost was equal to that of patients aged over 65 years.

Similarly, a study conducted in Spain showed that the average direct cost for the treatment of hospitalized patients was 2,332 Euros, whereas for outpatients the average cost was 698 Euros (13).

2.3 Long-term prognosis of community-acquired pneumonia

2.3.1 Magnitude of the problem

CAP is considered a major problem of public health due to its high morbimortality (14). According to data of the National Statistical Institute, 4,254 men and 3,998 women died from pneumonia in 1999 in Spain. The mortality rate in 2002 was 19.5 per 100,000 inhabitants, ranking as the ninth cause of death in Spain (15). In 2008, together with influenza, pneumonia was the seventh cause of mortality in the United States with 59,000 deaths in that year (16).

To a large extent, mortality depends on the place where the patients are treated. In outpatients, the rate is less than 3%, in patients admitted to a conventional unit, the

rate ranges from 5 to 10%, whereas in those patients who require admission to an intensive care unit amounts to 25% if they require orotracheal intubation and up to 50% if they require vasopressors (17).

Patients with pneumonia have a high risk of complications during the episode, such as requiring mechanical ventilation and vasopressors, or developing multiorgan failure. Most studies published to date have studied the relationship between pneumonia and short-term mortality. This way, some authors affirm that death related to the pneumonia episode mostly occurs within the first 15 days (18,19).

There are various factors associated with short-term mortality. The most accepted are etiology, comorbidities and the form of the disease. In most cases, the etiologic diagnosis is unknown. However, there are factors that can influence in a predominant manner on the appearance of the microorganism, such as geographic areas, age, residing in nursing homes, and comorbidities. This way, in those patients with *Pseudomonas aeruginosa* pneumonia, mortality ranges around 61%, whereas in pneumonia caused by enterobacteria mortality will be 35% and in pneumonia produced by *Legionella* or *Streptococcus pneumoniae* 15% (17). However, the most frequent germ in all series and areas is *Streptococcus pneumoniae* and, in this case, severity is influenced by factors such as bacteremia, bacterial load, serotypes, antimicrobial resistances, and comorbidities (20).

The incidence and severity of CAP is greater in patients with chronic respiratory diseases, since their capacity to respond to external aggressions is decreased (21). Similarly, there are various diseases that increase the probability of suffering from CAP, and some have been associated with a worse prognosis, such as cancer, neurological diseases, and diabetes mellitus (21).

The factors associated with increased short-term mortality due to pneumonia are multiple. A meta-analysis conducted by Fine et al. (17) included 33.148 patients and identified 11 variables associated with increased mortality, namely: male individuals; advanced age; neurological diseases; neoplasms; diabetes mellitus; hypothermia; tachypnea; hypotension; leucopenia; bacteremia; and multilobar involvement on chest radiograph. The global mortality of these patients was 13.7%, and the variables were:

age; comorbidities; and clinical, analytical, and radiological findings. All these factors were included in the severity score known as Pneumonia Severity Index (PSI).

Therefore, the short-term prognosis for CAP seems to be well established. However, there are data indicating that patients who survive a pneumonia episode have a high mortality rate, even in the medium and long term, with figures of 8, 21, and 36% after 90 days, one year, and five years, respectively (22). Despite the improvement in the diagnostic methods and the use of new and more effective broad-spectrum antibiotics, the picture does not seem to have changed substantially.

Often, an acute condition in older adults that requires hospitalization implies a subsequent clinical worsening. Recently, the need for hospital admission has been related to a higher mortality rate after one year in patients admitted for any reason. In this sense, Walter et al. (23) published a study in The Journal of the American Medical Association in 2001 in which they created an easy procedure to stratify individuals aged over 70 years into risk groups according to the risk of death after being admitted to hospital by any cause. The authors assessed a cohort of 3,163 patients and identified six variables (sex, congestive heart failure, cancer, previous functional state, creatinine, and albumin) as predictors of one-year mortality with an area under curve (AUC) of 0.75 in the derivation cohort and 0.79 in the validation cohort. Therefore, both were over the scores already known and well established for the prediction of one-year mortality, as the Charlson Index Score or Acute Physiology and Chronic Health Evaluation (APACHE), with AUC of 0.68 and 0.59, respectively.

Levine et al. (24) created and validated a similar prognostic index without the need for complementary evidence and using only data obtained from computer support with similar results, although with lower AUC values. Some authors have gone beyond creating scores to even predict 4-year mortality in outpatients and obtained good results.

Kaplan et al. (25) assessed patients admitted for pneumonia and found that in-hospital mortality rate was the half in the control group compared with the CAP group. One-year mortality after hospital discharge and adjusted for comorbidities was 33.6% among those patients who had been discharged with a diagnosis of CAP *versus*

24.9% in the control group without CAP (p = 0.001). In the control group, mortality increased with age and comorbidities; however, mortality in the CAP group persisted and was significantly more elevated. Bourdon et al. (2010) conducted a 7-year follow-up assessing 6,971 admitted patients retrospectively, of which 624 had diagnosis of CAP. Patients admitted for CAP were 40% more likely to die than those admitted for other reasons with a hazard ratio of 1.4.

Mortensen et al. (22) conducted a study included in the Patient Outcomes in Renal Transplantation (PORT) study and assessed admitted patients and outpatients (n = 1,555) with a diagnosis of CAP and a 5.9-year follow-up. The authors compared long-term mortality among those who had survived after 90 days of the episode with a control group of similar age. They observed that patients with CAP died more frequently and with significant differences. A recent study assessed a German cohort and described mortality after a CAP episode within one, five, and seven years with 17, 43, and 53%, respectively, compared with 4, 19, and 24% in a reference cohort with similar age and sex (26).

In the same vein, Yende et al. (27) assessed patients aged 70 to 79 years admitted to hospital for various reasons. The authors described that one third of patients admitted for CAP died after five years. In addition, they observed one-and five-year mortality, which was similar to mortality in those patients admitted for heart failure, cerebrovascular disease, or fracture; however, those rates were lower than mortality in patients admitted for cancer. The authors found an association between admission for CAP and 5-year mortality, independent of previous comorbidities.

A comprehensive Finnish study conducted during 12 years found that the mortality rate in survivors to CAP episodes was the double compared to mortality in those patients who had not suffered pneumonia, and it was even more elevated if the patients had suffered pneumococcal pneumonia (28).

More recently, Eurich et al. (29) compared 6,078 patients with CAP with 29,402 control patients matched for age, sex and site of treatment with a 10-year follow-up in Canada. The authors observed a greater mortality rate in the group with pneumonia,

even when they assessed admitted patients and outpatients with CAP separately and having excluded patients deceased until the first 90 days.

Therefore, these results make it clear that patients with CAP have increased mortality rates, also in the long term. However, the influence that the interaction between acute episodes and the various comorbidities and conditions may exert should be assessed carefully. Therefore, this disease is considered a major problem of public health and should be the subject of further investigations in order to optimize its management and, undoubtedly, improve its prognosis.

2.3.2 Causes of mortality

Mortensen et al. (30) reported 208 (9%) deaths after 90 days in a cohort of more than 2,000 patients with CAP from the PORT study. The most frequent intermediate cases were respiratory failure, cardiac conditions, and infectious diseases in decreasing order. On the other hand, once the underlying causes of death were assessed, neurological conditions, malignancies, and cardiac conditions were the most frequent in decreasing order. Moreover, the authors found that age and aspirations were predictors of the two types of mortality.

Bruns et al. (26) conducted a prospective observational study assessing patients with CAP and identified neoplasia as the most frequent cause of death (27%), followed by chronic obstructive pulmonary disease (19%), and cardiovascular disease (16%). Indeed, when compared to the general Dutch population, not only patients with CAP had higher mortality rates after one, five and seven years, but also had four times increased risk to have chronic obstructive pulmonary disease as their cause of death. Nevertheless, the fact that patients with chronic obstructive pulmonary disease have a higher incidence of CAP may lead to bias. In contrast, cardiovascular events have been postulated to contribute to more tan 30% of deaths in patients with CAP in the long term (31).

More recently, Adamuz et al. (32) assessed 1,284 patients discharged after a CAP episode and 7.2% of them died within a year. The authors found that comorbidity

conditions, rehospitalization within 30 days after discharge, and nursing home residence were independently associated with one-year mortality after hospital discharge. More interestingly, they determined causes of death and observed that infectious diseases were the main reason for one-year mortality, followed by acute cardiovascular events. Moreover, the mortality rate caused by infectious diseases was higher during the first six months and decreased progressively after that moment while cardiovascular events were stable throughout the follow-up.

Therefore, several authors suggest that high long-term mortality rate in patients with CAP could be due to a persistent inflammatory response after hospital discharge or even cardiovascular or neoplastic diseases that were not previously known and emerged after the episode.

2.3.3 Predictive factors of mortality

Age

The number of individuals aged over 65 years has increased in recent years and that number is expected to rise from 12% in 2000 to 20% in 2030, and even reaching the double in 2050 (33). In general, the older adult population suffers from a greater number of comorbidities and the functional status is often poor.

Hedlund et al. (34) suggested that the mortality rate increased after three years of a CAP episode and was even higher in patients aged over 50 years. However, Bracanti et al. (35) published a study with 141 patients admitted for CAP comparing different age groups with the group aged between 18 and 44 years. The differences found for 2-year mortality were not significant. The authors concluded that age was not associated with mortality and that the important factor was not the chronological age, but the physiological age.

Numerous articles published afterwards differ from Bracanti's findings and highlight age as one of the main predictors of mortality. What still remains to be clarified is the cut-off point at which age begins to be a risk factor. Some studies use 50 years,

whereas authors such as Sligl et al. (36) have used 70 years as a cut-off point. In a Canadian group, in which the authors compared a CAP group with a control group, they described a lowest absolute rate difference for mortality among patients aged <25 years, whereas patients aged >80 years had the highest absolute rate difference (29). However, the hazard ratio was higher in the first group (2.40 *vs*. 1.42).

Sex and race

Most studies point out that the male sex is associated with higher mortality rates (25,22,37). Similarly, some authors found an alarming difference regarding race, with increased 2-year mortality rate in black individuals compared with white individuals. In addition, this difference remained when the reason for admission was another, such as heart failure or cerebrovascular accident, among others (38).

Healthcare-associated-pneumonia (HCAP)

The definition of HCAP includes: patients hospitalized in an acute care hospital for two or more days within 90 days of infection; resided in a nursing home or long-term care facility; received recent intravenous antibiotic therapy, chemotherapy or wound care within the past 30 days of the current infection; attended a hospital or a hemodialysis clinic; or had a family member with a drug resistant pathogen. Nursing homes and long-term care facilities have been assessed as risk factors for drug-related problems.
An increasing prevalence of pneumonia caused by drug-related problems have been identified. The guidelines provided by the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA) in 2005 proposed a HCAP model in order to identify the increased risk of drug-related problems in patients from the community (3). These patients are known to have a worse prognosis, mostly due to poor functional status and treatment restrictions (39). Patients residing in nursing homes and long-term care facilities have an increased risk of death due to advanced age, high number of comorbidities, and poor functional status. Solh et al. (40) assessed 88 nursing home patients with severe pneumonia confirmed by culture and showed that both previous use of antibiotics and poor functional status were risk factors for drug-related problems. In that study, *S. aureus* was the predominant isolated pathogen (31%), followed by enteric gram-negative bacilli (28%), and *S.*

pneumoniae (25%). Nevertheless, other authors have described similarities in pathogen distribution between nursing home-acquired pneumonia and CAP (41). Part of the explanation for this heterogeneity may be the differences found when nursing homes or skilled nursing facilities are assessed in different countries.

In addition, the definition of HCAP has shown several limitations to identify drug-related problems in patients with CAP, especially outside the USA. Therefore the characteristics and functional status of patients classified as "nursing home residents" may be very different from one country to another.

In order to identify the factors associated with mortality and compare the differences between CAP and HCAP, Cecere et al. (42) conducted a study with 486 patients admitted for the two pathologies. Survival after two years was lower in patients aged under 65 years with HCAP than in patients aged over 65 years with CAP.

Disease severity

The majority of the scores created to date were intended to measure short-term complications. The CURB65 (confusion, urea, respiratory rate, blood pressure, and age >65) and the PSI score have proven to be useful in the prediction of 30-day mortality. At the time of making a long-term prognosis, authors such as Sligl and Johnstone (36,37) identified that those patients with higher PSI scores had greater one-and five-day mortality rates, respectively. This result may be due to the fact that, unlike the CURB65, the PSI score includes comorbidities such as heart failure, cancer, liver disease, kidney disease, and cerebrovascular disease among its variables. However, the CURB65 and the PSI scores have been recently assessed for long-term mortality in a 6-year follow-up study conducted with patients with CAP and the two scores exhibited excellent predictive accuracy, PSI being the best one though (43). It is worth noting that the two scores include blood urea nitrogen (BUN) among their variables. BUN has been associated with increased mortality among critically ill patients, independently of serum creatinine (44). Currently, BUN has not only been incorporated to risk scores for predicting pneumonia, but also to models for predicting myocardial infarction (45).

Capelastegui et al. (46) created a 90-day mortality prognostic index based on pre-illness functional status measured by Katz index, comorbid conditions measured by Charlson Index Score, and disease severity measured by CURB65 without considering age as a variable. Mortensen et al. (22) assessed long-term mortality among patients included in the Pneumonia Patient Outcomes Research Team (PORT) cohort study after excluding deaths up to 90 days after occurrence of CAP. The authors found that age, nursing home residence, and comorbid conditions were more strongly associated with long-term mortality rather than acute physiologic or laboratory findings. However, PSI risk classes were significantly associated with decreased long-term survival in this cohort with 5.9-year follow-up.

Recently, easy-to-use scores such as CURB65 and CRB65 have been compared with Charlson comorbidity index for one-year mortality prediction after a CAP episode with disappointing results (47). All the receiver operating characteristic (ROC) curve analyses showed a weak and comparable performance of the three indexes (AUC <0.70). However, it is worth noting that these two easy-to-use indexes showed similar predictive accuracy than the complex comorbidity index.

Other analyses have been proposed to be associated with long-term mortality after a CAP episode. Bracanti et al. (35) published a study conducted with 141 patients admitted for CAP and found that hematocrits and comorbidities were predictive factors of 2-year mortality. This way, it seems that not only comorbidities have an impact on long-term mortality, but also disease severity *per se* may have a role in long-term prognosis.

Comorbidities

Multiple comorbidities, such as cerebrovascular disease, cardiovascular disease, neoplasms, HIV, chronic obstructive respiratory disease, and deterioration of the functional state, have been associated with increased mortality in patients with CAP (25,27,37). Koskela et al. (48) assessed 245 patients with CAP of which 152 survived after 30 days and were followed up for five years. These authors found that patients suffering from diabetes died less frequently compared to those without diabetes with

new postprandial hyperglycemia and those without diabetes with no postprandial hyperglycemia (p <0.001).

The previous functional state seems to significantly influence on the mortality of these patients. Authors such as Sligl (36) related previous functional state to one-year mortality and Waterer (49) related it to 3-year mortality. Moreover, Mortensen et al. (22) considered the previous functional state as a risk factor for six-year mortality.

Dementia and cerebrovascular disease have also been considered risk factors by numerous studies (28,36). Bordon et al. (50) observed a shorter survival rate in patients aged over 65 years with cancer, dementia, and liver disease that had been admitted for CAP. The group of Edinburgh carried out an observational study with 1,348 patients admitted for CAP and observed that patients with poorer long-term outcome could be identified by using risk factors to identify risk of aspiration pneumonia (51). Similarly, neoplasia has been associated with a high mortality rate. In addition, a recent study showed that at least 10% of patients with a CAP episode are diagnosed with lung cancer or pulmonary metastases during the years following hospital admission.

Cardiovascular diseases seem to have elicited greater interest. A recent review suggested a higher incidence of cardiac complications after a CAP episode (52). In this sense, Dr Aliberti and Dr Ramírez (31) conducted a review in which they found an increased incidence of cardiovascular events, such as myocardial infarction, arrhythmias, and heart failure, in patients suffering from pneumonia. Systemic inflammation, coronary artery inflammation, platelet activation and thrombosis, endothelial dysfunction, and effects of CAP on the heart have been suggested as possible mechanisms for increased cardiovascular events following respiratory infections (52).

Corrales et al. (53) assessed 5,613 older adults enrolled at the Cardiovascular Health Study conducted between 1989 and 1994 in four communities of the United States. Patients with previous diagnosis of heart failure were excluded and participants were followed up until 2010. Of those older adults assessed, 1,315 developed pneumonia during follow-up and 652 were still alive and free of heart failure after 30 days of

discharge. The authors described an association between admission for pneumonia and increased risk of new-onset heart failure in the intermediate and long-term follow-up. This association remained significant even after adjusting for traditional risk factors including coronary heart disease. An Italian group studied 301 patients admitted for CAP with 17-month follow-up and compared patients who suffered cardiac complications during hospitalizations with those who did not (54). The authors observed a higher incidence of cardiovascular events as well as higher long-term mortality rate among patients who suffered in-hospital cardiac complications.

2.4 Biomarkers

2.4.1 Introduction

Bacterial products such as lipopolysaccharides or peptidoglycans play a primary role in the inflammatory response produced in the lower respiratory tract, because they stimulate the alveolar macrophages producing cytokines such as interleukins (IL-1, IL-6, IL-8) and tumor necrosis factor-alpha (55). These cytokines have been tested in order to measure the inflammatory response, but their detection in serum has been unhelpful due to their short half-life and their predominantly pulmonary production reaching low values in serum (56).

More emphasis has been placed in studies of acute phase reactant proteins that occur as a result of these cytokines stimulation. The measurement of these inflammatory mediators in serum is easier, because they have a longer half-life. Generally, plasma levels of inflammatory mediators seem to correlate with the severity of infectious diseases such as pneumonia.

C-reactive protein

It is worth mentioning that these mediators include the C-reactive protein (CRP), which is the most used in routine clinical practice. It was first described in 1930 at Oswald Avery's laboratory, when they tried to identify a protein capable of precipitating C-

polysaccharide of the pneumococcal cell wall in the serum of patients infected with *Streptococcus pneumoniae*. It is an acute phase protein as well as a non-specific inflammatory biomarker, but sensitive to systemic inflammation and tissue damage. Its main function is the activation of the complement system and other pro-inflammatory processes. Its synthesis occurs almost exclusively in hepatocytes mainly regulated by cytokines (IL-6 and IL-1). Extrahepatic synthesis in neurons, atheroma plaques, monocytes, and lymphocytes has been described. IL-6 is a very sensitive biomarker due to its rapid rise in infections; however, its low specificity, short half-life, low biostability, and high analytical cost make its clinical application limited (57).

In healthy young individuals, the average serum concentration of CRP is 0.8mg/L, but, in the acute phase, it can increase 500 and even up to 1000 times its baseline value, whether due to infection or inflammation. CRP synthesis begins immediately after an inflammatory stimulus achieving an increase in serum concentrations after approximately six hours. However, the maximum value is obtained after 48 hours, due to which, at an early infection stage, values can be relatively low. Its half-life is 19 hours and constant in healthy individuals.

It is a very sensitive marker, but with low specificity. This way, values between 3 and 10 mg/L may reflect various non-specific inflammation conditions, such as diabetes mellitus, obesity, smoking, low physical activity, alcohol consumption, and depression, among others (58).

It has been observed that CRP has anti-inflammatory and pro-inflammatory action. The first occurs by inducing the expression of the IL-1 receptor antagonist, increasing the release of IL-10, and inhibiting the IFN-gamma synthesis. The second occurs by activating the complement and increasing the release of IL-1, IL-6 and TNF-alpha, among others (58).

The most important factor for CRP concentration is its synthesis, which, in turn, is influenced by the degree of pathological stimulus. CRP acts in the defense mechanisms of the body and inhibits the harmful effects of an exacerbated inflammatory reaction.

Procalcitonin

Procalcitonin (PCT) is the propeptide of synthesized calcitonin hormone in thyroid C-cells and encoded by the CALC-I gene on chromosome 11. It is known as "hormokine" due to its production in the typical form of hormone by neuroendocrine cells of thyroid C-cells or K cells in the lungs, and in the form of cytokine by several parenchymatous cells (59).

In healthy individuals, PCT serum levels are undetectable and they increase significantly in different situations. The production of this glycoprotein during pathological processes occurs in extrathyroidal tissues, without leading to the increase of calcitonin and serum calcium. In fact, it has been found that its level also increases in thyroidectomized patients and septic situations.

Its origin in pathological circumstances is uncertain. Its release during infection is directly induced by bacterial toxins (endotoxins), or indirectly by humoral factors (IL-1B, IL-6 and tumor necrosis factors) and cells of the monocyte/macrophage system. The induction can be attenuated by cytokines released during viral infections (interferon-gamma) (60, 61).

Elevated PCT levels can be detected after two hours of bacterial infectious stimulation. Its increase is greater than that of CRP, but not as accelerated as the increase accomplished by other cytokines such as, for example, IL-6. PCT is very stable, even at room temperature, and it has a half-life of approximately 24 hours (62).

New biomarkers

Recently, data from a study on new biomarkers with cardiovascular profile, such as arginine vasopressin (AVP), have been published (63). AVP is a hormone produced in the paraventricular nucleus of the hypothalamus and is subsequently stored in the pituitary gland. The main function of AVP is the regulation of cardiovascular and osmotic homeostasis. In severe diseases, such as sepsis or cardiogenic shock, there is an imbalance in the regulation of water and AVP production is augmented by osmotic and hemodynamic stimuli.

AVP, also known as antidiuretic hormone, is attached to the platelets in more than 90%, which makes it very difficult to be measured. In addition, its half-life of 24 minutes and its inability to remain stable in plasma has made it necessary to develop a new technique for the measurement of a new fragment of the biomarker. C-terminal proAVP fragment, also known as copeptin, is a glycoprotein of 39 amino acids whose function is not accurately known. However, given its greater *ex vivo* stability and longer half-life, it could be used as an indirect measure of AVP in selected patients. Elevated levels of copeptin have been associated with acute and chronic heart failure. In addition, Kruger et al. (63) identified copeptin as an independent factor for mortality in patients with CAP.

Brain natriuretic peptide is a polypeptide of 32 amino acids that has been widely used for discriminating the cardiac origin of dyspnea. Natriuretic peptides inhibit the renin-angiotensin system that leads to increased natriuresis, dieresis, and vasodilation. Their production mainly occurs during stress of the transmural wall of the heart, due to increased volume or cardiac pressure. However, proinflammatory cytokines and the sympathetic nervous system have been identified as the stimulators of their secretion (64).

Brain natriuretic peptide and N-terminal pro-brain natriuretic peptide are widely established in routine clinical practice and included in international guidelines for heart failure. However, elevated levels of these biomarkers have been described in septic processes. According to Chrits Crain et al. (65), brain natriuretic peptide predicted mortality and therapeutic failure in patients with CAP after the exclusion of patients with history of heart failures and ischemic and hypertensive heart disease. Therefore, the cardiac pathology could not explain the results obtained and, thus, the increase in its levels could be related to the severity of pneumonia.

Proadrenomedullin (proADM) is the most stable fragment of adrenomedullin (ADM) degradation. ADM is a peptide of 52 amino acids and, similarly as PCT, belongs to the CALC gene family being encoded by the CALC-V gene. Its expression has been detected in numerous tissues; however, the highest levels have been observed in the adrenal medulla, ventricles, kidneys, and lungs. Normal values range from 2 to 3.5 ng/mL. However, the union of ADM to its receptor immediately after its production and

its short half-life (approximately 22 minutes) hinder its direct measurement; therefore, the measurement of its more stable fragment is very useful. ProADM is a potent vasodilator and has bactericidal properties in addition to its action in the modulation of the immune response (66).

Despite the cost of biomarkers, their complementary use has been proposed as a way to improve etiologic identification and treatment optimization, as well as to estimate clinical severity, evolution, and prognosis in patients (67).

2.4.2 Etiology and adjustment of antibiotic treatment

Usually, despite proper techniques, it is only possible to obtain an etiological diagnosis in 50% of cases. The most common pathogen described in the majority of published studies has been *Streptococcus pnenumoniae (68)*. The discrimination between typical and atypical bacteria that cause pneumonia is an important step for choosing a treatment of CAP. However, specific microbiological diagnosis has become complicated in the routine clinical practice. The radiological presentation has been used to discern between bacteria and viruses, but the results have not been conclusive. Since the etiologic agent is usually unknown, empirical antibacterial treatment based on the most likely causal pathogens is prescribed.

There is a variation in the antibacterial recommendations provided by guidelines for the management of CAP, and the need for specific coverage of atypical microorganisms is a key difference. Narrow-spectrum antibiotics are often as effective as broad-spectrum antibiotics and cause fewer adverse side effects. However, despite significant progress in recent years, the current methods for the identification of causal pathogens still have limitations.

As already explained by Prat et al. (69), CRP increases in the acute inflammatory response, including viral and bacterial infections, whereas PCT is a sensitive and specific marker for the diagnosis of systemic bacterial infection. However, its usefulness in localized infections and empyema is limited. For example, Masia et al. (70) observed that a biomarker such as PCT may play a role in the prediction of

microbial behavior in patients with low PSI scores; but this fact was not observed in patients with higher PSI scores. Kruger et al. (71) found significantly higher levels of PCT and CRP in patients with classic bacterial etiologies in comparison with those with atypical bacteria.

On the other hand, Niederman et al. (72) suggested that the combination of PCT and molecular testing with polymerase chain reaction for respiratory virus in patients with CAP could identify individuals that may be treated without antibiotics or with antiviral drugs, if the results showed a low PCT level and a positive polymerase chain reaction test for the virus.

Also, the prognostic value of proADM has been assessed based on the etiology, but the results were little satisfactory. Bello et al. (73) conducted a prospective study of patients with CAP classifying the etiology into three groups; typical bacteria; atypical bacteria (including viruses); and mixed bacteria. The authors found that this biomarker had a high predictive value of mortality, independently of the CAP etiology. This way, PCT was the best biomarker in discriminating between pneumonia by typical bacteria, atypical bacteria, or virus when compared with CRP and proADM.

During recent decades, strategies of early initiation and early switch to oral therapy have been thoroughly assessed. However, the optimal duration of antimicrobial therapy has not been well established. In this sense, the ProHOSP study assessed a control group and an intervention group using different cut-off points for PCT to decide whether the administration of antibiotics was required. Precisely, they observed that the use of PCT reduced the duration of antibiotic treatment from 12 to five days and with no significant differences in the onset of complications between the two groups (74).

However, in 2007, the IDSA/ATS provided recommendations for the duration of antibiotic treatment based on the stability criteria proposed by Halm et al (75). The guidelines suggested a minimum of 5-day treatment, patients' achievement of an afebrile state for 48 to 72 hours, and meeting no more than one CAP-associated instability criteria before therapy discontinuation (76). Most guidelines showed a weak evidence of current recommendations mainly based on expert opinions (77-79). It

seems that there is an agreement on an individualized approach, though arbitrary longer treatments remain prevalent. A recent clinical trial indicated that discontinuing antibiotic treatment based on clinical stability criteria after a minimum of five-day appropriate treatment did not show less clinical success than traditional treatment schedules (80).

2.4.3 Severity and prognosis

In the infectious process of CAP, between 5.7 and 14% of patients who require hospital admission will die, and this figure can raise up to a 50% in patients admitted to intensive care units (17). Also, medium- and long-term mortality rates remain high, with values of 8 and 21% within 90 days and one year, respectively (6).

Furthermore, it seems that patients admitted for a CAP episode have higher mortality rates—even in the long term—than those admitted for any other reason, as previously explained. The prognostic factors for mortality have been related to the germ-host interaction. Despite the growing emergence of germs that are resistant to antibiotics, such as *Streptococcus pneumoniae*, studies have statistically demonstrated that mortality is more associated with factors that depend on the patients than with resistance of germs.

Severity prognostic scores are static clinical score and lack information on the host inflammatory response. The concomitant use of certain biomarkers could provide objective criteria to make decisions with respect to these patients. Biomarkers are becoming the way to improve the predictive ability of clinical scores.

PCT and CRP are biomarkers that have been most frequently used and assessed in CAP (81-86). In this sense, Muller et al. (60) found a significant increase in PCT levels among patients of the group with PSI risk class V. However, the role of CRP seems to correlate with the presence of pneumonia, but not with its severity. In fact, some authors have stated that only very high CRP values can be used as indicators of the presence of CAP (81).

Most of the studies of biomarkers conducted to date in patients with CAP have assessed their ability to predict short-term mortality. Huang at al. (87) conducted a study in 28 different centers with 1,651 patients and demonstrated that PCT <0.1ng/mL was associated with a better prognosis, even in high-risk patients according to the PSI score. Interestingly, Menéndez et al. (88) observed that the addition of PCT levels to the PSI score did not improve predictive ability for 30-day mortality, though it improved the prediction by adding the CRP to the PSI and CURB65 scores. The German group observed that the PCT levels—but not the CRP levels—significantly increased with the severity of CAP measured by the CRB-65 score (63). In that same study, low PCT levels were associated with low mortality for all the risk classes of the CRB-65. There are studies that have indicated discrete differences in PCT levels between survivors and non-survivors. It seems that this diagnostic marker is useful for both adjustment of antibiotic treatment and as a prognostic marker (89).

To date, biomarkers alone had not demonstrated superiority on the scores to predict complications. In the last years, studies have been conducted with biomarkers of more cardiovascular profiles and found that proADM started gaining greater relevance. Pro-ADM has demonstrated superiority over CRP and PCT to predict the mortality of these patients more accurately (66). This fact could be due to the cardiovascular activity of this biomarker in addition to its immunomodulatory and antimicrobial effects.

There are several studies that have highlighted the improvement in prognostic value of risk scores with pro-ADM. For example, Huang et al. (90) found that high pro-ADM levels exhibited an additional stratified risk to the high risk class measured by the PSI score. In another study, Chirst Crain et al. (91) described that the combination of proADM and the PSI score improved the prediction of mortality. Albrich et al. (92) showed that a new index, such as the CURB65-A based on the combination of the CURB65 score and pro-ADM, could accurately predict 30-day mortality, as well as adverse effects defined as death from any cause, intensive care unit admission, or any disease complication within 30 days. Other authors have assessed the addition of proADM in different severity scores with satisfactory results for both severe complications and short-term mortality (93).

The role of biomarkers in short-term prediction seems to be more clear. However, long-term mortality is more difficult to predict. Recently, the red blood cell distribution—a determination that measures the heterogeneity of erythrocyte volume—has been associated with increased 30-day morbimortality (94). Furthermore, Bello et al. (95) observed that from a cut-off point of 14, it had a higher predictive power for mortality than other predictive biomarkers and, in addition, the prediction improved in the long term.

However, the biomarker that has proven to be better than the rest for predicting long-term mortality in these patients was proADM. The German group CAPNEZT has assessed the role of biomarkers, both in the short and long term (71). They observed the validity of proADM as a predictive marker of survival within 28 and 180 days, comparable with the CRB-65 score. In addition, the predictive ability of the CRB65 score improved significantly when proADM was added. Furthermore, some authors have described improvement such as longer-term predictive ability for mortality (6 years) by adding proADM to the PSI and CURB65 scores (43).

Guertler et al. (96) obtained biomarkers at days three, five, and seven, as well as on the day of discharge, among patients with CAP included in a multicenter trial with 18-month follow-up after hospital discharge. The authors found that the male sex, chronic obstructive pulmonary disease, neoplastic disease, and the highest quartile of peak proADM level were independent risk factors for long-term mortality. Interestingly, initial presentation with temperature >38.7 °C, chills, and the highest quartile of CRP were independent protective factors. Without a doubt, proADM seems to have gained the first place in the prediction of long-term mortality in CAP patients.

As mentioned earlier, it is worth noting the transcendent role of cardiovascular diseases as main cause of medium-and long-term mortality in these patients. Biomarkers can be of great utility to identify a persistent chronic inflammation state initiated after a CAP episode, which can lead to the development of cardiovascular diseases (97,98).

2.5 Clinical prediction rules

2.5.1 Introduction

Clinical prediction rules (CPR) were firstly developed to improve physicians' decision-making as they are a powerful tool to provide an outcome, hence, to estimate the probability that a certain outcome is present or will occur in an individual. These prediction rules, also known as risk scores, usually combine patient characteristics, physical examination data or laboratory data. They aim to standardize clinical data interpretation, trying to avoid medical errors and minimizing the use of costly diagnostic testing. An example would be prediction rules for diagnosis of pulmonary embolism, which actually avoid many computed tomographic. Clinical judgment is the first step when assessing a patient, however, clinical prediction rules provide more accurate and less variable estimates.

CPR have been developed for many conditions, for instance, to determine the likelihood of death within 4 years in patients with coronary artery disease, to identify children with increase probability for urinary tract infections or to identify patients who are likely to develop postoperative vomiting after anesthesia. Moreover, they can help physicians not only assessing patient prognosis, but also guiding treatment location and strategies. Once we focused on CAP, the initial evaluation leads to assess severity of disease in order to predict the likely clinical outcomes of the patient. This information can be used to help clinical decision-making in terms of site of care, extent of laboratory work-up, and therapeutic interventions. Clinical judgment has shown a poor predictive value to predict clinical outcomes, thus, CPR were developed to support physician in the approach of assessing severity and outcomes. More interestingly, they use the diagnostic properties of sensitivity, specificity, and positive and negative likelihood ratios leading to a more practical use, readily applied to individual patients.

In the last decades, an increasing number of papers have been published concerning prediction rules. Indeed, 6,744 papers were published in 1995 compared to 15,662 in 2005. There is an overwhelming number of prediction rules for the same outcome,

especially in some specific topics, such as, over 100 prognostic models for predicting outcome after brain trauma (99), over 100 models for prostate cancer (100), or 45 models for cardiovascular events after being diagnosed with diabetes (101). However, most articles are focused on the development of the rule and little is known concerning other methodological issues. Many reviews have suggested limitations in reporting data quality from the development of prediction rules (102,103). In a recent review of predictive models, performance measures, i.e., calibration and discrimination were only reported in 12% and 27% of studies, respectively (102). Rigorous methodoly should be used when elaborating CPR.

In this sense, in an attempt to improve quality of reported data, The Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) Initiative developed a set of recommendations for the reporting of studies developing, validating, or updating a prediction model, whether for diagnostic or prognostic purposes (104). The TRIPOD Statement is a checklist of 22 items, developed essentially for transparent reporting of a prediction model study (105).

As explained in the TRIPOD statement, the derivation of a prediction model should start by selecting predictors and combining them into a multivariable model. For short-term prognosis logistic regression is commonly used while Cox regression is used for long-term prognostic outcomes. These studies should always include some form of internal validation to quantify any optimism in the predictive performance of the developed model and adjust the model for overfitting. External validation tipically use the same predictor but tested in a different setting by other investigators. It is important to specifically report all methodological issues in order to accurately replicate the performed model.

There are two important aspects for the performance of a model that should be always reported. The first one is discrimination, which refers to the ability of the score to differentiate between patients who do and do not experience the outcome event. For survival models is measured by the concordance index (*C*-index), which equals the area under the receiver- operating characteristic curve for logistic prediction models. The second one is calibration, which reflects the agreement between predictions from the model and observed outcomes. In addition other measures of overall performance

can be reported, such as, explained variation ($R2$) and the Brier score. Finally, all developed prediction model should be compared to already published models, ideally in a quantitative manner.

2.5.2 CPR for assessment of CAP severity.

In order to establish the severity of CAP, different authors and scientific societies have created a series of rules or severity scores that allow predicting short-term evolution in patients. The best-known prognostic scores are the PSI, created by Fine et al. (106), and the CURB-65 created by Lim at al. (107). These scores are very useful in the optimization of antibiotic treatment, as well as in the decision-making for admissions. In addition, the implementation of the severity scores has shown a reduction in the number of hospital admissions of patients with CAP.

The PSI score was created with a large cohort of patients and validated in another cohort. This score is based on 20 variables related to age, comorbidity, clinical and radiological signs, and analytical data. Depending on the punctuation obtained, the patients are classified into five groups according to the increase in risk of 30-day mortality, namely: group 1 will include patients aged under 50 years, without comorbidities and with normal physical condition, corresponding to the risk class I, without the need for analytical determinations and with a mortality rate between 0.1 and 2.8%; group 2 would obtain less than 70 points; group 3 from 71 to 90; group 4 from 91 to 130; and group 5 would obtain more than 130 points.

This way, patients of low risk classes (I-III) could be treated as outpatient patients and the rest would require hospital admission. Specifically, the patients of risk class III could be treated at home or require a short length of hospital stay. Patients of group 4 would have a probability of mortality between 8.2 and 9.3%, and group 5 would exhibit a high mortality rate (31 to 37%). This is a good severity score, since subsequent works have validated its prognostic reliability.

The British Thoracic Society initially created the CURB (108) and, subsequently, Lim at al.(107) modified it by incorporating age and using the acronym CURB-65. This

score uses five variables and stratifies the patients according to the score with probability of mortality between 0.7% if they obtain 0, and 40% if they obtain 4 points or more.

However, the two scores have limitations. The first underestimates severity, especially in young patients without comorbidities, and the second does not include blood oxygen saturation among its variables. The two scores have a high negative predictive value to identify the patients who will develop complications. On the other hand, their positive predictive value is unsatisfactorily low to prescribe admission to intensive care units. Usually, these patients tend to be younger and exhibit less number of comorbidities, due to which it is not surprising that, when age is included as one of the important criteria, the results obtained by these scores are worse for predicting intensive care unit admissions.

The IDSA/ATS created a new score to predict which patients should be treated in intensive care units (76). It contains two major criteria (invasive mechanical ventilation and septic shock requiring vasopressor drugs) and eight minor criteria (respiratory rate >30 breaths per minute; PaO2/FiO2 <250 mmHg; multilobar infiltrates observed on the chest radiograph; confusion/disorientation; uremia >20 mg/dL; leukopenia <4,000 leukocytes/mm^3; thrombocytopenia <100,000 platelets/mm^3; hypothermia <36 ºC and hypotension requiring aggressive fluid therapy). The presence of one major criterion or the sum of at least three minor criteria will indicate the need for admission to intensive care units or those with intensive monitoring. However, the obviousness of the major criteria limits the operation of this score, even though it has a validated predictive ability.

Charles et al. (109) created the SMART-COP (systolic blood pressure, multilobar chest radiography involvement, albumin level, respiratory rate, tachycardia, confusion, oxygenation, and arterial pH) score with the purpose of establishing the need for intensive respiratory or vasopressor support. It consists of eight clinical and analytical variables with different cut-off points according to age. The patients were classified into four risk groups on the basis of the need for mechanical ventilation. España et al. (110) created a new prognostic score (CAP-SCAP), to predict in-hospital mortality and/or the need for mechanical ventilation and/or onset of septic shock during hospital

admission in patients with CAP. This score consists of eight variables measured at the time of diagnosis, namely: pH <7.30 and systolic blood pressure <90, as major criteria, and confusion; respiratory rate >30 breaths/min; urea nitrogen >30; multilobar radiographic infiltrates, PaO2/FiO2 <250; and age >80, as minor criteria. From a cut-off point (>9 points would be equivalent to two minor criteria or one major criterion), it is recommended that patients are monitored or admitted to intermediate respiratory care units/intensive care units, whereas those with a score less than nine are classified as low risk and can be treated as outpatients.

The objectives of stratifying patients with CAP in groups are multiple. On the one hand, defining what type of patients can be treated as outpatients, and on the other hand, identifying those patients that require greater control or being monitored in intermediate respiratory care units/intensive care units. All these prognostic models predict the probability of mortality in percentage terms and help decide which patients require hospitalization and who can be treated as outpatients. However, the heterogeneity of CAP limits their predictive ability. This limitation implies the need of using "clinical judgment", which is certainly difficult to define in objective terms.

In addition, the scores are not able to measure the mechanisms of the inflammatory response of the organ affected against the microorganism, nor can predict the individual responses of the patients to the established treatments. They only predict short-term mortality and, to date, scores to predict long-term mortality after a CAP episode have not been created.

3. JUSTIFICATION

CAP continues to be a leading cause of morbidity and mortality worldwide (14). The annual incidence of CAP ranges from 5 to 11 cases per 1000 adults and accounts for considerable healthcare costs (7,8). The severity of illness has been a matter of concern in recent decades since it has been related to short-term prognosis. In this sense, different CAP guidelines have suggested different risk scores in order to predict 30-day mortality.

Recently, increasing interest has emerged concerning long-term prognosis. Despite current evidence about risk factors for one-year mortality after CAP, it seems that predicting long-term prognosis after an episode of CAP remains challenging. To date, no risk scores have been developed in order to predict one-year mortality in hospitalized patients with CAP.

In addition, the utility of biomarkers has been widely evaluated to predict poor outcomes in CAP. Most researchers have focused on short-term outcomes. However, several authors have suggested that a few biomarkers could also be useful to predict long-term prognosis. Little is known about how the addition of biomarkers could improve long-term prediction.

In an attempt to clarify this issue, three different cohorts were assessed in this study. The first one was evaluated in order to develop a one-year prediction score among hospitalized patients with CAP from January 2001 to July 2009 at the Hospital of Galdakao-Usansolo.

The second one was tested in hospitalized patients with CAP in which blood samples were obtained from June 2008 to July 2009 at the Hospital of Galdakao-Usansolo, to assess whether biomarkers are useful for predicting one-year mortality. Finally, a third cohort was assessed to investigate long-term prognosis among hospitalized patients with CAP from June 2001 to November 2006 in the Veterans Affairs Medical Center of Louisville, Kentucky.

4. HYPOTHESES AND OBJECTIVES

4.1 Hypotheses

Study I. One-year mortality prediction among hospitalized patients with CAP in Galdakao-Usansolo Hospital

1. In patients admitted for CAP, it is possible to identify clinical variables relating to one-year mortality after hospital admission.

2. Depending on the variables previously identified, it is possible to create a prognostic index that can help in the stratification of one-year mortality prediction in patients admitted for CAP.

3. A prognostic index specifically created for the prediction of one-year mortality may have greater predictive ability than usual risk scores in patients admitted for CAP.

Study II. Role of biomarkers for one-year mortality prediction among hospitalized patients with CAP in Galdakao-Usansolo Hospital

1. The severity at the time of clinical diagnosis measured by biomarkers or risk scores may be associated with one-year mortality in patients admitted for CAP.

2. The incorporation of inflammatory response biomarkers to risk scores could improve the ability for predicting one-year mortality.

3. The decrease in levels of inflammation biomarkers from the time of diagnosis until three to five days could help in predicting one-year mortality in patients admitted for CAP.

Study III. One-year mortality prediction among hospitalized patients with CAP in the Veterans Affairs Medical Center of Louisville, Kentucky, USA

1. The variables of patients admitted for CAP to a Veterans Hospital in the United States will differ from the sample of study I.

2. The creation of a prognostic index for long-term mortality in patients of an American cohort admitted for CAP to a Veterans Hospital could help professional health teams to better identify the patients with high mortality risk in order to perform enhanced monitoring.

4.2 Objectives

Primary

Study I. One-year mortality prediction among hospitalized patients with CAP in Galdakao-Usansolo Hospital

1. To assess the factors associated with one-year mortality in patients admitted after a CAP episode.

2. To create and validate a prognostic index for one-year mortality in patients admitted after a CAP episode.

3. To compare the predictive ability of existing severity scores and the new prognostic index for one-year mortality.

Secondary:

Study II. Role of biomarkers for one-year mortality prediction among hospitalized patients with CAP in Galdakao-Usansolo Hospital

1. To assess the relationship between severity scores and levels of biomarkers of systemic inflammation (CRP, proADM, and PCT) obtained at the time of diagnosis and one-year mortality in patients admitted for CAP.

2. To determine the predictive ability of biomarkers and prognostic scores and associate them in order to improve the predictive value.

3. To assess the relationship between the evolution of biomarkers levels from admission to three to five days and one-year mortality in patients admitted for CAP.

Study III. One-year mortality prediction among hospitalized patients with CAP in the Veterans Affairs Medical Center of Louisville, Kentucky, USA

1. To assess the differences between the variables of a sample from a Veterans Hospital in the United States and the variables of study I.

2. To create a predictive score for long-term mortality in an American cohort of patients admitted for CAP to a Veterans Hospital.

5. METHODS

STUDY I. ONE-YEAR MORTALITY PREDICTION AMONG HOSPITALIZED PATIENTS WITH CAP IN GALDAKAO-USANSOLO HOSPITAL.

5.1. Study design

This was an observational, prospective study of adults aged ≥18 years admitted to the Hospital of Galdakao-Usansolo, from January 2001 to July 2009 with a diagnosis of CAP. The entire cohort was divided into two parts in order to develop a one-year mortality predictive model in the first cohort (the derivation cohort) that was validated using the second cohort (the validation cohort).

Firstly, a subset of variables considered clinically important to predict one-year mortality were selected. Secondly, the relationships between those variables and one-year mortality was assessed and statistically significant variables were considered in a multivariate analysis. Once the predictive variables were identified, a weighted score was developed and validated in the validation cohort. At the same time, the score was divided into three categories: mild, moderate and high risk groups. Finally, the predictive accuracy of the score was compared to other risk scores.

5.2. Setting and study population

The study was carried out at the Hospital of Galdakao-Usansolo (Galdakao, Spain), a 400-bed teaching hospital in the Basque Country (northern Spain) that serves a population of 300,000 inhabitants. This medical institution belongs to the network of public hospitals of the Basque Health Care Service, which provides free unrestricted care to nearly 100% of the population.

The Pneumology Department staff is composed of full-time physicians qualified in standardized national residency programs. Since 2000, the team has developed a consolidated line of research with a clear influence on science confirmed by loads of publications. The Infections Division of the Pneumology Department has developed a clinical guideline for CAP management that is still working and that has led to many publications. It should be highlighted that this team developed a specific score to predict severe CAP, the SCAP score, with a clear impact on the literature.

5.3 Patient selection criteria

5.3.1. Diagnosis definition

Pneumonia was defined as pulmonary infiltrate on chest X-ray not seen previously plus at least one symptom compatible with pneumonia such as cough, fever, dyspnea, and/or chest pain (106).

5.3.2 Inclusion criteria

Hospitalized patients diagnosed with CAP were recruited from January 2001 to July 2009. Eligible patients were ≥18 years old, hospitalized with a diagnosis of CAP.

5.3.3 Exclusion criteria

. Death within the first 15 days from diagnosis.

. Had been discharged from an acute care hospital, an onsite subacute care unit, or a palliative care unit within the previous 14 days.

. Infected with the human immunodeficiency virus.

. Chronically immunosuppressed, defined as:

. Solid organ transplantation

. Post-splenectomy

. Receiving ≥10 mg/day prednisone or equivalent for more than 30 days

. Being on other immunosuppressive agents

. Having neutropenia, i.e., $<1.0 \times 10^9$/L neutrophils

5.4 Sample size estimation

Studies of predictive model development indicate that it is necessary to include at least 10 events of the dependent variable of interest (in this case: mortality, major complications, relapses, or readmissions) for each independent variable included in the multivariate logistic regression model [111,112]. Therefore, we estimated that at least 100 events of the dependent variable in the sample are required in order to

ensure that the regression model would adequately converge. Previous data indicate that the number of events of the dependent variable mortality would be >15% of patients operated on in the first year, higher that the expected percentages of other parameters. We therefore estimated that more than 300 events of any of the dependent variables of interest should be included. Thus, we consecutively collected all new cases until the sample size was achieved.

5.5 Missing data

No assumptions were made for missing data, analyzing only the available data.

5.6 Data collection

At baseline, the demographic and clinical data for each patient were collected from medical records, including comorbidities, physical examination, radiological presentation, analytics as well as complications during hospitalizations. Antibiotic treatment was assessed according to Spanish Pulmonology and Thoracic Surgery Society (SEPAR) guidelines (113).

Disease severity was determined with the PSI, CURB65, and SCAP scores, calculated within the first 24 hours after diagnosis (106,107,110). One-year mortality was retrospectively assessed by the computer system support of the Basque Health Care Service.

5.7 Ethics and confidentiality issues

All participants provided signed informed consent before their inclusion in the study and after being informed and having discussed the goals, risks, and potential benefits of the study. Patient rights were protected in line with the Declaration of Helsinki. The project was approved by the hospitals' ethical review boards.

In order to preserve patient data confidentiality, restricted access to the database was limited to a single person, with a user name and password. Similarly, patient identifying information was managed separately from the rest of the study information.

5.8 Definitions of variables

● Primary outcome was one-year mortality after admission for CAP.

Patients who died within the first 15 days after diagnosis were excluded in order to avoid the impact of severity of illness on mortality.

● Secondary outcomes

- Patient condition at the time of diagnosis

Demographics, comorbidities, physical examination, radiological presentation and analytics.

. Alcohol consumption: More than 80 g/day of alcohol intake.

. Nursing home: Being a nursing home resident.

. Aspiration: Suspicion of aspiration at diagnosis, usually seen in patients with difficulties swallowing.

. Diabetes mellitus: Patients with diabetes under treatment with oral antidiabetic agents or insulin therapy.

. COPD: Chronic pulmonary obstructive disease including chronic bronchitis and emphysema.

. Cancer: History of cancer.

. CHF: Patients with exertional dyspnea, paroxysmal nocturnal dyspnea and responding symptomatically or in a physical examination to treatment with digitalis, diuretics or afterload reducers drugs. Patients without symptomatic improvement after medication or those without improvement in physical examination were not included.

. CAD: Patients with a history of acute or chronic coronary artery disease.

. CVD: Patients with a clinical or radiological diagnosis of cerebrovascular accident or transient ischemic attack.

. Dementia: Chronic cognitive impairment.

. Renal failure: Chronic kidney disease or abnormal blood levels of creatinine.

. Confusion: Altered mental status, previously not reported disorientation of place, time or person.

. Pleural effusion (X-ray): Pleural effusion on the X-ray at diagnosis.

. Bilateral/multilobar (X-ray): Bilateral or multilobar involvement on the X-ray at diagnosis.

. Mixed radiological pattern: Both alveolar and interstitial pattern on the X-ray.

● Treatment administration

. Previous antibiotic treatment.

. Antibiotic according to SEPAR guidelines.

. Time until first antibiotic dose.

. Corticosteroids administration: systemic corticosteroids administration during hospitalization.

● Complications during hospitalization

. Intensive Care Unit (ICU) admission: ICU admission during hospitalization.

. Intermediate Respiratory Care Unit (IRCU) admission: IRCU admission during hospitalization.

. Mechanical ventilation: Need for invasive mechanical ventilation.

. Septic shock: Sepsis-induced hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities that may include but are not limited to lactic acidosis, oliguria, or an acute alteration in mental status. Patients receiving

inotropic or vasopressor agents may not be hypotensive at the time that perfusion abnormalities are measured (114).

. Need for vasopressors: Need for vasopressor agents.

. Respiratory failure: Presence of pO_2/FiO_2 <300.

. Renal failure: Abnormal blood levels of creatinine, not previously reported.

. Pleural effusion: Development of pleural effusion not reported at the time of diagnosis.

. Empyema: Pus in the pleural space.

. Antibiotic adverse events: appearance of symptoms such as diarrhea attributable to antibiotics.

. Embolism: Pulmonary embolism diagnosis by computerized tomography.

. Deep vein thrombosis diagnosis by ultrasonography.

. Decompensated comorbidities: Exacerbation of previously diagnosed diabetes mellitus, asthma, COPD, heart disease, neurological disease, or renal failure.

● Severity of illness at the time of diagnosis

PSI, CURB65 and SCAP scores were used to assess the severity of illness at admission. The PSI and CURB65 were both developed and validated for 30-day mortality while the SCAP score was developed and validated for in-hospital mortality and/or need for mechanical ventilation and/or septic shock.

The PSI score was elaborated in the USA by Fine et al. (106) and is based on 20 weighted variables including, age, sex, comorbidities, vital signs, analytical data, and radiological presentation. Patients are stratified into five risk categories depending on 30-day mortality risk. In the original study, mortality rates were 0.1%, 0.6%, 0.9%, 9.3%, and 27% for risk classes I, II, III, IV, and V, respectively.

The CURB65 score was elaborated by the British Thoracic Society and designed by Lim et al. (107). It is composed of five variables, with one point for each: confusion,

urea 7 mmol/L, respiratory rate >30/min, low systolic (<90 mm Hg) or diastolic (<60 mm Hg) blood pressure, and age >65 years. Scores ranged from 0 to 5 points based on 30-day mortality risk (score 0, 0.7%; score 1, 2.1%; score 2, 9.2%; scores 3-5, 15-40%).

The SCAP score was elaborated by España et al. (110), based on two major criteria (pH <7.30 and systolic blood pressure <90 mmHg) and six minor criteria (confusion, respiratory rate >30 breaths/min, BUN >30 mg/dL, multilobar/bilateral X-ray, PaO_2/FiO_2 <250 mmHg, and age >80 years). Based on eight weighted variables, patients are stratified into mild (0-9 points), moderate (10-19 points), and high (>20 points) risk groups.

5.9 Statistical analysis

Descriptive statistics included frequency tables and means and standard deviations (SD) or medians and interquartile ranges (IQRs). No assumptions were made in relation to missing values.

The entire cohort was split randomly into derivation (50%) and validation (50%) sets. To assess the homogeneity of both samples, categorical variables were compared with the chi-squared and Fisher's exact tests, and continuous variables with Student's t-tests or non-parametric Wilcoxon tests.

A univariate analysis using the chi-squared/Fisher's exact test (categorical variables) or t-test (continuous effects) was performed to identify the variables related to one-year mortality. Variables with statistically significant results at p <0.20 were entered into the multivariate model.

Firstly, a logistic regression model to select the variables for the prediction rule was performed. The model was replicated in the validation cohort. The area under the curve (AUC) of the model (AUC ≥0.80 means a good discrimination) and the odds ratios (OR) and 95% confidence intervals (CI) of all selected variables were provided. For the assessment of the goodness-of-fit of the model, the Hosmer-Lemeshow test was performed (a p-value ≥0.05 represents good calibration of the model).

Secondly, a survival multivariate model was carried out with the selected variables. The hazard ratios (HR) and 95% confidence intervals (CI) of all selected variables were provided. The beta coefficients from the survival model were used to weight the relative importance of each variable for the calculation of the prediction score. For weights, the beta coefficient for each predictor variable in the model was divided by the variable with the lowest beta coefficient and rounded to the nearest whole number. This produced a "relative weight" of each variable in relation to its ability to predict each outcome. The model was replicated in the validation cohort.

Thirdly, the weights of the variables for each patient were added together to produce the prediction scores for each patient and three categories were established (low, moderate, and high) based on predicted versus observed one-year mortality. Risk categories were replicated in the validation cohort.

Fourthly, the associations between PSI, CURB65, SCAP, and one-year CAPSI were assessed by hazard ratios (HR) and 95% confidence intervals (CI) in the derivation and the validation cohorts. Kaplan-Meier survival curves were used to assess operating severity scores for one-year mortality.

Fifthly, the predictive accuracy of the different risk scores was assessed in the derivation and the validation cohorts by the C-index. Akaike information criteria (AIC) and R-squared (R^2) were provided in both cases. To assess the ability of the model to match predicted and observed one-year mortality rates in all developed survival models, the Greenwood-Nam D'Agostino (GND) method was used.

All effects were considered significant at $p<0.05$, unless otherwise stated. All statistical analysis was performed using SAS for Windows, version 9.4 (SAS Institute, Cary, NC). Figures were prepared using R version 3.3.0.

STUDY II. ROLE OF BIOMARKERS FOR ONE-YEAR MORTALITY PREDICTION AMONG HOSPITALIZED PATIENTS WITH CAP IN GALDAKAO-USANSOLO HOSPITAL.

5.1. Study design

This was an observational, prospective study of adults aged ≥18 years admitted to Hospital of Galdakao-Usansolo, from June 2008 to July 2009 with a diagnosis of CAP and in whom blood samples could be obtained for biomarker analysis at the time of diagnosis as well as after 3-5 days when possible. The predictive accuracy of the risk scores and biomarkers at diagnosis was assessed for one-year mortality. In addition, the evolution of biomarker levels between time points was evaluated for the one-year mortality prediction.

5.2. Setting and study population

The study was carried out at the Hospital of Galdakao-Usansolo (Galdakao, Spain), a 400-bed teaching hospital in the Basque Country (northern Spain) that serves a population of 300,000 inhabitants. This medical institution belongs to the network of public hospitals of the Basque Health Care Service, which provides free unrestricted care to nearly 100% of the population.

5.3 Patient selection criteria

4.3.1. Diagnosis definition

Pneumonia was defined as pulmonary infiltrate on chest X-ray not seen previously plus at least one symptom compatible with pneumonia such as cough, fever, dyspnea, and/or chest pain (106).

5.3.2 Inclusion criteria

Hospitalized patients diagnosed with CAP were recruited from January 2001 to July 2009. Eligible patients were ≥18 years old, hospitalized with a diagnosis of CAP.

5.3.3 Exclusion criteria

. Death within the first 15 days from diagnosis.

. Had been discharged from an acute care hospital, an onsite subacute care unit, or a palliative care unit within the previous 14 days.

. Infected with the human immunodeficiency virus.

. Chronically immunosuppressed, defined as:

- . Solid organ transplantation
- . Post-splenectomy
- . Receiving ≥10 mg/day prednisone or equivalent for more than 30 days
- . Being on other immunosuppressive agents
- . Having neutropenia, i.e., <1.0 $x10^9$/L neutrophils

5.4 Sample size estimation

Studies of predictive model development indicate that is necessary to include at least 10 events of the dependent variable of interest (in this case: mortality, major complications, relapses, or readmissions) for each independent variable included in the multivariate logistic regression model (111,112). Therefore, we estimated that at least 100 events of the dependent variable in the sample are required in order to ensure that the regression model would adequately converge. Previous data indicate that the number of events of the dependent variable mortality would be >15% of patients operated on in the first year, higher that the expected percentages of other parameters. We therefore estimated that more than 300 events of any of the dependent variables of interest should be included. Thus, we consecutively collected all new cases until the sample size was achieved.

5.5 Missing data

No assumptions were made for missing data, analyzing only the available data.

5.6 Data collection

At baseline, the demographic and clinical data for each patient were collected from medical records, including comorbidities, physical examination, radiological presentation, analytics as well as complications during hospitalization. Antibiotic treatment was assessed according to Spanish Pulmonology and Thoracic Surgery Society (SEPAR) guidelines (113). Disease severity was determined with the PSI, CURB65, and SCAP scores, calculated within the first 24 hours after diagnosis (106,107,110). Blood samples were obtained at diagnosis as well as 3-5 days later when possible in order to analyze CRP, PCT, and proADM levels. All patients were evaluated at day 30 in a medical consultation. One-year mortality was retrospectively assessed by the computer system support of the Basque Health Care Service.

CRP was quantified by immunoturbidimetry with an analytical sensitivity of 1 mg/L. PCT was analyzed by electrochemiluminescence with an analytical sensitivity of 0.02 ng/mL. PADM was analyzed by a sandwich immunoassay using TRACE technology (time-resolved amplified cryptate emission) with a sensitivity of 0.05 nmol analytical/L.

5.7 Ethics and confidentiality issues

All participants provided signed informed consent before their inclusion in the study and after being informed and having discussed the goals, risks, and potential benefits of the study. Patient rights were protected in line with Declaration of Helsinki. The project was approved by the hospitals' ethical review boards.

In order to preserve patient data confidentiality, restricted access to the database was limited to a single person, with a user name and password. Similarly, patient identifying information was managed separately from the rest of the study information.

5.8 Definitions of variables

● Primary outcome was one-year mortality after admission for CAP.

Patients who died within the first 15 days after diagnosis were excluded in order to avoid the impact of severity of illness on mortality.

● Secondary outcomes: See section I for definitions.

- Patient conditions at the time of diagnosis.

- Treatment administration.

- Complications during hospitalization.

- Severity of illness at the time of diagnosis measured by risk scores.

- Biomarker levels at the time of diagnosis (CRP, PCT, and proADM).

- Biomarker levels at 3-5 days (CRP, PCT, and proADM).

5.9 Statistical analysis

Descriptive statistics included frequency tables and means and standard deviations (SD) or medians and interquartile ranges (IQRs). No assumptions were made in relation to missing values. Biomarker values were compared between risk score levels: PSI (I-III vs. IV-V), CURB65 (0-1 vs. ≥2), SCAP (0-1 vs. ≥2), and one-year CAPSI (≤3 vs.>3), by non-parametric Wilcoxon tests. In addition, the predictive accuracy of one-year mortality for each biomarker was assessed by a survival model. The hazard ratios (HR) and 95% confidence intervals (CI) of all selected variables were provided. Similarly, the predictive accuracy of one-year mortality for each risk score was assessed and compared to PSI, CURB65, SCAP, and one-year CAPSI.

Finally, whether the inclusion of biomarkers significantly increased the predictive ability of risk scores was assessed by comparing the C-index of the nested survival models. Thus, the model including the risk score with the biomarker was compared to the model with the risk score itself.

In addition, the above mentioned analyses were performed including all deaths within one year.

ProADM changes were calculated by subtracting the biomarker value at 3-5 days from the baseline value so that a positive difference meant an improvement. The hazard ratios (HR) and 95% confidence intervals (CI) of ProADM changes were provided, adjusted by PSI, SCAP, CURB65, and one-year CAPSI as well as proADM baseline values. Predictive accuracies were assessed by the C-index. The same analyses were performed after the inclusion of all deaths within one year and after the exclusion of those patients who died from 15 days to one year.

All effects were considered significant at $p<0.05$, unless otherwise stated. All statistical analysis was performed using SAS for Windows, version 9.4 (SAS Institute, Cary, NC).

STUDY III. ONE-YEAR MORTALITY PREDICTION AMONG HOSPITALIZED PATIENTS WITH CAP IN THE VETERANS AFFAIRS MEDICAL CENTER OF LOUISVILLE, KENTUCKY.

5.1. Study design

This was a retrospective, observational study of a cohort of adult patients admitted to the Veterans Affairs Medical Center of Louisville, Kentucky, from June 2001 to November 2006 with a diagnosis of CAP. One-year and five-year mortality was obtained in order to develop one-year and five-year prediction scores.

5.2. Setting and study population

The Division of Infectious Diseases at the University of Louisville School of Medicine is a nationally and internationally recognized clinical research program in infectious disease under the direction of Dr. Julio Ramirez. It is dedicated to excellence in patient care, teaching and research with Dr. Paula Peyrani as director of the Clinical Research Unit.

Numerous manuscripts have been published by members of the team as well as a large number of presentations at national and international conferences. There are different areas of research, mostly focused on pneumonia, HIV/AIDS, influenza, antimicrobial stewardship, multidrug-resistant organisms, disease surveillance, and statistical process control. All research activities are supported by a Computational Epidemiology Unit, which takes care of all the analysis.

The division is the headquarters of the Community-Acquired Pneumonia Organization (CAPO) with a database including over 7,000 patients from 15 countries. In addition, a funded project was carried out on the incidence of influenza and other viruses in Kentucky. The group recently carried out a randomized clinical trial, Rapid Empiric Treatment with Oseltamivir Study (RETOS), in nine hospitals in the city of Louisville. At the moment, there are other two studies that are actively enrolling patients. The first study is a population-based study to define the clinical and economic burden of pneumococcal pneumonia in hospitalized adult patients in Jefferson County, Kentucky

(HAPPI). The second one is a funded study on *Streptococcus pneumoniae* serotypes in adults 18 years and older with radiographically confirmed CAP.

Jefferson County was founded in 1780 and is one of 120 counties of the state of Kentucky in the USA. In 2007, the county had a population of 709,264 inhabitants and a population density of 695 inhabitants/km². The county seat is Louisville. There are nine hospitals in Jefferson County and, at the moment, the Division of Infectious Diseases has more than 50 research associates engaged in screening, enrollment, and data collection from patients with CAP in those hospitals. A total of 89,363 patients were hospitalized in Jefferson County from May 2014 to April 2015. A total of 4,578 patients were hospitalized with CAP in Jefferson County from May 2014 to April 2015.

One of those hospitals is The Veterans Affairs Medical Center. Services are available to more than 150,000 veterans living in a 35-county area of the Kentuckiana area. Robley Rex Veterans Affairs Medical Center provides a continuum of care through an integrated health care delivery system. Today's Veterans Health Administration (VHA) originated during the Civil War as the first federal hospitals and domiciliary ever established for the nation's volunteer forces. The VHA is the largest of three administrations that comprise the U.S. Department of Veterans Affairs. The VHA's primary mission is to provide medical care and services to America's military veterans.

5.3 Patient selection criteria

5.3.1. Diagnosis definition

A CAP diagnosis was made if patients met the following criteria:

The presence of a new pulmonary infiltrate on chest radiograph or CT scan at the time of hospitalization, plus at least one of the following three criteria (76):

- New or increased cough

- Abnormal temperature (<35.6°C or >37.8°C)

- Abnormal serum leukocyte count (leukocytosis, left shift, or leukopenia) as defined by local laboratory values.

5.3.2 Inclusion criteria

Hospitalized patients diagnosed with a diagnosis of CAP from June 2001 to November 2006.

5.3.3. Exclusion criteria

. Death within the first 15 days from diagnosis.

. Had been discharged from an acute care hospital, an onsite subacute care unit, or a palliative care unit within the previous 14 days.

. Infected with the human immunodeficiency virus.

. Chronically immunosuppressed, defined as:

- . Solid organ transplantation
- . Post-splenectomy
- . Receiving ≥10 mg/day prednisone or equivalent for more than 30 days
- . Being on other immunosuppressive agents
- . Having neutropenia, i.e., <1.0 $x10^9$/L neutrophils

5.4 Missing data

No assumptions were made for missing data, analyzing only the available data.

5.5 Data collection

At baseline, the demographic and clinical data for each patient were collected from medical records, including comorbidities, physical examination, radiological presentation, analytics as well as complications during hospitalizations.

5.6 Ethics and confidentiality issues

This study was approved by the Veterans Affairs Medical Center Institutional Review Board. For several years, the Human Subjects Protection Program Office has offered an in-service education program for all researchers, coordinators and administrators associated with the University of Louisville and its affiliated institutions. The Offices of the Executive Vice President for Research and the Executive Vice President for Health Affairs have mandated that all researchers, including study coordinators and all other key study personnel, attend human subject protections training. Beginning July 1 2000, the Human Subjects Protection Program Office no longer considers initial or continuing reviews of protocols without certification of participation in such a course. It is obvious to the Institutional Review Board that the efficient approval and continuing review of protocols is enhanced if the researchers are better acquainted with the basic principles, standards and requirements of human subject protections as they pertain to local institutions.

For the reasons mentioned above, I carried out the Collaborative Institutional Training Initiative (CITI) program before reviewing the database. A description of the courses is provided below:

- Human subjects and HIPAA – Research-Biomedical Research.

- Human subjects and HIPAA – Research-Social, Behavioral or Educational Research.

- HIPAA Privacy - covers Component Workforce Members with access to PHI.

- Institutional Compliance – funded researcher

- Institutional Compliance – U of L general population

- Same as curriculum group

- Conflict of interest

5.7 Definitions of variables

● Primary outcomes were one-year and five-year mortality after admission for CAP.

Patients who died within the first 15 days after diagnosis were excluded in order to avoid the impact of severity of illness on mortality.

● Secondary outcomes: See section 1 for definitions.

- Patient condition at the time of diagnosis.

Demographics, comorbidities, physical examination, and analytics.

. Hypertension: patients with elevated blood pressure on drug treatment.

. Liver disease: cirrhosis or other chronic liver disease such as active chronic hepatitis.

5.8 Statistical analysis

Categorical variables were compared with those from study I with the chi-squares and Fisher's exact tests, and continuous variables with Student's t-tests or non-parametric Wilcoxon tests. One-year CAPSI was assessed for the study II sample by the C-index.

Prediction scores for one-year and five-year mortality were created. For each outcome, the same methods were utilized. First, a clinically meaningful subset of variables was selected based on physician input. Second, multicollinearity was assessed using variance inflation factor (VIF) values. Variables with a VIF>10 were considered collinear and were either evaluated in combination or dropped. Third, a genetic algorithm (R package "glmulti") was used to select the best-fit model based on the Akaike information criterion (AIC) (115). The beta coefficients from the logistic regression models were used to weight the relative importance of each variable for the calculation of the prediction score. For weights, the beta coefficient for each predictor variable in the model was divided by the variable with the lowest beta coefficient. This produced a "relative weight" of each variable in relation to its ability to predict each outcome. The weights of the variables for each patient were added together to produce the prediction scores for each patient.

Receiver operating characteristic (ROC) curves were used to calculate the discriminatory ability of each score in the prediction of each outcome. One score was created for one-year mortality and was assessed via the area under the ROC curve

(AUC). The same score was evaluated for predicting five-year mortality. A new score was created with a subset of variables selected specifically to predict five-year mortality. R version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria) was used for all analyses.

6. RESULTS

STUDY I. ONE-YEAR MORTALITY PREDICTION AMONG HOSPITALIZED PATIENTS WITH CAP IN GALDAKAO-USANSOLO HOSPITAL.

6.1 Descriptive statistics.

A total of 2,351 patients, with 1,208 and 1,143 in the derivation and validation cohorts, respectively, were included. Baseline characteristics and comorbidities are shown in Table 1. The mean age (SD) of the entire cohort was 69 (16.58) years, with 784 (33.35%) ≥80 years old. Both cohorts were similar except for the COPD rate, which was more frequent in the validation cohort.

Table 1. Baseline characteristics and comorbidities of hospitalized patients with CAP in the derivation cohort, the validation cohort, and the entire cohort.

	Derivation (n=1208)	**Validation (n=1143)**	**Entire cohort (n=2351)**	**p-value**
Age, mean (SD)	69.68 (16.51)	69.94 (16.66)	69.81 (16.58)	0.58
Age, n (%)				0.73
≥80 years	407 (33.69%)	377 (32.98%)	784 (33.35%)	
<80 years	801 (66.31%)	766 (67.02%)	1567 (66.65%)	
Sex, n (%)				
Male	788 (65.23%)	752 (65.79%)	1540 (65.50%)	0.79
Female	420 (34.77%)	391 (34.21%)	811 (34.50%)	0.79
AC, n (%)	63 (5.23%)	52 (4.59%)	115 (4.92%)	0.50
Nursing home, n (%)	86 (7.12%)	68 (5.95%)	154 (6.55%)	0.28
Aspiration	44 (3.64%)	36 (3.15%)	80 (3.40%)	0.57
Comorbidities, n (%)				
Diabetes mellitus	191 (15.92%)	171 (15.13%)	362 (15.54%)	0.61
COPD	278 (23.11%)	335 (29.54%)	613 (26.23%)	0.0004
Cancer	76 (6.29%)	54 (4.72%)	130 (5.53%)	0.10
CHF	81 (6.71%)	99 (8.66%)	180 (7.66%)	0.09
CAD	119 (9.88%)	105 (90.74%)	224 (9.58%)	0.62
CVD	105 (8.69%)	94 (8.22%)	199 (8.46%)	0.71
Dementia	123 (10.18%)	107 (9.36%)	230 (9.84%)	0.58
Renal failure	87 (7.20%)	89 (7.79%)	176 (7.49%)	0.64

Data are presented as n (%). AC: Alcohol consumption; COPD: Chronic obstructive pulmonary disease; CHF; Congestive heart failure; CAD; Coronary artery disease; CVD; Cerebrovascular disease.

Table 2 shows the physical examination and radiological presentation data. Both the derivation and validation cohorts were similar, with a predominantly alveolar pattern and about 23% presenting multilobar and or bilateral involvement.

Table 2. Physical examination and radiological presentation of hospitalized patients with CAP in the derivation cohort, the validation cohort, and the entire cohort.

	Derivation (n=1208)	**Validation (n=1143)**	**Entire cohort (n=2351)**	**p-value**
Confusion, n (%)	131 (10.84%)	116 (10.15%)	247(10.51%)	0.59
***HR* ≥125 beats/min, n (%)**	116 (9.60%)	117 (10.24%)	233 (9.91%)	0.63
RR ≥30 breaths/min, n (%)	175 (14.49%)	179 (15.66%)	354 (15.06%)	0.45
SBP <90 mmHg, n (%)	52 (4.30%)	45 (3.94%)	97 (4.13%)	0.68
DBP <60 mmHg, n (%)	207 (17.29%)	200 (17.68%)	407 (17.48%)	0.83
BT ≥40°C, n (%)	4 (0.33%)	7 (0.61%)	11 (0.47%)	0.37
X-ray, n (%)				
Pleural effusion	123 (10.18%)	112 (9.80%)	235 (10%)	0.78
Bilateral/multilobar	266 (22.07%)	264 (23.14%)	530 (22.59%)	0.55
Radiological pattern, n (%)				0.58
Alveolar	1188 (98.75)	1129 (99.04%)	2317 (98.81%)	
Interstitial	13 (1.08%)	9 (0.79%)	22 (0.94%)	
Mixed	4 (0.33%)	2 (0.18%)	6 (0.26%)	

Data are presented as n (%). *HR*: Heart rate; RR: Respiratory rate; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; BT: Body temperature.

Table 3 shows the analytical data with almost half of the population presenting with respiratory insufficiency while one third showed a BUN >30 mg/dL. Nearly 80% of patients in both groups received adherent antibiotic treatment according to SEPAR guidelines within the first 8 hours. In addition, corticosteroid administration was slightly more frequent in the validation cohort (Table 4).

Table 3. Analytical data of hospitalized patients with CAP in the derivation cohort, the validation cohort, and the entire cohort.

	Derivation (n=1208)	**Validation (n=1143)**	**Entire cohort (n=2351)**	**p-value**
Glucose ≥250 mg/dL, n (%)	102 (8.44%)	95 (8.31%)	197 (8.38%)	0.94
BUN >30 mg/dL, n (%)	333 (27.57%)	328 (28.70%)	661 (28.12%)	0.55
Sodium <130 mmol/L, n (%)	79 (6.54%)	73 (6.39%)	152 (6.47%)	0.93
Hematocrit <30%, n (%)	32 (2.65%)	25 (2.19%)	57 (2.42%)	0.50
PaO_2 <60 mmHg, n (%)	534 (44.21%)	490 (42.87%)	1024 (43.56%)	0.53
pH <7.35, n (%)	56 (4.64%)	48 (4.20%)	104 (4.42%)	0.62

Data are presented as n (%). BUN: Blood urea nitrogen.

Table 4. Antibiotic and systemic corticosteroid treatment of hospitalized patients with CAP in the derivation cohort, the validation cohort, and the entire cohort.

	Derivation (n=1208)	**Validation (n=1143)**	**Entire cohort (n=2351)**	**p-value**
Antibiotic, n (%)				
Previous antibiotic	269 (22.31%)	263 (23.09%)	532 (22.69%)	0.66
Antibiotic according to SEPAR guidelines	964 (79.80%)	929 (81.35%)	1893 (80.55%)	0.35
Antibiotic within first 4 h	705 (60.62%)	667(60.53%)	1372 (60.57%)	0.96
Antibiotic within first 8 h	966 (83.06%)	933 (84.66%)	1899 (83.84%)	0.30
Corticosteroids, n (%)	327 (27.07%)	357 (31.23%)	684 (29.09%)	0.03

Data are presented as n (%). SEPAR: Spanish Pulmonology and Thoracic Surgery Society.

There were no statistical differences in terms of complications among the derivation and validations cohorts. However, COPD exacerbations and decompensated neurological diseases were significantly more frequent in the validation cohort(table 5).

Table 5. Complications during hospitalization among hospitalized patients with CAP in the derivation cohort, the validation cohort, and the entire cohort.

	Derivation (n=1208)	**Validation (n=1143)**	**Entire cohort (n=2351)**	**p-value**
ICU admission, n (%)	54 (4.47%)	52 (4.55%)	106 (4.51%)	>.99
IRCU admission, n (%)	55 (4.55%)	51 (4.46%)	106 (4.51%)	0.92
Need for IMV, n (%)	18 (1.49%)	14 (1.22%)	32 (1.36%)	0.60
Shock, n (%)	49 (4.06%)	42 (3.67%)	91 (3.87%)	0.67
Need for vasopressors, n (%)	36 (3.64%)	31 (3.40%)	67 (3.52%)	0.80
Respiratory failure, n (%)	560 (46.36)	523 (45.76%)	1083 (46.07%)	0.77
Renal failure, n (%)	100 (8.28%)	98 (8.57%)	198 (8.42%)	0.82
Pleural effusion, n (%)	54 (4.47%)	60 (5.25%)	114 (4.85%)	0.39
Empyema, n (%)	8 (0.66%)	5 (0.44%)	13 (0.55%)	0.58
Antibiotic AE, n (%)	99 (8.20%)	77 (6.74%)	176 (7.49%)	0.18
Embolism, n (%)	6 (0.50%)	5 (0.44%)	11 (0.47%)	>.99
DVT, n (%)	4 (0.33%)	3 (0.26%)	7 (0.30%)	>.99
Decompensated comorbidities, n (%)				
Diabetes mellitus	62 (5.13%)	41 (3.59%)	103 (4.38%)	0.07
Asthma	19 (1.57%)	22 (1.92%)	41 (1.74%)	0.53
COPD	43 (3.56%)	64 (5.60%)	107 (4.55%)	0.02
Heart disease	44 (3.64%)	38 (3.32%)	82 (3.49%)	0.74
Neurological disease	9 (0.75%)	19 (1.66%)	28 (1.19%)	0.05
Renal failure	28 (2.32%)	22 (1.92%)	50 (2.13%)	0.57

Data are presented as n (%). ICU: Intensive care unit; IRCU: Intermediate respiratory care unit; IMV: Invasive mechanical ventilation; AE: Adverse events; DVT: Deep vein thrombosis; COPD: Chronic obstructive pulmonary disease.

Table 6 shows baseline severity measured by risk scores. The mean PSI (SD) score was 91.39 (32.73) and 91.58 (31.65) in the derivation and the validation cohorts, respectively (p = 0.88). The mean CURB65 (SD) score was 1.63 (1.06) and 1.67 (1.05) in the derivation and the validation cohorts, respectively (p = 0.88). The mean SCAP (SD) score was 7.67 (7.58) and 7.71 (7.26) in the derivation and the validation cohorts, respectively (p = 0.90). About 50% of the cohort was defined as severe by the PSI score, 20% by the CURB65 score, and 40% by SCAP score.

Table 6. Baseline severity of hospitalized patients with CAP in the derivation cohort, the validation cohort, and the entire cohort, measured by risk scores.

	Derivation (n=1208)	**Validation (n=1143)**	**Entire cohort (n=2351)**	**p-value**
PSI mean (SD)	91.39 (32.73)	91.58 (31.65)	91.48 (32.20)	0.88
PSI, n (%)				0.40
I	158 (13.08%)	148 (12.95%)	306 (13.02%)	
II	157 (13%)	128 (11.20%)	285 (12.12%)	
III	298 (24.67%)	268 (23.45%)	566 (24.07%)	
IV	464 (38.41%)	481 (42.08%)	945 (40.20%)	
V	131 (10.84%)	118 (10.32%)	249 (10.59%)	
PSI, n (%)				0.13
I-III	613 (50.75%)	544 (47.59%)	1157 (49.21%)	
IV-V	595 (49.25%)	599 (52.41%)	1194 (50.79%)	
CURB65 mean (SD)	1.63 (1.06)	1.67 (1.04)	1.65 (1.05)	0.88
CURB65, n (%)				0.66
0	213 (17.63%)	186 (16.27%)	399 (16.97%)	
1	302 (25%)	287 (25.11%)	589 (25.05%)	
2	450 (37.25%)	422 (36.92%)	872 (37.09%)	
3	207 (17.14%)	215 (18.81%)	422 (17.95%)	
4	32 (2.65%)	32 (2.80%)	64 (2.72%)	
5	4 (0.33%)	1 (0.09%)	5 (0.21%)	
CURB65, n (%)				0.36
0-2	965 (79.88%)	895 (78.30%)	1860 (79.12%)	
3-5	243 (20.12%)	248 (21.70%)	491 (20.88%)	
SCAP mean (SD)	7.67 (7.58)	7.71 (7.26)	7.69 (7.43)	0.90
SCAP, n (%)				0.19
0	369 (30.55%)	313 (27.38%)	682 (29.01%)	
1	349(28.89%)	371 (32.46%)	720 (30.63%)	
2	387 (32.04%)	367 (32.11%)	754 (32.07%)	
3	87 (7.20%)	83 (7.26%)	170 (7.23%)	
4	16 (1.32%)	9 (0.79%)	25 (1.06%)	
SCAP, n (%)				0.87
0-1	718 (59.44%)	684 (59.84%)	1402 (59.63%)	
2-4	490 (40.56%)	459 (40.16%)	949 (40.37%)	

Data are presented as n (%) or mean (SD). PSI: Pneumonia severity index; CURB65: Confusion, urea, respiratory rate, blood pressure, age >65. SCAP: Severe community acquired pneumonia.

In total, 208 (7.99%) patients died during hospitalization, while 251 patients died before 15 days from diagnosis. After deaths before 15 days were excluded, one-year mortality was 10.63%, respectively. No differences were observed between the derivation and the validation cohorts in terms of mortality (Table 7).

Table 7. Mortality rates of hospitalized patients with CAP in the derivation cohort, the validation cohort, and the entire cohort, after the exclusion of deaths before 15 days from diagnosis.

	Derivation (n=1208)	**Validation (n=1143)**	**Entire cohort (n=2351)**	**p-value**
30-day mortality, n (%)	23 (1.90%)	16 (1.40%)	39 (1.66%)	0.42
45-day mortality, n (%)	30 (2.48%)	27 (2.36%)	57 (2.42%)	0.89
90-day mortality, n (%)	60 (4.97%)	51 (4.46%)	111 (4.72%)	0.63
180-day mortality, n (%)	88 (7.28%)	77 (6.74%)	165 (7.02%)	0.63
One-year mortality, n (%)	131 (10.84%)	119 (10.41%)	250 (10.63%)	0.74

Data are presented as n (%).

6.2 Univariate analysis

In order to identify possible predictors of one-year mortality we first performed univariate analysis, taking into account the variables more likely associated with that outcome.

Table 8 shows the baseline characteristics and comorbidities among survivors and non-survivors. The mean (SD) age in survivors was 68.46 years (16.71) and 79.71 years (10.23) in non-survivors (p <0.0001). Compared with survivors at one year, non-survivors were older and were more frequently nursing home residents. Once comorbidities were analyzed, there were no statistical differences in diabetes mellitus, COPD, or CAD. However, cancer, congestive heart failure, cerebrovascular disease, and dementia were more common in people who died within one year of CAP diagnosis.

Table 8. Baseline characteristics and comorbidities of survivors and non-survivors at one year in the derivation cohort.

	Alive (n=1077)	**Dead (n=131)**	**p-value**
Age, mean (SD)	68.46 (16.71)	79.71 (10.23)	<0.0001
Age ≥80 years, n (%)	323 (79.36%)	84 (20.64%)	<0.0001
Sex, n (%)			0.44
Male	698 (64.81%)	90 (68.70%)	
Female	379 (35.19%)	41 (31.30%)	
AC, n (%)	58 (5.40%)	5 (3.88%)	0.67
Nursing home, n (%)	56 (5.20%)	30 (22.90%)	<0.0001
Aspiration	27 (61.36%)	17 (38.64%)	<0.0001
Comorbidities, n (%)			
Diabetes mellitus	166 (15.50%)	25 (19.38%)	0.25
COPD	249 (23.18%)	29 (22.48%)	0.91
Cancer	59 (5.48%)	17 (12.98%)	0.0033
CHF	65 (6.04%)	16 (12.21%)	0.01
CAD	101 (9.40%)	18 (13.95%)	0.12
CVD	80 (7.43%)	25 (19.08%)	<0.0001
Dementia	81 (7.53%)	42 (32.56%)	<0.0001
Renal failure	72 (6.69%)	15 (11.45%)	0.07

Data are presented as n (%) or mean (SD). AC: Alcohol consumption; COPD: Chronic obstructive pulmonary disease; CHF; Congestive heart failure; CAD; Coronary artery disease; CVD; Cerebrovascular disease.

Table 9 shows the physical examination, radiological presentation and analytics data among survivors and non-survivors. Non-survivors presented more frequently confusion and a respiratory rate ≥30 breaths/min compared to survivors. In terms of analytics, people who died presented more commonly BUN >30 mmol/L, hematocrit <30%, and respiratory insufficiency.

Table 9. Physical examination, radiological presentation, analytics and treatment of survivors and non-survivors at one year in the derivation cohort.

	Alive (n=1077)	**Dead (n=131)**	**p-value**
Physical examination, n (%)			
Confusion	96(8.91%)	35 (26.72%)	<0.0001
HR ≥125 beats/min	108 (10.03%)	8 (6.11%)	0.21
RR ≥30 breaths/min	144 (13.37%)	31 (23.66%)	0.0035
SBP <90 mmHg	46 (4.27%)	6 (4.58%)	0.82
DBP <60 mmHg	181 (16.93%)	26 (20.31%)	0.32
BT ≥40°C	4 (0.37%)	0 (0%)	>.99
X-ray, n (%)			
Pleural effusion	114 (10.58%)	9 (6.87%)	0.22
Multilobar/bilateral	233 (21.67%)	33 (25.38%)	0.37
Radiological pattern, n (%)			0.68
Alveolar	1060 (98.60%)	128 (98.46%)	
Interstitial	11 (1.02%)	2 (1.54%)	
Mixed	4 (0.37%)	0 (0%)	
Analytics, n (%)			
Glucose ≥250 mg/dL	91 (8.45%)	11 (8.40%)	>.99
BUN >30 mg/dL	270 (25.07%)	63 (48.09%)	<0.0001
Sodium <130 mmol/L	69 (6.41%)	10 (7.63%)	0.57
Hematocrit <30%	24 (2.23%)	8 (6.11%)	0.02
PaO_2 <60 mmHg	458 (42.53%)	76 (58.02%)	0.0010
pH <7.35	47 (4.36%)	9 (6.87%)	0.19
Treatment, n (%)			
Previous antibiotic	242 (22.51%)	27 (20.61%)	0.66
Antibiotic according to SEPAR guidelines	862 (80.04%)	102 (77.86%)	0.56
Antibiotic within first 4 h	618 (59.71%)	87 (67.97%)	0.08
Antibiotic within first 8 h	861 (83.19%)	105 (82.03%)	0.71
Corticosteroids	282 (26.18%)	45 (34.35%)	0.06

Data are presented as n (%). *HR:* Heart rate; RR: Respiratory rate; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; BT: Body temperature; BUN: Blood urea nitrogen; SEPAR: Spanish Pulmonology and Thoracic Surgery Society.

Severe sepsis was observed more commonly in non-survivors, as were respiratory insufficiency and renal failure. Compared with survivors at one year, non-survivors more frequently developed decompensations from previous cardiac and neurologic diseases (Table 10).

Table 10. Complications during hospitalization of survivors and non-survivors at one year in the derivation cohort.

	Alive (n=1077)	**Dead (n=131)**	**p-value**
ICU admission, n (%)	53 (4.92%)	1 (0.76%)	0.02
IRCU admission, n (%)	52 (4.83%)	3 (2.29%)	0.26
Need for IMV, n (%)	18 (1.67%)	0 (0%)	0.25
Shock, n (%)	44 (4.09%)	5 (3.82%)	>.99
Need for vasopressors, n (%)	36 (4.06%)	0 (0%)	0.03
Respiratory failure, n (%)	480 (44.57%)	80 (61.07%)	0.0003
Renal failure, n (%)	85 (7.89%)	15 (11.45%)	0.18
Pleural effusion, n (%)	47 (4.36%)	7 (5.34%)	0.65
Antibiotic AE, n (%)	90 (8.36%)	9 (6.87%)	0.73
Embolism, n (%)	4 (0.37%)	2 (1.53%)	0.13
DVT, n (%)	3 (0.28%)	1 (0.76%)	0.37
Decompensated comorbidities, n (%)			
Diabetes mellitus	55 (5.11%)	7 (5.34%)	0.83
Asthma	19 (1.76%)	0 (0%)	0.25
COPD	35 (3.25%)	8 (6.11%)	0.13
Heart disease	35 (3.25%)	9 (6.87%)	0.0467
Neurological disease	5 (0.46%)	4 (3.05%)	0.01
Renal failure	22 (2.04%)	6 (4.58%)	0.11

Data are presented as n (%). ICU: Intensive care unit; IRCU: Intermediate respiratory care unit; IMV: Invasive mechanical ventilation; AE: Adverse events; DVT: Deep vein thrombosis; COPD: Chronic obstructive pulmonary disease.

Table 11 shows severity of illness among survivors and non-survivors. Patients who died within one year were more severely ill at the time of diagnosis or at the index admission, as evidenced by higher risk scores.

Table 11. Severity of illness measured by risk scores of survivors and non-survivors at one year in the derivation cohort.

	Alive (n=1077)	**Dead (n=131)**	**p-value**
PSI mean (SD)	88.23 (31.60)	117.35 (30.36)	<0.0001
PSI, n (%)			<0.0001
I	157 (14.58%)	1 (0.76%)	
II	150 (13.93%)	7 (5.34%)	
III	282 (26.18%)	16 (12.21%)	
IV	400 (37.14%)	64 (48.85%)	
V	88 (8.17%)	43 (32.82%)	
PSI, n (%)			<0.0001
I-III	589 (54.69%)	24 (18.32%)	
IV-V	488 (45.31%)	107 (81.68%)	
CURB65 mean (SD)	1.55 (1.03)	2.31 (1.03)	<0.0001
CURB65, n (%)			<0.0001
0	206 (19.13%)	7 (5.34%)	
1	285 (26.46%)	17 (12.98%)	
2	399 (37.05%)	51 (38.93%)	
3	166 (15.41%)	41(31.30%)	
4	18 (1.67%)	14 (10.69%)	
5	3 (0.28%)	1 (0.76%)	
CURB65, n (%)			<0.0001
0-2	890 (82.64%)	75 (57.25%)	
3-5	187 (17.36%)	56 (42.75%)	
SCAP mean (SD)	7.05 (7.30)	12.77 (7.93)	<0.0001
SCAP, n (%)			<0.0001
0	357 (33.15%)	12 (9.16%)	
1	324 (30.08%)	25 (19.08%)	
2	320 (29.71%)	67 (51.15%)	
3	63 (5.85%)	24 (18.32%)	
4	13 (1.21%)	3 (2.29%)	
SCAP, n (%)			<0.0001
0-1	681 (63.23%)	37 (28.24%)	
2-4	396 (36.77%)	94 (71.76%)	

Data are presented as n (%) or mean (SD). PSI: Pneumonia severity index; CURB65: Confusion, urea, respiratory rate, blood pressure, age>65. SCAP: Severe community acquired pneumonia.

6.3 Multivariate analysis

From the identification of variables related to one-year mortality, we proceeded to try to combine them in a single multivariate model. We first performed multivariable logistic regression model which identified age ≥80 years, CHF, dementia, respiratory rate ≥30 breaths/min and BUN ≥30 mg/dL as predictors of one-year mortality (Table 12).

Regarding the discriminatory ability of the model in the derivation cohort, the receiver operating characteristic (ROC) curve was 0.78 (0.73-0.82) and 0.79 (0.75-0.83) in the validation cohort. The Hosmer-Lemeshow calibration test was 0.05 in the derivation cohort and 0.01 in the validation cohort.

Table 12. Multivariate logistic regression model for one-year mortality in the derivation cohort and the validation cohort.

	Derivation cohort			**Validation cohort**		
Variables	**Beta (s.e.)**	**OR (95% CI)**	**p-value**	**Beta (s.e.)**	**OR (95% CI)**	**p-value**
Age (years)						
≥80 vs. <80	0.98 (0.21)	2.66 (1.77, 4.00)	<0.001	0.82 (0.22)	2.28 (1.48, 3.50)	<0.001
CHF						
Yes vs. No	0.74 (0.32)	2.10 (1.13, 3.90)	0.02	0.75 (0.29)	2.12 (1.19, 3.75)	0.01
Dementia						
Yes vs. No	1.45 (0.24)	4.27 (2.68, 6.78)	<0.001	1.64 (0.25)	5.16 (3.17, 8.41)	<0.001
RR (breaths/min)						
≥30 vs. <30	0.64 (0.24)	1.89 (1.18, 3.04)	0.009	0.64 (0.25)	1.89 (1.17, 3.07)	0.01
BUN (mg/dL)						
>30 vs. ≤30	0.71 (0.20)	2.02 (1.36, 3.01)	<0.001	0.54 (0.21)	1.71 (1.13, 2.60)	0.01
AUC	0.78 (0.73-0.82)			0.79 (0.75-0.83)		
H-L	0.05			0.01		

Beta (s.e): Beta regression coefficient with standard error; OR: Odds ratio; CI: Confidence interval; AUC: Area under the curve. CHF: Congestive heart failure; RR: Respiratory rate; BUN: Blood urea nitrogen. H-L: Hosmer Lemeshow.

6.4 Score development

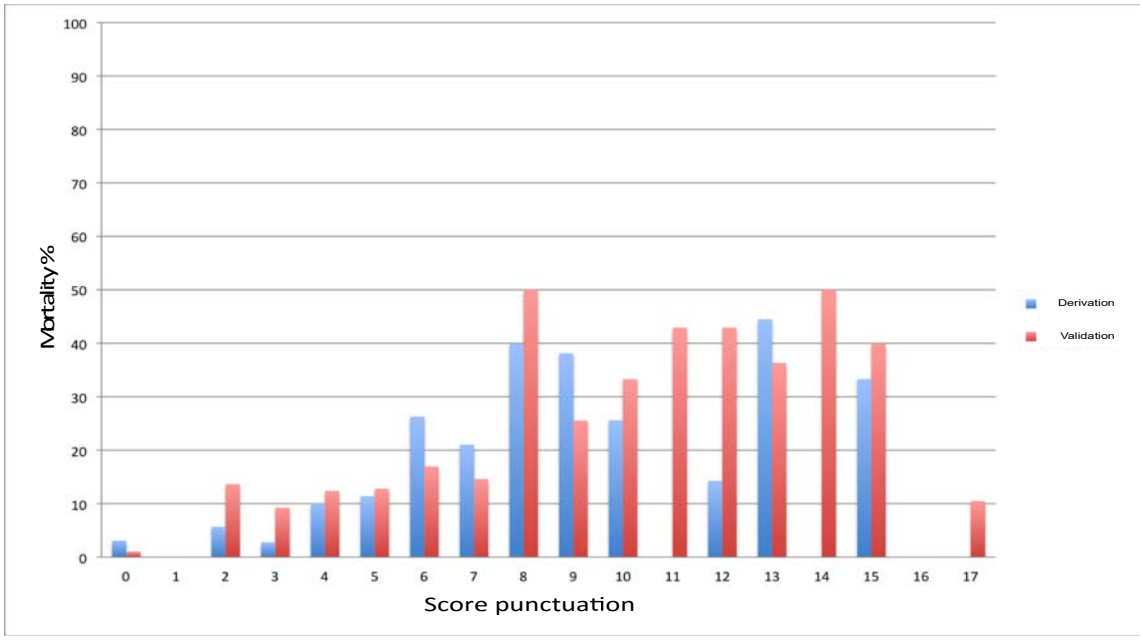
The logistic regression model was satisfactorily replicated in the multivariable survival analysis with similar p-values (Table 13). In order to develop a one-year mortality CAP severity index, now called the one-year CAPSI (community acquired pneumonia severity index), a prediction score was developed using the beta coefficients to weight the relative importance of the categories of each variable. Dementia being weighted with 6 points, followed by age ≥80 scored with 4 points, BUN >30 mg/dL scored with 3 points, and CHF and respiratory rate ≥30 breaths/min, both scored with 2 points. The prediction score distribution for each patient in the derivation and the validation cohort is shown in Figure 1.

Table 13. Multivariate survival analysis for one-year mortality in the derivation cohort and the validation cohort, i.e. one-year CAPSI.

	Derivation cohort				**Validation cohort**		
Variables	**Beta (s.e.)**	**HR (95% CI)**	**p-value**	**Weight**	**Beta (s.e.)**	**HR (95% CI)**	**p-value**
Age (years)				4			
≥80 vs. <80	0.87 (0.20)	2.39 (1.63,3.50)	<0.001		0.74 (0.21)	2.10 (1.40,3.15)	0.0003
CHF				2			
Yes vs. No	0.57 (0.27)	1.78 (1.05,3)	0.0331		0.52 (0.24)	1.68 (1.04,2.72)	0.03
Dementia				6			
Yes vs. No	1.20 (0.20)	3.33 (2.25,4.91)	<0.001		1.38 (0.21)	3.98 (2.64,5.99)	<0.001
RR (breaths/min)				2			
≥30 vs. <30	0.49 (0.21)	1.63 (1.09,2.45)	0.018		0.49 (0.21)	1.63 (1.08,2.47)	0.02
BUN (mg/dL)				3			
>30 vs. ≤30	0.66 (0.18)	1.93 (1.35,2.75)	<0.0003		0.44 (0.19)	1.55 (1.07,2.24)	0.02
GND test	0.03				0.23		

Beta (s.e): Beta regression coefficient with standard error; HR: Hazard ratio; CI: Confidence interval. CHF: Congestive heart failure; RR: Respiratory rate; BUN: Blood urea nitrogen. GND test: Greenwood-Nam-D'agostino calibration test for the one-year CAPSI as a continuous variable.

Figure 1. One-year CAPSI distribution in the derivation cohort and validation cohort.



For each unit increase in the score, the one-year mortality risk increased by 24% (1.24 (1.19, 1.28), HR (95%CI)). The one-year CAPSI was then categorized into three risk groups: low, moderate, and high risk, according to the one-year CAPSI risk score (Table 14). One-year mortality risk ranged from 3.35% in the lowest group to 28.38% in the highest group in the derivation cohort.

Similarly, one-year mortality risk ranged from 4.21% in the lowest group to 25% in the highest group in the validation cohort. Therefore, an 82-year-old patient with dementia would have 9.91 (6.30, 15.59) (HR (95%CI)) times higher probability of dying one year after an admission for CAP. At the same time, a 50-year-old patient with congestive heart failure and a respiratory rate of 32 breaths/min would have a 3.19 (1.75, 5.83) (HR (95%CI)) times higher probability of dying one year after an admission for CAP.

Table 14. Multivariate survival analysis for one-year mortality in the derivation cohort and the validation cohort by risk stratification groups.

	Derivation cohort			**Validation cohort**		
Variables	**Dead/exposed**	**HR (95% CI)**	**p-value**	**Dead/exposed**	**HR (95% CI)**	**p-value**
One-year CAPSI*	-	1.24 (1.19, 1.28)	<0.001		1.21 (1.17, 1.26)	<0.001
One-year CAPSI						
0-3	24/717 (3.35%)	Reference		29/689 (4.21%)	Reference	
4-5	19/184 (10.33%)	3.19 (1.75, 5.83)	0.0002	21/168 (12.5%)	3.03 (1.73, 5.32)	<0.001
>5	86/303 (28.38%)	9.91 (6.30, 15.59)	<0.001	69/276 (25%)	5.95 (3.86, 9.19)	<0.001
GND test	0.98			0.93		

HR: Hazard ratio; CI: Confidence interval. GND test: Greenwood-Nam-D'agostino calibration test for the one-year CAPSI as categorical variable. *Hazard risk of each increase in one unit in the one-year CAPSI.

6.5 Validation, discrimination, calibration and classification measures

The C-index of the one-year CAPSI as a continuous variable in the derivation cohort was 0.76 (0.024), the AIC was 1707.43, and R^2 was 8.8%. In the validation cohort, the C-index of the one-year CAPSI as a continuous variable was 0.77 (0.025), the AIC was 1589.23, and R^2 was 8.5%. When the one-year CAPSI was measured as a categorical variable, i.e. the one-year CAPSI risk score, the C-index of the derivation cohort was 0.72 (0.021), the AIC was 1715.30 and R^2 was 8.2%. In the validation cohort, the C-index of the one-year CAPSI as a categorical variable was 0.70 (0.023), the AIC was 1589.23 and R^2 was 6.3%.

Table 15 shows the statistical measures of performance with different cut-offs of the one-year CAPSI. For a cut-off point of four for the one-year CAPSI, the results of the statistical measures of performance were sensitivity 81.40%, specificity 64.47%, positive predictive value (PPV) 21.56%, and negative predictive value (NPV) 96.65% with an accuracy of 66.28% for the derivation cohort. In the validation cohort, sensitivity was 75.63%, specificity 65.09%, PPV 20.27%, and NPV 95.79% with an accuracy of 66.20%.

For a cut-off of six for the one-year CAPSI, sensitivity was 66.67%, specificity 79.81%, PPV 28.38%, and NPV 95.23% with an accuracy of 78.41% in the derivation cohort. In the validation cohort, sensitivity was 57.98%, specificity 79.59%, PPV 25%, and NPV 94.17% with an accuracy of 77.32%.

For a cut-off of eight for the one-year CAPSI, sensitivity was 39.53%, specificity 90.70%, PPV 33.77%, and NPV 95.59% with an accuracy of 85.22% in the derivation cohort. In the validation cohort, sensitivity was 40.34%, specificity 90.83%, PPV 34.04%, and NPV 92.84% with an accuracy of 85.53%.

The Greenwood-Nam-D'agostino (GND) calibration test for survival models for the multivariate model was 0.002 and 0.49 in the derivation and the validation cohorts, respectively. The GND calibration test for the survival model for the one-year CAPSI as a continuous variable was 0.03 and 0.23 in the derivation and the validation cohorts, respectively.

Finally, the GND calibration test for the survival model for one-year CAPSI as a categorical variable, i.e. the one-year CAPSI risk score, was 0.98 and 0.93 in the derivation and the validation cohorts, respectively.

Table 15. Statistical measures of performance with different cut-offs for one-year CAPSI.

	Sensitivity (%) (95%CI)	**Specificity (%) (95% CI)**	**PPV (%) (95%CI)**	**NPV (%) (95%CI)**	**Accuracy (%) (95%CI)**
Derivation					
≥4	81.40 (73.59-87.70)	64.47 (61.52-67.33)	21.56 (17.99-25.48)	96.65 (95.06-97.84)	66.28 (63.53-68.95)
≥6	95.23 (93.63-96.52)	78.41 (75.97-80.70)	66.67 (57.83-74.72)	79.81 (77.29-82.18)	28.38 (23.37-33.82)
≥8	39.53 (31.04-48.52)	90.70 (88.80-92.37)	33.77 (26.29-41.91)	92.59 (90.84-94.10)	85.22 (83.08-87.17)
Validation					
≥4	75.63 (66.91-83.03)	65.09 (62.06-68.02)	20.27 (16.63-24-32)	95.79 (94.01-97.16)	66.20 (63.36-68.95)
≥6	57.98 (48.59-66.97)	79.59 (76.97-82.03)	25 (20-30.54)	94.17 (92.38-95.64)	77.32 (74.77-79.73)
≥8	40.34 (31.45-49.72)	90.83 (88.88-92.53)	34.04 (26.28-42.49)	92.84 (91.06-94.37)	85.53 (83.3487.52)

PPV: Positive predictive value; NPV: Negative predictive value; CI: Confidence interval.

6.6 Comparison with other scores

The association between the severity of illness, measured by different risk scores, and one-year mortality in the derivation is shown in Table 16. Higher scores on PSI, CURB65, SCAP, and one-year CAPSI were associated with a higher risk of one-year mortality (Figures 2-5).

Table 16. Hazard ratios for the association between the severity of illness measured by risk scores and one-year mortality in the derivation cohort.

One-year mortality	**Beta (s.e.)**	**HR (95% CI)**	**p-value**
PSI	0.91 (0.11)	2.49 (2.02,3.06)	<0.0001
PSI			
I-III	Reference		
IV-V	1.61 (0.23)	4.99 (3.21,7.77)	<0.0001
CURB65	0.67 (0.08)	1.95 (1.66,2.30)	<0.0001
CURB65			
≤2	Reference		
>2	1.20 (0.18)	3.31 (2.34,4.68)	<0.0001
SCAP	0.67 (0.08)	1.95 (1.66,2.30)	<0.0001
SCAP			
<2	Reference		
≥2	1.41 (0.19)	4.09 (2.79, 5.98)	<0.0001
One-year CAPSI	0.21 (0.02)	1.24 (1.19,1.28)	<0.0001
One-year-CAPSI			
≤3	Reference		
>3	1.97 (0.23)	7.17 (4.62,11.74)	<0.0001

Beta (s.e): Beta regression coefficient with standard error; HR: Hazard ratio; CI: Confidence interval. PSI: Pneumonia severity index; CURB65: Confusion, urea, respiratory rate, blood pressure, age>65; SCAP: Severe community-acquired pneumonia; one-year CAPSI: one-year community-acquired severity index.

Figure 2. Kaplan-Meier survival curve for the derivation cohort, stratified by PSI risk groups.

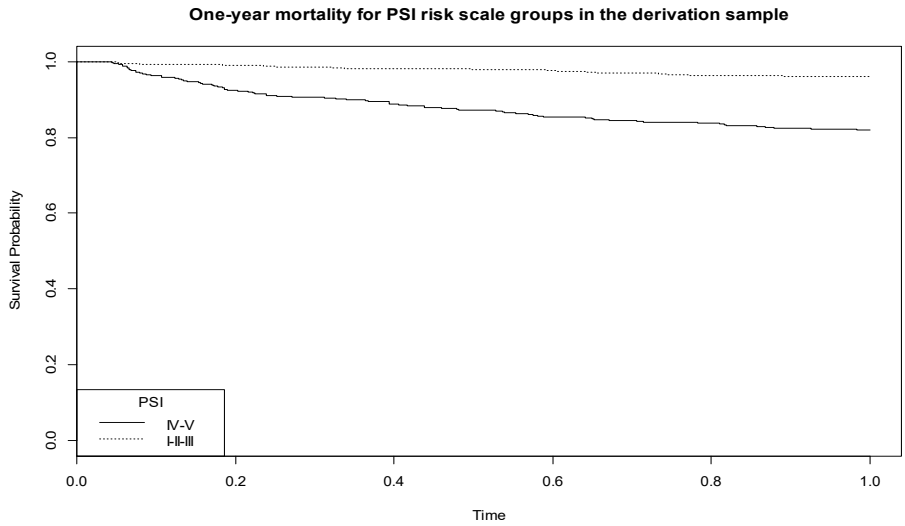


Figure 3. Kaplan-Meier survival curve for the derivation cohort, stratified by CURB65 risk groups.

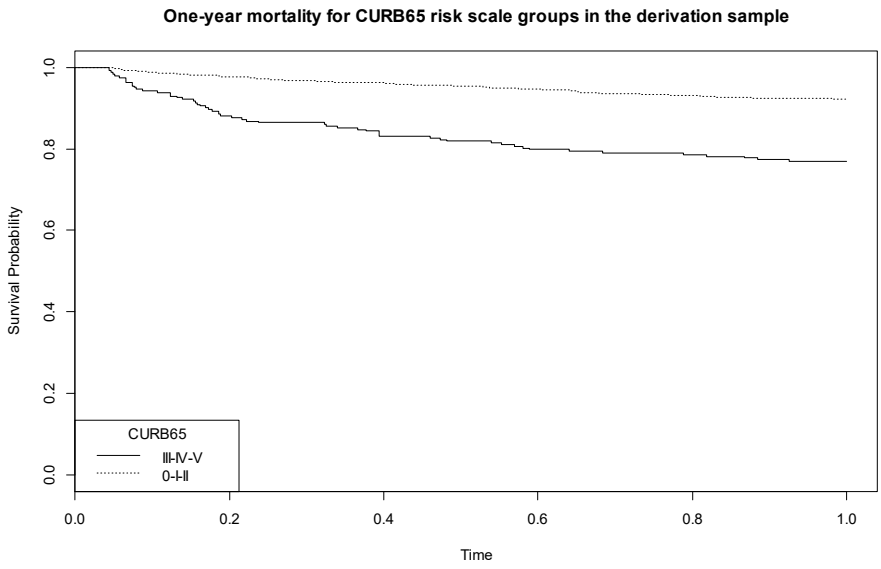


Figure 4. Kaplan-Meier survival curve for the derivation cohort, stratified by SCAP risk groups.

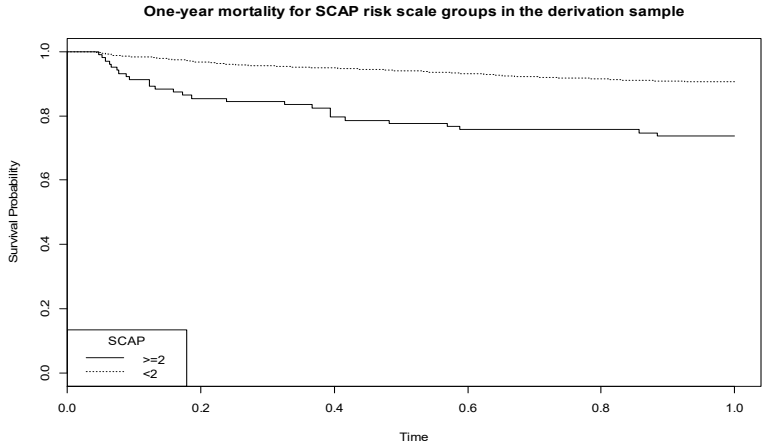


Figure 5. Kaplan-Meier survival curve for the derivation cohort, stratified by one-year CAPSI risk groups.

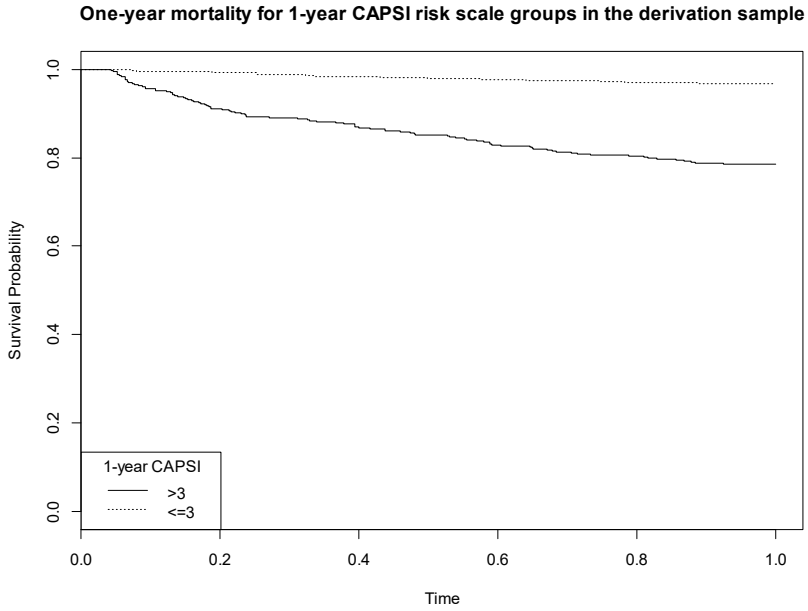


Table 17 shows the association between the severity of illness, measured by risk scores, and one-year mortality in the validation cohort. Higher scores on PSI, CURB65, SCAP, and one-year CAPSI were associated with a higher risk of one-year mortality (Figures 6-9).

Table 17. Hazard ratios for the association between the severity of illness measured by risk scores and one-year mortality in the validation cohort.

One year mortality	**Beta (s.e.)**	**HR (95% CI)**	**p-value**
PSI	1.10 (0.12)	3.00 (2.35,3.83)	<0.0001
PSI			
I-III			
IV-V	2.38 (0.33)	10.82 (5.66, 20.68)	<0.0001
CURB65	0.72 (0.09)	2.08 (1.74, 2.49)	<0.0001
CURB65			
≤2	Reference		
>2	1.17 (0.18)	3.22 (2.24,4.61)	<0.0001
SCAP	0.69 (0.09)	2.00 (1.66,2.41)	<0.0001
SCAP			
<2	Reference		
≥2	1.39 (0.20)	4.03 (2.71, 6.00)	<0.0002
One-year CAPSI	0.20 (0.02)	1.23 (1.18,1.28)	<0.0001
One-year CAPSI			
≤3	Reference		
>3	1.67 (0.21)	5.29 (3.48,8.05)	<0.0001

Beta (s.e): Beta regression coefficient with standard error HR: Hazard ratio; CI: Confidence interval. PSI: Pneumonia severity index; CURB65: Confusion, urea, respiratory rate, blood pressure, age>65. SCAP: Severe community acquired pneumonia; one-year CAPSI: one-year community-acquired severity index.

Figure 6. Kaplan-Meier survival curve for the validation cohort, stratified by PSI risk groups.

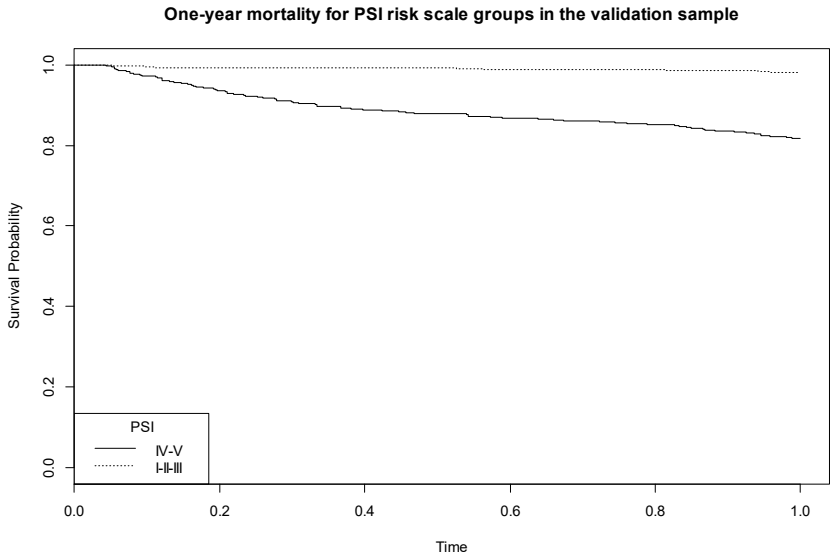


Figure 7. Kaplan-Meier survival curve for the validation cohort, stratified by CURB65 risk groups.

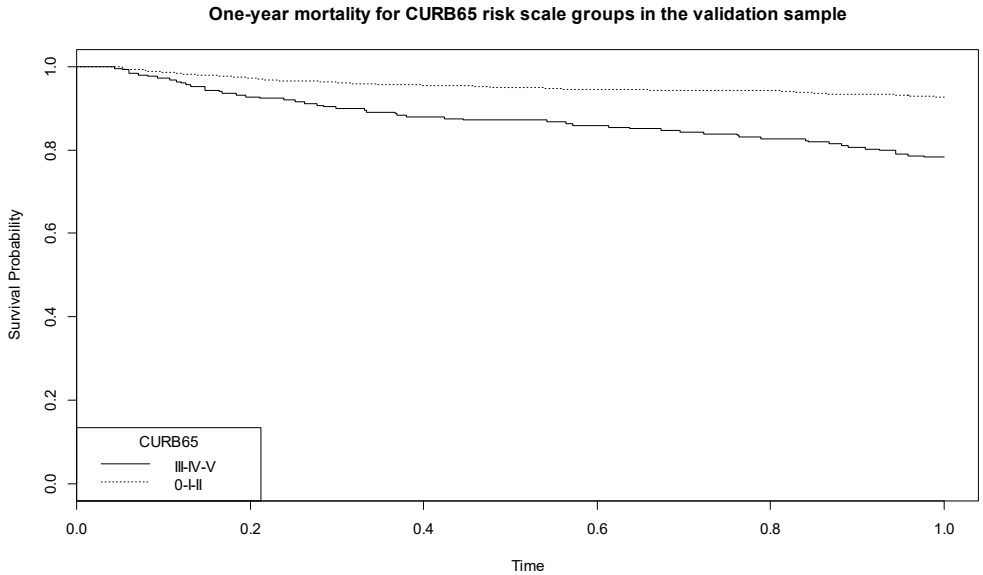


Figure 8. Kaplan-Meier survival curve for the validation cohort, stratified by SCAP risk groups.

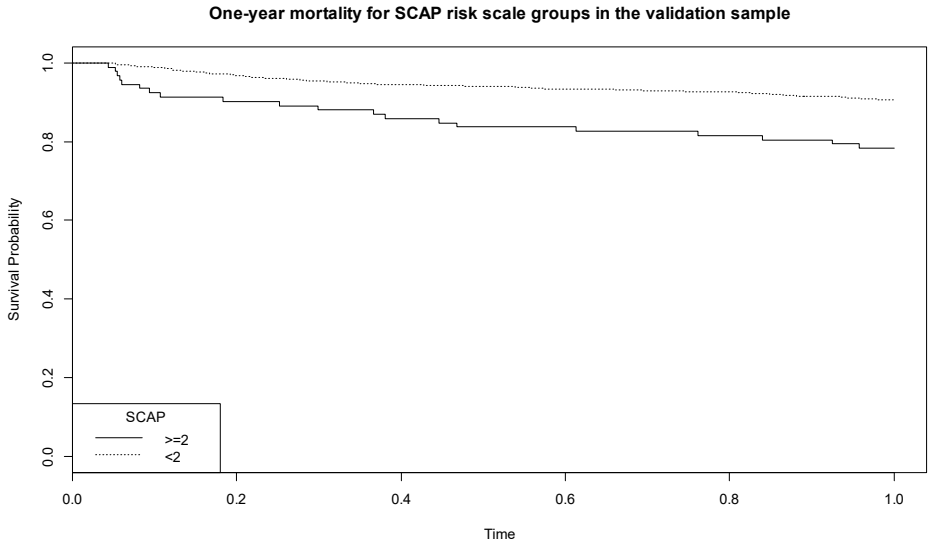


Figure 9. Kaplan-Meier survival curve for the validation cohort, stratified by one-year CAPSI risk groups.

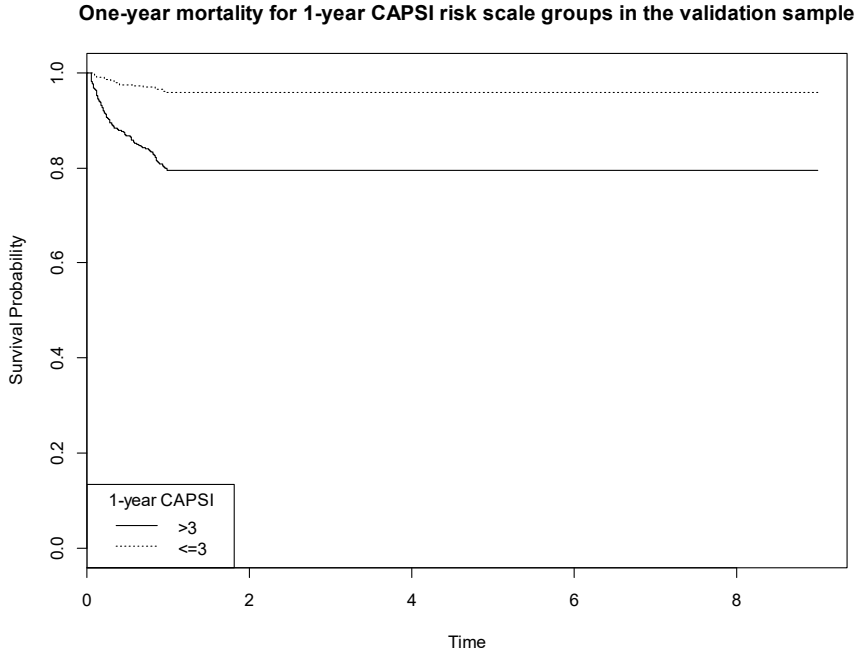


Table 18 shows the predictive accuracy of different risk scores as continuous variables for one-year mortality in the derivation and the validation cohorts. One-year CAPSI showed the best predictive accuracy in the derivation cohort with a C-index of 0.76, followed by PSI with a C-index of 0.73 (p=0.18), CURB65 0.69 (p=0.009) and SCAP 0.70 (p=0.025). Likewise, one-year CAPSI showed the best predictive accuracy in the validation cohort with a C-index of 0.77, followed by PSI with a C-index of 0.75 (p=0.39), CURB65 0.71 (p=0.03), and SCAP 0.70 (p=0.01). The p values refer to statistical differences between one-year CAPSI C-index with other prediction scores.

Table 18. Predictive accuracy and goodness of fit for one-year mortality of continuous risk scores.

	Derivation			**Validation**		
	C-index	**AIC**	**R^2**	**C-index**	**AIC**	**R^2**
PSI	0.73 (0.024)	1750.74	7.6%	0.75 (0.025)	1556.01	9.1%
CURB65	0.69 (0.024)	1782.87	5.2%	0.71 (0.025)	1598.38	5.7%
SCAP	0.70 (0.024)	1784.05	5.1%	0.70 (0.025)	1608.79	4.8%
One-year CAPSI	0.76 (0.024)	1707.43	8.8%	0.77 (0.025)	1562.67	8.5%

AIC: Akaike information criterion; R^2: R-square. PSI: Pneumonia severity index; CURB65: Confusion, urea, respiratory rate, blood pressure, age>65. SCAP: Severe community acquired pneumonia; one-year CAPSI: one-year community-acquired severity index.

Table 19 shows the predictive accuracy of different risk scores as categorical variables for one-year mortality in the derivation and the validation cohorts. One-year CAPSI showed the best predictive accuracy in the derivation cohort with a C-index of 0.72, followed by PSI with a C-index of 0.67 (p=0.065), CURB65 0.62 (p<0.001) and SCAP 0.67 (p=0.065). Likewise, one-year CAPSI showed the best predictive accuracy in the validation cohort with a C-index 0.70, followed by PSI with a C-index of 0.71 (p=0.519), CURB65 0.62 (p=0.02), and SCAP 0.67 (p=0.36). The p values refer to statistical differences between one-year CAPSI C-index with other prediction rules.

Table 19. Predictive accuracy and goodness of fit for one-year mortality of categorical risk scores.

	Derivation			Validation		
	C-index	**AIC**	**R^2**	**C-index**	**AIC**	**R^2**
PSI	0.67 (0.022)	1780.09	5.4%	0.71 (0.023)	1569.64	8%
CURB65	0.62 (0.017)	1805.63	3.3%	0.62 (0.019)	1628.26	3.2%
SCAP	0.67 (0.021)	1787.01	4.8%	0.67 (0.012)	1611.58	4.6%
one-year CAPSI	0.72 (0.021)	1715.30	8.2%	0.70 (0.023)	1589.23	6.3%

AIC: Akaike information criterion; R^2: R-square. PSI: Pneumonia severity index; CURB65: Confusion, urea, respiratory rate, blood pressure, age>65. SCAP: Severe community acquired pneumonia.

Figures 10 and 11 show the ROC analysis for continuous risk scores in the derivation and validation cohorts. Figures 12 and 13 show ROC analysis for categorical risk scores in the derivation and validation cohorts.

Figure 10. ROC curve analysis for continuous risk scores in the derivation cohort.

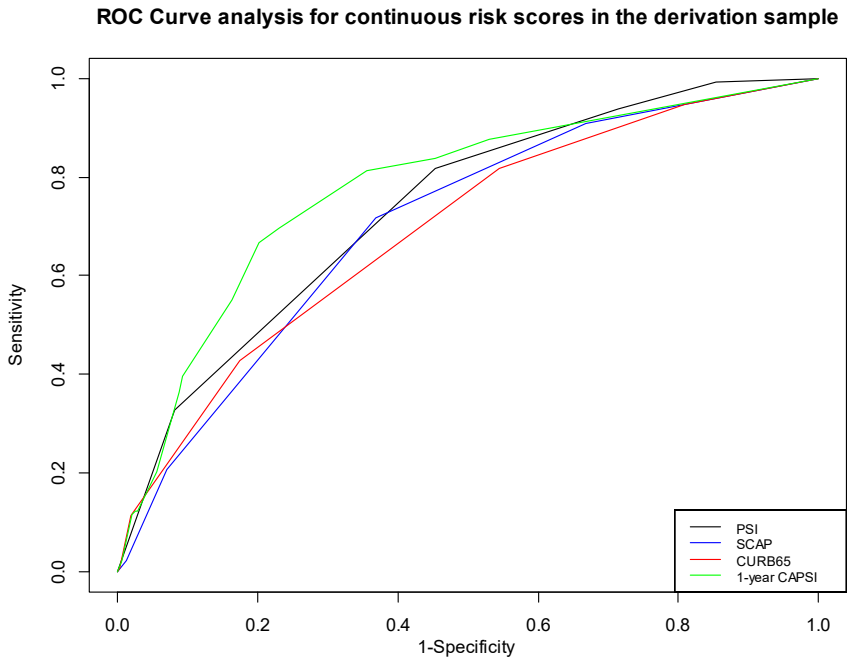


Figure 11. ROC curve analysis for continuous risk scores in the validation cohort.

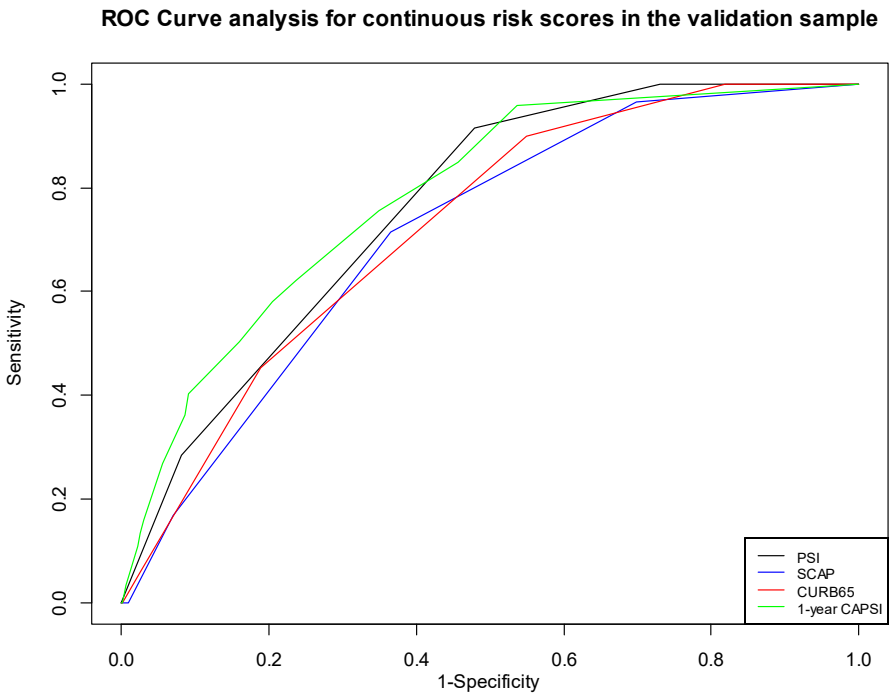


Figure 12. ROC curve analysis for categorical risk scores in the derivation cohort.

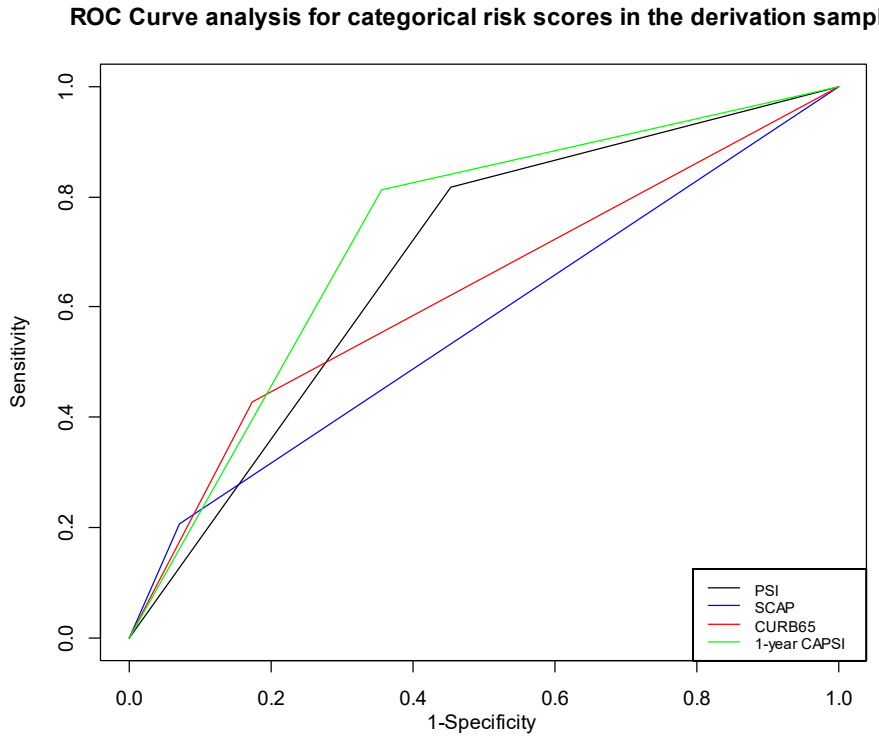
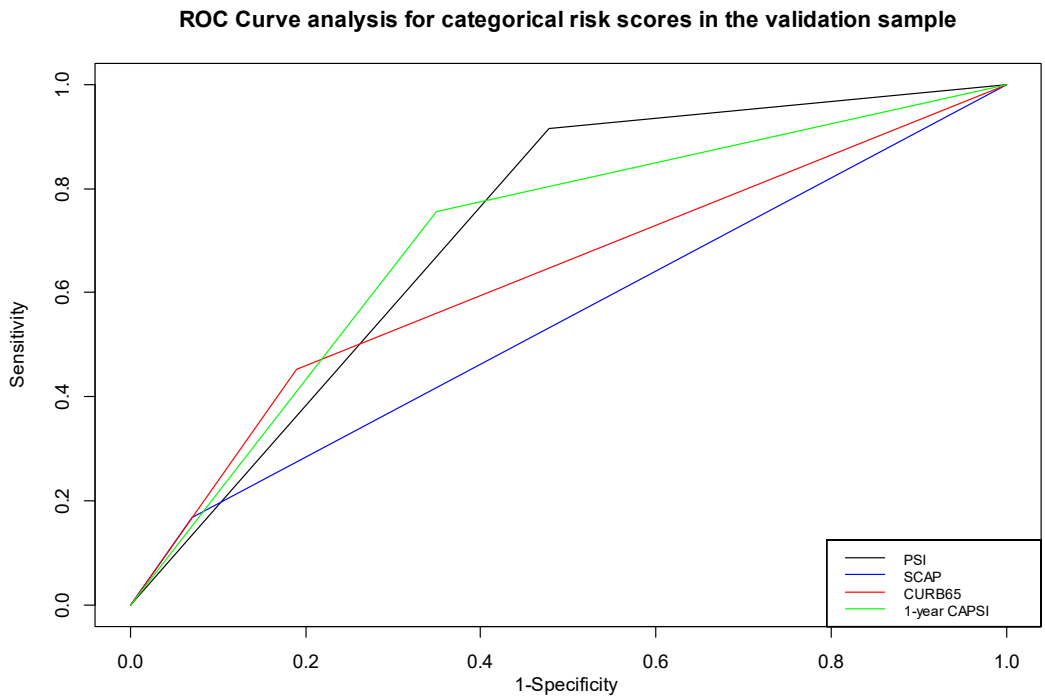


Figure 13. ROC curve analysis for categorical risk scores in the validation cohort.



STUDY II. ROLE OF BIOMARKERS FOR ONE-YEAR MORTALITY PREDICTION AMONG HOSPITALIZED PATIENTS WITH CAP IN GALDAKAO-USANSOLO HOSPITAL.

6.1 Descriptive statistics

For this second study, 231 patients in whom blood samples could be obtained were included after the exclusion of deaths within 15 days of diagnosis. Of these patients, 38.10% were ≥80 years old, male sex was more frequent and 21.21% had been on previous antibiotic treatment. COPD was the most frequent comorbidity, with diabetes mellitus and CVD being the second and third, respectively (Table 20).

Table 20. Baseline characteristics and comorbidities of hospitalized patients with CAP in which blood samples were obtained.

	n=231
Age	
<80 years	143 (61.9%)
≥80 years	88 (38.10%)
Sex	
Male	154 (66.67%)
Female	77 (33.33%)
Previous antibiotic	49 (21.21%)
Comorbidities	
Diabetes mellitus	40 (17.32%)
COPD	56 (24.24%)
Cancer	12 (5.19%)
Liver disease	7 (3.03%)
CHF	19 (8.23%)
CVD	28 (12.12%)
Dementia	28 (12.12%)
Renal failure	22 (9.52%)

Data are presented as n (%). COPD: Chronic obstructive pulmonary disease; CHF; Congestive heart failure; CVD; Cerebrovascular disease.

Table 21 shows the physical examination and radiological presentation data. Around 20% of the patients presented with confusion, diastolic blood pressure less than 60 mmHg and bilateral and or multilobar involvement at diagnosis.

Table 21. Physical examination and radiological presentation of hospitalized patients with CAP in which blood samples were obtained.

	n=231
Physical examination, n (%)	
Confusion	46 (19.91%)
HR ≥125 beats/min	31 (13.42%)
RR ≥30 breaths/min	17 (7.36%)
SBP <90 mmHg	4 (1.73%9
DBP <60 mmHg	44 (19.05%)
BT ≥40°C	1 (0.43%)
X-ray, n (%)	
Pleural effusion	24 (10.39%)
Bilateral/multilobar	43 (18.61%)
Radiological pattern, n (%)	
Alveolar	227 (98.27%)
Interstitial	3 (1.30%)
Mixed	1 (0.43%)

Data are presented as n (%). *HR*: Heart rate; RR: Respiratory rate; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; BT: Body temperature.

Table 22 shows the analytical data with 43.72% suffering from respiratory insufficiency, almost 30% presenting with a BUN higher than 30 mg/dL and 6.9% presenting with glucose >250 mg/dL. More than 80% of patients received adherent antibiotic treatment according to SEPAR guidelines and within the first 8 hours. In addition, nearly 40% received corticosteroids during hospitalization (Table 23).

Table 22. Analytical data of hospitalized patients with CAP in which blood samples were obtained.

	n=231
Analytics, n (%)	
Glucose >250 mg/dL	16 (6.93%)
BUN >30 mg/dL	67 (29%)
Sodium <130 mmol/L	13 (5.63%)
Hematocrit <30	11 (4.76%)
PaO_2 <60 mmHg	101 (43.72%)
pH arterial <7.35	13 (5.63%)

Data are presented as n (%). BUN: Blood urea nitrogen.

Table 23. Antibiotic and systemic corticosteroid treatment of hospitalized patients with CAP in which blood samples were obtained.

	n=231
Antibiotic, n (%)	
Previous antibiotic	49 (21.21%)
Antibiotic according to SEPAR guidelines	193 (83.91%)
Antibiotic within first 4 h	164 (73.54%)
Antibiotic within first 8 h	202 (90.58%)
Corticosteroids, n (%)	91 (39.39%)

Data are presented as n (%). SEPAR: Spanish Pulmonology and Thoracic Surgery Society.

Table 24 shows complications during hospitalization, the most frequent one being respiratory failure. Of these patients, 15.58% required admission to the IRCU and 5.19% admission to the ICU. However, only eight patients required vasopressors and only one patient needed invasive ventilation.

Table 24. Complications during hospitalization among hospitalized patients with CAP in which blood samples were obtained.

	n=231
ICU admission, n (%)	12 (5.19%)
IRCU admission, n (%)	36 (15.58%)
Need for IMV, n (%)	1 (0.43%)
Severe sepsis, n (%)	103(44.59%)
Need for vasopressors, n (%)	8 (3.46%)
Respiratory failure, n (%)	98 (42.42%)
Renal failure, n (%)	31 (13.42%)
Pleural effusion, n (%)	21 (9.09%)
Antibiotic AE, n (%)	10 (4.33%)
Embolism, n (%)	1 (0.43%)
DVT, n (%)	2 (0.87%)
Decompensated comorbidities, n (%)	
Diabetes mellitus	14 (6.06%)
Asthma	9 (3.90%)
COPD	10 (4.33%)
Heart disease	10 (4.33%)
Neurological disease	10 (4.33%)
Renal failure	8 (3.46%)

Data are presented as n (%). ICU: Intensive care unit; IRCU: Intermediate respiratory care unit; IMV: Invasive mechanical ventilation; AE: Adverse events; DVT: Deep vein thrombosis; COPD: Chronic obstructive pulmonary disease.

Table 25 shows the severity of illness at diagnosis. The mean PSI (SD) score was 93.30 (36.14), the mean CURB65 (SD) score was 1.71 (1.09), and the mean SCAP score was 7.79 (7.57). About 50% of the cohort was defined as severe by the PSI score, 23% by the CURB65 score and 42% by the SCAP score.

Table 25. Baseline severity of hospitalized patients with CAP in which blood samples were obtained.

	n=231
PSI mean (SD)	93.30 (36.14)
PSI, n (%)	
I	32 (13.85%)
II	26 (11.26%)
III	54 (23.38%)
IV	86 (37.23%)
V	33 (14.29%)
PSI, n (%)	
I-III	112 (48.48)
IV-V	119 (51.52%)
CURB65 mean (SD)	1.71 (1.09)
CURB65, n (%)	
0	39 (16.88%)
1	52 (22.51%)
2	86 (37.23%)
3	44 (19.05%)
4	10 (4.33%)
5	-
CURB65, n (%)	
0-2	177 (76.62%)
3-5	54 (23.38%)
SCAP mean (SD)	7.79 (7.57)
SCAP, n (%)	
O	68 (29.44%)
1	65 (28.14%)
2	75 (32.47%)
3	21 (9.09%)
4	2 (0.87%)
SCAP, n (%)	
0-1	133 (57.58%)
2-4	98 (42.42%)
One-year CAPSI mean (SD)	3.43 (3.69)
One-year CAPSI, n (%)	
≤3	129 (55.84%)
>3	102 (44.16%)

Data are presented as n (%) or mean (SD). PSI: Pneumonia severity index; CURB65: Confusion, urea, respiratory rate, blood pressure, age >65. SCAP: Severe community acquired pneumonia.

Table 26 shows the mortality rate excluding deaths within the first 15 days as well as including all deaths up to one year. Within one year, 51 (19.78%) patients died including all deaths, 20 patients during hospitalization, 7 after discharge up to 15 days after diagnosis, and 24 patients 15 days after diagnosis up to one year. After the exclusion of 27 patients who died within 15 days of diagnosis, 24 (10.39%) died within one year.

Table 26. Mortality rates of hospitalized patients with CAP in whom blood samples could be obtained (n=231).

Including all deaths within one year	**N= 258**
In-hospital mortality, n (%)	20 (7.75%)
15-day mortality[1], n (%)	27 (10.47%)
One-year mortality[2], n (%)	51 (19.78%)
Excluding deaths within 15 days	**N= 231**
One-year mortality, n (%)	24 (10.39%)

[1]Including in-hospital mortality, [2]Including all deaths within one year. Data are presented as n (%).

6.2 Biomarkers and risk scores predictive accuracy for one-year mortality, after the exclusion of deaths within 15 days

Table 27 shows the relationship between biomarker levels obtained at the time of diagnosis and severity of illness, measured by risk scores after the exclusion of deaths within the first 15 days. More severe patients measured by PSI, CURB65, SCAP, and one-year CAPSI had significantly higher levels of proADM. In addition, more severe patients measured by the one-year CAPSI had significantly lower levels of CRP.

Table 27. Relation between biomarkers and severity of illness, measured by risk scores[1].

	CRP	**PCT**	**ProADM**
PSI			
I-III (n=112)	218.7 (97-323)	0.49 (0.10-2.41)	1.00 (0.77-1.37)
IV-V (n=119)	177.4 (62.10-285.6)	0.36 (0.15-2.56)	1.64 (1.14-2.41)
p-value	0.14	0.99	<0.0001
CURB65			
≤2 (n=177)	182.2 (81-305.3)	0.37 (0.10-2.09)	1.16 (0.83-1.62)
>2 (n=54)	198.25 (73-341.9)	0.87 (0.20-3.68)	1.97 (1.31-2.67)
p-value	0.36	0.08	<0.0001
SCAP			
<2 (n=133)	210.55 (89.6-289.6)	0.52 (0.12-2.41)	1.01 (0.80-1.40)
≥2 (n= 98)	176.1 (64.0-341.9)	0.35 (0.14-2.13)	1.68 (1.23-2.41)
p-value	0.24	0.73	<0.0001
One-year CAPSI			
≤3 (n=129)	243.7 (91-353.3)	0.64 (0.12-2.75)	1.05 (0.78-1.56)
>3 (n=102)	147.85 (62.1-256.9)	0.3 (0.13-1.44)	1.58 (1.14-2.05)
p-value	0.0025	0.08	<0.0001

[1]After exclusion of deaths within 15 days. Data are presented as median (IQR) of each biomarker. CRP: C reactive protein; PCT: Procalcitonin; ProADM: Proadrenomedullin; PSI: Pneumonia severity index. CURB65: Confusion, Urea, Respiratory rate, Blood pressure, age>65. SCAP: Severe community-acquired. Pneumonia; one-year CAPSI: one-year community-acquired pneumonia severity index.

Table 28 shows the Cox regression model with the predictive ability of biomarkers for one-year mortality as continuous variables showing a poor predictive accuracy with a C-index of 0.57 for CRP (p=0.11), 0.51 for PCT (p value=0.55), and 0.64 for proADM (p=0.39).

Table 28. Survival models of the predictive accuracy of biomarkers for one-year mortality, as continuous variables[1].

One-year mortality	HR (95% CI)	C-index	AIC	R^2	p-value
CRP	0.99 (0.99,1.00)	0.57 (0.05)	257.91	1.2%	0.11
PCT	0.98 (0.91,1.05)	0.51 (0.06)	225.04	0.2%	0.55
proADM*	1.01 (0.99,1.04)	0.64 (0.06)	259.04	0.3%	0.39

[1]After exclusion of deaths within 15 days. *for 0.1- nmol/L increment. HR: Hazard ratio; CI: Confidence interval; AIC: Akaike information criterion; R^2: R-square. CRP: C reactive protein; PCT: Procalcitonin; ProADM: Proadrenomedullin.

Table 29 shows the Cox regression model with the predictive ability of risk scores for one-year mortality. All the scores demonstrated a high predictive capacity, with a C-index of 0.78 (0.05) for one-year CAPSI (p=<0.001).

Table 29. Predictive accuracy of risk scores for one-year mortality, as continuous variables[1].

One-year mortality	HR (95% CI)	C-index	AIC	R^2	p-value
PSI	4.20 (2.28, 7.72)	0.80 (0.06)	226.00	13.8%	<0.001
CURB65	1.96 (1.32, 2.90)	0.70 (0.06)	247.43	5.8%	<0.001
SCAP	2.64 (1.76, 3.96)	0.77 (0.06)	236.95	9.6%	<0.001
one-year CAPSI	1.21 (1.11,1.32)	0.75 (0.06)	243.18	7%	<0.001

[1]After exclusion of deaths within 15 days. HR: Hazard ratio; CI: Confidence interval; AIC: Akaike information criterion; R^2: R-square. PSI: Pneumonia Severe Index. CURB65: Confusion, Urea, Respiratory rate, Blood pressure, age>65. SCAP: Severe Community Acquired Pneumonia; one-year CAPSI: one-year community-acquired pneumonia severity index.

Table 30 shows risk scores prediction ability for one-year mortality once proADM was added. In all cases, proADM failed to improve the predictive accuracy. The C-index values were PSI + proADM 0.82 (0.06), CURB65 + proADM 0.70 (0.06), SCAP + proADM 0.77 (0.06), and one-year CAPSI + proADM 0.75 (0.06) (p values= 0.05, 0.42, 0.38, 0.83, respectively).

Table 30. Nested model comparison to assess risk scores ability with the proADM value added[1].

One-year mortality	**C-index**	**AIC**	**p-value**
PSI	0.80 (0.06)	226.00	Ref.
PSI + ProADM	0.82 (0.06)	224.04	0.05
CURB65	0.70 (0.06)	247.43	Ref.
CURB65 + ProADM	0.70 (0.06)	248.77	0.42
SCAP	0.77 (0.06)	236.95	Ref.
SCAP + ProADM	0.77 (0.06)	238.17	0.38
One-year CAPSI	0.75 (0.06)	243.18	Ref.
One-year CAPSI + ProADM	0.75 (0.06)	245.14	0.83

[1]After exclusion of deaths within 15 days. AIC: Akaike information criterion; R^2: R-square. P-value indicate the statistical significance comparing with the same model without the biomarker. ProADM: Proadrenomedullin; PSI: Pneumonia Severe Index. CURB65: Confusion, Urea, Respiratory rate, Blood pressure, age>65. SCAP: Severe Community Acquired Pneumonia; one-year CAPSI: one-year community-acquired pneumonia severity index.

6.3 Biomarkers and risk scores predictive accuracy for one-year mortality, with the inclusion of all deaths within one year

In order to assess the impact of short-term mortality, a similar analysis was carried out including all deaths. Table 31 shows the relationships between biomarker levels obtained at the time of diagnosis and the severity of illness, measured by risk scores including all deaths up to one year. Similarly, more severe patients measured by PSI, CURB65, SCAP, and one-year CAPSI had significantly higher levels of proADM. In addition, more severe patients, measured by one-year CAPSI, had significantly lower levels of CPR at diagnosis.

Table 31. Relation between biomarkers and severity of illness, measured by risk scores[1].

	CRP	**PCT**	**ProADM**
PSI			
I-III (n=113)	219.3 (103-328)	0.48 (0.09-2.41)	1.00 (0.77-1.38)
IV-V (n=145)	177.4 (72.6-279.1)	0.43 (0.15-2.99)	1.68 (1.17-2.51)
p-value	0.11	0.75	<0.0001
CURB65			
≤2 (n=187)	181.1 (81-297.6)	0.36 (0.09-2.09)	1.17 (0.83-1.67)
>2 (n=71)	200.3 (90.3-355.5)	0.93 (0.2-3.87)	2.06 (1.49-2.93)
p-value	0.65	0.01	<0.0001
SCAP			
<2 (n=135)	211 (89.6-289.6)	0.52 (0.12,2.41)	1.01 (0.80-1.43)
≥2 (n=123)	174 (73-341.9)	0.43 (0.15-2.98)	1.74 (1.27-2.54)
p-value	0.34	0.96	<0.0001
One-year CAPSI			
≤3 (n=130)	244.35 (91-353.3)	0.66 (0.13-1.81)	1.06 (0.78-1.56)
>3 (n=128)	149.7 (65.5,257.85)	0.31 (0.14-1.81)	1.67 (1.18-2.28)
p-value	0.0038	0.13	<0.0001

[1]Including all deaths within one year. Data are presented as median (IQR).CRP: C reactive protein; PCT: Procalcitonin; ProADM: Proadrenomedullin. PSI: Pneumonia Severe Index; CURB65: Confusion, Urea, Respiratory rate, Blood pressure, age>65; SCAP: Severe Community Acquired Pneumonia; one-year CAPSI: one-year community-acquired pneumonia severity index.

Table 32 shows the Cox regression models with the predictive ability of biomarkers for one-year mortality including all deaths within one year. ProADM showed a high predictive accuracy for one-year mortality with a C-index of 0.71 (0.04), (p<0.001). However, both CRP and PCT showed a low predictive accuracy for one-year mortality (C-index 0.54 (0.04), p=0.24; C-index 0.53 (0.04), p=0.47). All risk scores showed a high predictive accuracy for one-year mortality when all deaths were included (Table 33).

Table 32. Predictive accuracy of biomarkers for one-year mortality.

One-year mortality	**HR (95% CI)**	**C-index**	**AIC**	**R^2**	**p-value**
PCR	1.00 (0.99,1.00)	0.54 (0.04)	556.52	0.6%	0.24
PCT	1.01 (0.98,1.04)	0.53 (0.04)	485.71	0.2%	0.47
PROADM*	1.03 (1.02, 1.04)	0.71 (0.04)	518.52	5.8%	<0.001

[1]Including all deaths within one year. HR: Hazard ratio; CI: Confidence interval; AIC: Akaike information criterion; R^2: R-square. CRP: C reactive protein; PCT: Procalcitonin; ProADM: Proadrenomedullin. *for 0.1-unit increment

Table 34 shows the risk scores when the proADM value was added when all deaths within one year were included in the analysis. ProADM failed to improve the predictive accuracy of the PSI score for one-year mortality 0.79 (0.04), p=0.15. The predictive ability of CURB65 significantly improved when proADM was added, i.e. 0.74 (0.04), p=0.0498. ProADM failed to improve the predictive accuracy of the SCAP score for one-year mortality, i.e. 0.80 (0.04), p= 0.21. Finally, the predictive accuracy of the one-year CAPSI improved up to 0.83 (0.04) when proADM was added, p=0.010.

Table 33. Predictive accuracy of risk scores for one-year mortality[1].

One-year mortality	HR (95% CI)	C-index	AIC	R^2	p-value
PSI	3.27 (2.20,4.85)	0.77 (0.04)	481.37	18.8%	<0.001
CURB65	2.15 (1.64,2.83)	0.71 (0.04)	500.70	12.3%	<0.001
SCAP	2.95 (2.23,3.92)	0.79 (0.04)	473.09	21.4%	<0.001
one-year CAPSI	1.27 (1.20,1.35)	0.81 (0.04)	474.91	20.9%	<0.001

[1]Including all deaths within one year. HR: Hazard ratio; CI: Confidence interval; AIC: Akaike information criterion; R^2: R-square. PSI: Pneumonia Severe Index. CURB65: Confusion, Urea, Respiratory rate, Blood pressure, age>65. SCAP: Severe Community Acquired Pneumonia; one-year CAPSI: one-year community-acquired pneumonia severity index.

Table 34. Nested model comparison to assess the predictive accuracy of risk scores when the proADM value was added[1].

One-year mortality	C-index	AIC	p-value
PSI	0.77 (0.04)	481.37	Ref.
PSI + ProADM	0.79 (0.04)	481.34	0.15
CURB65	0.71 (0.04)	500.70	Ref.
CURB65 + ProADM	0.74 (0.04)	498.75	0.0498
SCAP	0.79 (0.04)	473.09	Ref.
SCAP + ProADM	0.80 (0.04)	473.54	0.21
One-year CAPSI	0.81 (0.04)	474.91	Ref.
One-year CAPSI + ProADM	0.83 (0.04)	470.61	0.010

[1]Including all deaths within one year. AIC: Akaike information criterion; R^2: R-squared. ProADM: Proadrenomedullin; PSI: Pneumonia Severe Index. CURB65: Confusion, Urea, Respiratory rate, Blood pressure, age>65. SCAP: Severe Community Acquired Pneumonia; one-year CAPSI: one-year community-acquired pneumonia severity index.

6.4 Role of serial biomarkers levels in one-year mortality prediction

Descriptive values of biomarker levels at diagnosis, at 3-5 days and changes from the first 24 hours to 3-5 days are shown in Table 35. Biomarker changes was calculated by subtracting the biomarker value at 3-5 days from the baseline value. In an attempt to assess the predictive accuracy of biomarkers over time, blood samples were obtained from 117 patients at 3-5 days.

Table 35. Biomarker levels at diagnosis and at 3-5 days.

Biomarker	**24 hours**	**3-5 days**	**Change***
CRP	200.3 (81,353.3)	78 (44,148)	94 (-2.5, 212.2)
PCT	0.52 (0.15,2.36)	0.32 (0.13,0.88)	0.19 (0.001,1.7)
ProADM	1.28 (0.92,1.82)	0.86 (0.651.14)	0.32 (0.10,0.78)

*Change was calculated by subtracting the biomarker value at 3-5 days from the baseline value. Data are presented as median (IR)

Taking into account that proADM showed better predictive accuracy for one-year mortality than the other biomarkers, a subanalysis was carried out with this specific biomarker. ProADM change was obtained by subtracting the proADM value at 3-5 days from the proADM value at the time of diagnosis.

Table 36 shows the predictive accuracy of proADM changes for one-year mortality among three different samples adjusted by proADM value at baseline: after the exclusion of deaths within 15 days from diagnosis, including all deaths within one year, and excluding patients who died from 15 days to one year. In all cases, proADM changes showed a statistically significant predictive accuracy for one-year mortality. Hence, for each 0.1-nmol/L decrease in proADM from admission to 3-5 days, mortality rate decreases 8% for one-year mortality, excluding deaths within 15 days from diagnosis.

Table 36. Predictive accuracy of proADM change for one-year mortality[]

One-year mortality	HR (95% CI)	C-index	AIC	R^2	p-value
ProADMchange[1]	0.92 (0.84,1.00)	0.72 (0.08)	143.23	3.4%	0.04
ProADMchange[2]	0.88 (0.83,0.93)	0.78 (0.06)	193.80	15.2%	<0.001
ProADMchange[3]	0.87 (0.78,0.92)	0.92 (0.11)	50.48	15.5%	<0.001

[] Adjusted by proADM value at baseline.[1]Excluding deaths within 15 days of diagnosis, [2]Including all deaths within one year, [3]Excluding patients who died from 15 days after diagnosis to one year. The p values refer to the proADMchanges. HR: Hazard ratio; CI: Confidence interval; AIC: Akaike information criterion; R^2: R-square.ProADM difference: obtained by subtracting the proADM value at 3-5 days from proADM value at the time of diagnosis;

Table 37 shows the predictive accuracy of the proADM change for one-year mortality after the exclusion of deaths within 15 days, adjusted by risk scores and the proADM value at baseline. In this case, ProADM changes failed to predict one-year mortality. The same analysis was carried out including all deaths within one year, as shown in table 38. For each 0.1-nmol/L decrease in proADM from admission to 3-5 days, the mortality rate decreased by 9% when adjusted by the one-year CAPSI and proADM baseline value.

Table 37. Predictive accuracy of proADM change for one-year mortality among different risk scores, after the exclusion of deaths ≤ 15 days[].

One-year mortality	HR (95% CI)	C-index	AIC	R^2	p-value
ProADMchange* (PSI)	1.02 (0.91, 1.13)	0.70 (0.08)	129.35	5.6%	0.76
ProADMchange* (SCAP)	0.94 (0.84, 1.04)	0.76 (0.08)	137.79	8.9%	0.24
ProADMchange* (CURB65)	0.93 (0.84,1.02)	0.70 (0.08)	142.40	5.6%	0.13
ProADMchange*(one-year CAPSI)	0.95 (0.86, 1.05)	0.75 (0.08)	141.76	6%	0.32

[]Adjusted by severity and proADM value at baseline, *for each 0.1-nmol/L increment. The p values refer to the proADMchanges. HR: Hazard ratio; CI: Confidence interval; AIC: Akaike information criterion; R^2: R-square. ProADM difference: obtained by subtracting PRADM value at 3-5 days from proADM value at the time of diagnosis; PSI: Pneumonia Severe Index. CURB65: Confusion, Urea, Respiratory rate, Blood pressure, age>65. SCAP: Severe Community Acquired Pneumonia; one-year CAPSI: one-year community-acquired pneumonia severity index.

Table 38. Predictive accuracy of proADM difference for one-year mortality among different risk scores, including all deaths within one year[1].

One-year mortality	HR (95% CI)	C-index	AIC	R^2	p-value
ProADMchange* (PSI)	0.92 (0.86,0.98)	0.83 (0.06)	187.09	20.5%	0.007
ProADMchange* (SCAP)	0.88 (0.83,0.94)	0.79 (0.06)	187.81	20.1%	<0.001
ProADMchange* (CURB65)	0.87 (0.82,0.93)	0.78 (0.06)	189.74	18.9%	<0.001
ProADMchange*(one-year CAPSI)	0.91 (0.85,0.96)	0.80 (0.06)	188.20	19.9%	0.0015

[1]Adjusted by severity and proADM value at baseline,*for each 0.1-nmol/L increment. HR: Hazard ratio; CI: Confidence interval; AIC: Akaike information criterion; R^2: R-square. ProADM difference: obtained by subtracting PRADM value at 3-5 days from ProADM value at the time of diagnosis; PSI: Pneumonia Severe Index. CURB65: Confusion, Urea, Respiratory rate, Blood pressure, age>65. SCAP: Severe Community Acquired Pneumonia; one-year CAPSI: one-year community-acquired pneumonia severity index.

In addition, the same analysis was carried out after excluding patients who died between 15 days from diagnosis and one year (Table 39). ProADM changes adjusted by severity showed a high predictive accuracy with a C-index of 0.94 (0.11) for one-year CAPSI. For each 0.1-nmol/L decrease in proADM from admission to 3-5 days, the mortality rate decreased by 11% when adjusted by the one-year CAPSI and proADM value at baseline.

Table 39. Predictive accuracy of the proADM difference for one-year mortality among different risk scores, excluding patients who died between 15 days after diagnosis and one year[1].

One-year mortality	HR (95% CI)	C-index	AIC	R^2	p-value
ProADMchange* (PSI)	0.86 (0.79,0.93)	0.92 (0.11)	51.23	16.04%	0.0003
ProADMchange* (SCAP)	0.84 (0.77,0.92)	0.90 (0.11)	49.02	17.9%	<0.0001
ProADMchange* (CURB65)	0.79 (0.71,0.90)	0.94 (0.11)	43.92	21.4%	0.0001
ProADMchange*(one-year CAPSI)	0.89 (0.82,0.96)	0.94 (0.11)	44.99	20.70%	0.004

[1]Adjusted by severity and proADM value at baseline, *for each 0.1-nmol/L increment. HR: Hazard ratio; CI: Confidence interval; AIC: Akaike information criterion; R^2: R-square. ProADM difference: obtained by subtracting PRADM value at 3-5 days from ProADM value at the time of diagnosis; PSI: Pneumonia Severe Index. CURB65: Confusion, Urea, Respiratory rate, Blood pressure, age>65. SCAP: Severe Community Acquired Pneumonia; one-year CAPSI: one-year community-acquired pneumonia severity index.

STUDY III. ONE-YEAR MORTALITY PREDICTION AMONG HOSPITALIZED PATIENTS WITH CAP IN THE VETERANS AFFAIRS MEDICAL CENTER OF LOUISVILLE, KENTUCKY.

6.1 Descriptive statistics

A total of 455 patients were included in the analysis. Of these, 121 (27%) patients died within one year while 265 (58%) of patients died within five years. All patients were male, 39.56% were older than 75, and almost half of the cohort were current smokers. Hypertension, COPD, and CAD were the most frequent comorbidities. In addition, almost half of the cohort had an albumin <3.5 and a BUN >20 mg/dL (Tables 40 and 41).

Table 40. Baseline characteristics and comorbidities of hospitalized patients with CAP.

	n=455
Age ≥75 years	180 (39.56%)
Sex (male)	455 (100%)
Current smoker	191 (42.26%)
BMI <21	40 (8.93%)
Nursing home resident	17 (3.74%)
Suspicion of aspiration	18 (4.25%)
Hypertension	320 (70.33%)
Diabetes	157 (34.51%)
COPD	227 (49.89%)
Cancer	58 (12.75%)
CHF	117 (25.71%)
CAD	198 (43.52%)
CVD	57 (12.53%)
Dementia	39 (9.21%)
Renal disease	67 (14.73%)
Liver disease	15 (3.3%)

Data are presented as n (%). BMI: Body mass index; COPD: Chronic obstructive pulmonary disease; CHF: Congestive heart failure; CAD: Coronary artery disease; CVA: Cerebrovascular disease.

Table 41. Physical examination and analytics of hospitalized patients with CAP.

	n=455
Respiratory rate >30 breaths/min	44 (9.67%)
BUN >20 mg/dL	237 (52.43%)
Albumin <3.5 mg/dL	216 (47.47%)
Hematocrit <30%	26 (5.71%)
Platelets <100x10^9/L or >400x10^9/L, n (%)	78 (17.18%)

Data are presented as n (%). BUN: blood urea nitrogen.

Patient sociodemographic characteristic and comorbidities were compared between study I and study III (Table 42). Patients in study III were all men, were significantly younger, and more frequently presented diabetes mellitus, COPD, cancer, CHF, CAD, CVD, and renal failure. In addition, patients in study III were more severe at admission, measured by PSI, and more frequently had a respiratory rate ≥30 breaths/min, BUN >30 mg/dL, and hematocrit <30% compared with patients in study I.

From the initial 2351 patients at Galdakao-Usansolo Hospital, 250 (10.63%) patients died within one year after the exclusion of deaths within the first 15 days, while 120 (27.71%) patients died in the sample of patients hospitalized at the Veterans Affairs Medical Center in Louisville, Kentucky.

One-year CAPSI was applied to this sample and it failed to properly validate the previous results with a C-index of 0.62 (0.03), AIC of 1405.44, and R^2 5.1%.

Table 42. Comparison of patient sociodemographic characteristics and comorbidities between study I and study III.

	STUDY I	**STUDY III**	**p-value**
Age, n (%)			0.0001
≥80 years	784 (33.35%)	115 (24.42%)	
<80 years	1567 (66.65%)	356 (75.58%)	
Sex, n (%)			<0.0001
Male	1540 (65.50%)	471 (100%)	
Female	811 (34.50%)	0 (0%)	
Nursing home, n (%)	154 (6.55%)	20 (4.25%)	0.05
Aspiration	80 (3.40%)	20 (4.28%)	0.33
Comorbidities, n (%)			
Diabetes mellitus	362 (15.54%)	160 (33.97%)	<0.0001
COPD	613 (26.23%)	235 (49.89%)	<0.0001
Cancer	130 (5.53%)	69 (14.65%)	<0.0001
CHF	180 (7.66%)	120 (25.48%)	<0.0001
CAD	224 (9.58%)	198 (42.04%)	<0.0001
CVD	199 (8.46%)	55 (11.68%)	0.03
Dementia	230 (9.84%)	48 (10.28%)	0.79
Renal failure	176 (7.49%)	70 (14.86%)	<0.0001
Respiratory rate ≥30 breaths/min	354 (15.06%)	48 (10.19%)	0.005
BUN >30 mg/dL	661 (28.12%)	116 (24.63%)	0.12
Hematocrit <30%	57 (2.42%)	31 (6.58%)	<0.0001
PSI mean (SD)	91.48 (32.20)	97.23 (37.24)	0.0019
PSI, n (%)			0.0063
I-III	1157 (49.21%)	199 (42.25%)	
IV-V	1194 (50.79%)	272 (57.75%)	

Data are presented as n (%) or mean (SD); COPD: Chronic obstructive pulmonary disease; CHF: Congestive heart failure; CAD: Coronary artery disease; CVA: Cerebrovascular disease; BUN: Blood urea nitrogen.

6.2 Univariate analysis

Table 43 shows the patient characteristics among survivors and non-survivors at one year. Compared to those who survived at one year, non-survivors were older, were more frequently nursing home residents, and more frequently had cancer, COPD, CVD, and dementia. In addition, non-survivors presented with lower levels of albumin and hematocrit and more frequently had BUN >20 mg/dL and platelet counts <100,000 or >400,000/L.

Table 43. Characteristics among survivors and non-survivors at one year.

Variable	**Alive**	**Dead**	**p-value**
Age, median (IQR)	70 (22)	75 (12)	<0.001
Age ≥75 years, n (%)	118 (35)	62 (51)	0.002
Current smoker, n (%)	146 (44)	45 (37)	0.198
BMI <21, n (%)	26 (8)	14 (12)	0.259
Nursing home resident, n (%)	5 (1)	12 (10)	<0.001
Suspicion of aspiration, n (%)	10 (3)	8 (7)	0.179
Hypertension, n (%)	231 (69)	89 (74)	0.417
Diabetes, n (%)	113 (34)	44 (36)	0.656
COPD, n (%)	167 (50)	60 (50)	>0.999
Cancer, n (%)	15 (4)	43 (36)	<0.001
CHF, n (%)	83 (25)	34 (28)	0.544
CAD, n (%)	140 (42)	58 (48)	0.285
CVD, n (%)	32 (10)	24 (20)	0.006
Dementia, n (%)	19 (6)	20 (17)	0.002
Renal disease, n (%)	48 (14)	19 (16)	0.765
Liver disease, n (%)	9 (3)	6 (5)	0.241
Respiratory rate >30 breaths/min, n (%)	30 (9)	14 (12)	0.472
BUN >20 mg/dL, n (%)	164 (49)	73 (61)	0.033
Albumin <3.5 mg/dL, n (%)	148 (44)	68 (56)	0.026
Hematocrit <30%, n (%)	9 (3)	17 (14)	<0.001
Platelets <100x10^9/L or >400x10^9/L, n (%)	44 (13)	34 (28)	<0.001
pO_2/FiO_2 <250 mmHg, n (%)	85 (46)	31 (43)	0.78

Data are presented as n (%) and median (IQR). BMI: Body mass index; COPD: Chronic obstructive pulmonary disease; CHF: Congestive heart failure; CAD: Coronary artery disease; CVA: Cerebrovascular accident; BUN: blood urea nitrogen.

Those patients who died within five years were also older, were more frequently nursing home residents, and more frequently had cancer, COPD, CVD, and dementia. Similarly, non-survivors at five years presented with lower levels of albumin and hematocrit and more frequently had BUN >20 mg/dL and platelet counts <100,000 or >400,000/L (Table 44).

Table 44. Characteristics among survivors and non-survivors at five years.

Variable	**Alive**	**Dead**	**p-value**
Age, median (IQR)	66 (20.8)	74 (17)	<0.001
Age ≥75 years, n (%)	55 (29)	125 (47)	<0.001
Current smoker, n (%)	84 (45)	107 (40)	0.384
BMI <21, n (%)	12 (6)	28 (11)	0.133
Nursing home resident, n (%)	2 (1)	15 (6)	0.011
Suspicion of aspiration, n (%)	4 (3)	14 (5)	0.218
Hypertension, n (%)	130 (68)	190 (72)	0.468
Diabetes, n (%)	67 (35)	90 (34)	0.842
COPD, n (%)	82 (43)	145 (55)	0.017
Cancer, n (%)	8 (4)	50 (19)	<0.001
CHF, n (%)	40 (21)	77 (29)	0.064
CAD, n (%)	71 (37)	127 (48)	0.028
CVD, n (%)	18 (9)	38 (14)	0.148
Dementia, n (%)	7 (4)	32 (12)	0.009
Renal disease, n (%)	25 (13)	42 (16)	0.503
Liver disease, n (%)	4 (2)	11 (4)	0.292
Respiratory rate >30 breaths/min, n (%)	15 (8)	29 (11)	0.335
BUN >20 mg/dL, n (%)	88 (47)	149 (57)	0.036
Albumin <3.5 mg/dL, n (%)	78 (41)	138 (52)	0.022
Hematocrit >30%, n (%)	3 (2)	23 (9)	0.001
Platelets $<100x10^9$/L or $>400x10^9$/L, n (%)	21 (11)	57 (22)	0.004
pO_2/FiO_2 <250 mmHg, n (%)	47 (47)	69 (44)	0.798

Data are presented as n (%) and median (IQR). BMI: Body mass index; COPD: Chronic obstructive pulmonary disease; CHF: Congestive heart failure; CAD: Coronary artery disease; CVA: Cerebrovascular accident; BUN: blood urea nitrogen.

6.3 Multivariate analyses and score development

Table 45 shows the one-year prediction score. A score based on age ≥75 years, cancer, CHF, dementia, albumin <3.5mg/dL and platelets <100.000 or >400.000/L could predict one-year mortality with an AUC of 0.77. When the same score was used to predict five-year mortality, the AUC was 0.70. Representation of the score for one-year and five-year mortality is shown in Figure 14.

Table 45. One-year mortality prediction score.

Variable	Beta (se)	Statistic	p-value	Weight
Intercept	-2.28 (0.26)	-8.78	<0.001	
Age ≥75 years	0.65 (0.26)	2.51	0.01	2
Cancer	2.52 (0.34)	7.29	<0.001	7
CHF	0.40 (0.28)	1.44	0.15	1
Dementia	1.25 (0.37)	3.38	<0.0001	4
Albumin <3.5 mg/dL	0.55 (0.25)	2.18	0.03	2
Platelets<100x10^9/Lor>400x10^9/L	0.72 (0.31)	2.32	0.02	2
ONE YEAR AUC		**0.77**		
FIVE YEARS AUC		**0.70**		

Beta (s.e): Beta regression coefficient with standard error; AUC: Area under the curve; BMI: Body mass index; CHF: Congestive heart failure;

Table 46 shows the five-year prediction score. Age ≥75 years old, aspiration, being nursing home resident, cancer, CHF, underweight, and platelets <100,000 or >400,000/L could predict five-year mortality with an AUC of 0.69. Representation of this second score for five-year mortality is shown in Figure 15.

Table 46. Five-year mortality prediction score.

Variable	Beta (s.e)	Statistic	p-value	Weight
Intercept	-0.42 (0.17)	-2.50	0.01	
Age ≥75	0.95 (0.23)	4.05	<0.001	2
BMI <21	0.92 (0.44)	2.08	0.04	2
Nursing home	1.94 (1.06)	1.82	0.07	3
Aspiration	0.85 (0.60)	1.40	0.16	2
Cancer	1.4 (0.41)	3.41	0.0006	2
CHF	0.80 (0.27)	2.94	0.003	2
Platelets <100x10^9/L or >400x10^9/L	0.75 (0.31)	2.41	0.02	1
AUC	**0.69**			

Beta (s.e): Beta regression coefficient with standard error; AUC: Area under the curve; BMI: Body mass index; CHF: Congestive heart failure

Figure 14. Representation of the initial score to predict one-year and five-year mortality.

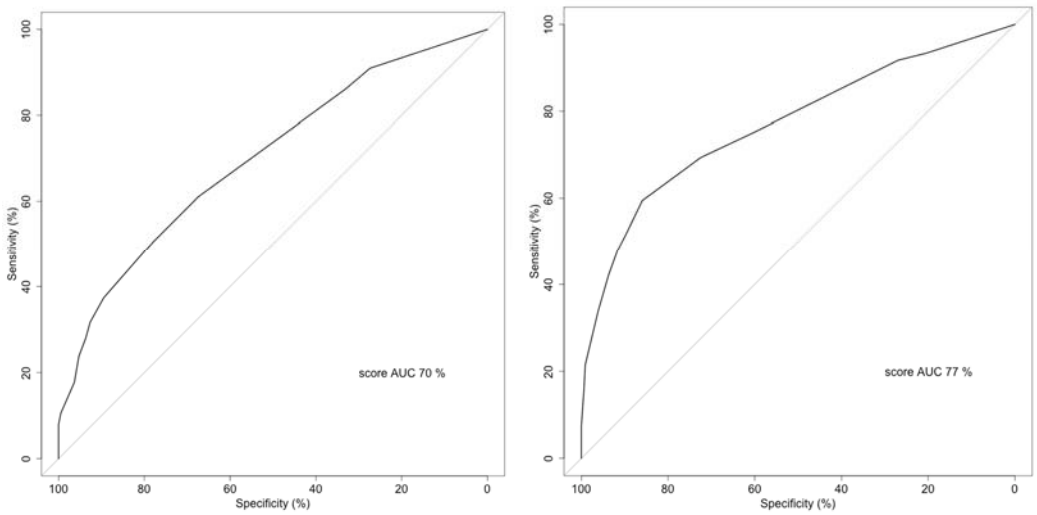
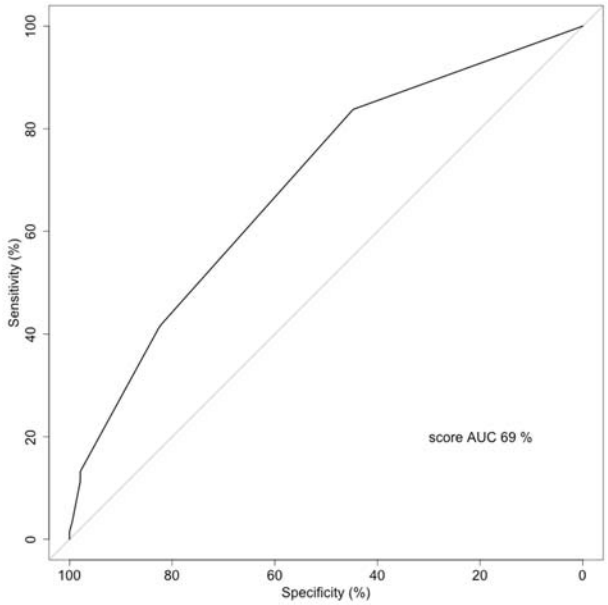


Figure 15. Representation of the second score to predict five-year mortality.



7. DISCUSSION

7.1 Overall interpretation of results

There are three major issues in this study:

1. This study indicates that long-term mortality in hospitalized patients with CAP is high. An easy-to-use score with five variables can help physicians identify those patients with CAP at high risk of death within one year of an index admission. A weighted score, called the one-year CAPSI, constructed by age ≥80, CHF, dementia, BUN >30 mg/dL and a respiratory rate of ≥30 breaths/min can predict one-year mortality with a high predictive accuracy. Indeed, one-year CAPSI showed significantly better predictive accuracy than CURB65 and SCAP.

2. In recent decades, increasing interest has emerged concerning biomarkers. In this sense, this study demonstrates that proADM is associated with the severity of disease measured by severity scores. Hence, patients with more severe disease at diagnosis present higher levels of proADM. After the exclusion of deaths within 15 days, only 24 patients died within one year. Biomarkers showed poor predictive accuracy for one-year mortality and were not able to improve the prediction ability of risk scores for one-year mortality when added to the scores. In a subanalysis carried out including all deaths up to one year, proADM showed the best predictive ability for one-year mortality and, when added to the one-year CAPSI, the prediction ability of the score was significantly improved.

On the other hand, a decrease in proADM from the first 24 hours to 3-5 days, adjusted by proADM value at baseline, was associated with a significantly reduced risk of death at one year. However, once it was adjusted by severity of disease and proADM baseline value, only when all deaths within one year were analyzed was associated with a significantly reduced risk of death at one year, meaning that, based on our sample, its predictive ability is mainly for short-term mortality.

3. Long-term mortality was assessed in an external cohort at the Veterans Affairs Medical Center of Louisville, Kentucky. Patients from this study differed from the patients in study I in terms of sociodemographics and comorbidities. Hence, the one-year CAPSI failed to properly validate previous results when applied to this sample. Thus, a specific cohort with different variables from one-year CAPSI was developed for one-year mortality with a high predictive accuracy and based on age ≥75 years, cancer, CHF, dementia, albumin <3.5mg/dL and platelets <100,000 10^9/L or >400,000 10^9/L. However, it seems that predicting mortality on a longer time prediction model is more difficult. In fact, the same score was tested for five-year mortality with a decrease in predictive ability. Another specific score was developed for five-year mortality but the predictive accuracy was not as high as expected.

7.2. Comparison with the literature

7.2.1. STUDY I: This study indicates that long-term mortality in hospitalized patients with CAP is high. An easy-to-use score with five variables can help physicians identify those patients with CAP at high risk of death within one year of an index admission. A weighted score, called the one-year CAPSI, constructed by age ≥80, CHF, dementia, BUN >30 mg/dL and a respiratory rate of ≥30 breaths/min can predict one-year mortality with a high predictive accuracy. Indeed, one-year CAPSI showed significantly better predictive accuracy than CURB65 and SCAP.

Despite advances in supportive care, CAP continues to be a leading cause of morbidity and mortality worldwide (14). Along with influenza, is currently the eighth leading overall cause of death in the United States (116). However, this mortality is only related to short-term mortality. Most researchers have focused their interest on the first months after an episode of pneumonia. It has been postulated that deaths within 15 days of a pneumonia diagnosis are related to the acute episode. Consequently, those patients were excluded from the present study in order to avoid the immediate impact of pneumonia on mortality. Increasing interest is emerging concerning the long-term prognosis after pneumonia, with mortality rates between 10-20% in the literature (6,14). However, predicting long-term mortality remains challenging.

In the present study and coinciding with literature, the one-year mortality rate in the entire cohort after the exclusion of deaths within 15 days of diagnosis was as high as 10%. This increased risk has been found to be independent of previous comorbid diseases (27). However, the impact on prognosis of the interaction between an acute episode and comorbidities should be cautiously assessed. It has been suggested that patients hospitalized with CAP have higher long-term mortality rates. Furthermore, it seems that the mortality rate is even higher than those patients hospitalized for other reasons. In this sense, Bordon et al. (50) identified a 40% higher risk of death within 7 years after a hospitalization for CAP when compared to patients hospitalized for other reasons. Recently, a German study compared mortality rates after an episode of CAP with a control group and observed 17%, 43%, and 53% mortality rates at 2, 5 and, 7

years, respectively, among patients with CAP versus 4%, 19%, and 24% in the control group (71).

In this sense, specific prognostic indices for one-year mortality after hospitalization for any reason have been developed (23,24,117). Walter et al. (23) identified that male sex, functional status, CHF, cancer, creatinine, and low albumin are risk factors for one-year mortality in older adults after a hospitalization. However, the authors limited their analysis to patients over 70 years of age and to all patients discharged from a general medical service at a tertiary care hospital. The prognostic index developed in the present study focused on patients with CAP. Moreover, all age groups were considered, which actually makes it more useful due to the similarity to real life, as in daily clinical practice.

The one-year CAPSI is a one year prognostic index that weights dementia with 6 points, age ≥80 with 4 points, BUN >30 mg/dL with 3 points, and 2 points for both RR ≥30 breaths/min and CHF. Therefore, an 82-year-old patient with congestive heart failure would have a 9.91 (6.30,15.59), HR (95%CI) times higher probability of dying one year after an admission for CAP. At the same time, a 50-year-old patient with a respiratory rate of 32 breaths/min and 50 mg/dL of BUN would have a 3.19 (1.75, 5.83), HR (95%CI)) times higher probability of dying one year after an admission for CAP.

Dementia was the best predictor of one-year mortality in hospitalized patients with CAP. Dementia is defined as chronic cognitive impairment; its origin is usually due to cerebrovascular disease, which is closely related to inflammation (28,36). Patients with CAP suffer an inflammatory storm during the acute episode, which could lead to a worsening of previously existing inflammation. Chronic persistent inflammation after an acute episode with CAP could lead to the high long-term mortality of these patients.

There are other variables usually related to dementia in clinical practice, such as being a nursing home resident, having poor functional status, and aspiration. Being a nursing home resident is included in the HCAP concept. The definition of HCAP was developed and published in the 2005 ATS/IDSA guidelines, in order to identify an increased risk of drug resistant pathogens in patients coming from the community (76). The HCAP concept included any patient who was hospitalized in an acute care hospital for two or more days within 90 days of the infection, who resided in a nursing

home or long-term care facility, received recent intravenous antibiotic therapy, chemotherapy or wound care within the past 30 days of the current infection, attended a hospital or hemodialysis clinic, or who had a family member infected with a drug-resistant pathogen. Patients with HCAP are known to have a worse prognosis, mostly due to poor functional status and treatment restrictions (39). Moreover, Cecere et al. (42) described high long-term mortality among patients with HCAP, i.e. even higher than those patients with CAP. However, HCAP was not assessed as a different entity in this study and only 6% of the population lived in a nursing home. In addition, functional status measured by the Katz index was postulated to be a 90-day mortality predictor after an episode of CAP by Capelastegui et al. (46). However, previous functional status could not be assessed in the present study.

Patients suffering from dementia usually have problems related to swallowing, which leads to aspiration. As reported by Lanspa et al. (118), a clinical diagnosis of aspiration pneumonia is associated with confusion, nursing home residence, and cerebrovascular disease. However, these authors observed a 2.3 odds ratio for mortality, after adjusting for age, disease severity, and comorbidities. Nevertheless, clinician-diagnosed aspiration was assessed in this study and only dementia was significantly associated with one-year mortality in the multivariate analysis, probably underlying the poor functional status of these patients. In addition, there is a problem with definitions in studies assessing aspiration, and it usually becomes difficult to differentiate aspiration pneumonitis from aspiration pneumonia (119).

The second most powerful predictor of one-year mortality was age ≥80. Sir William Osler stated that “Pneumonia may well be called the friend of the aged”. However, doubts have arisen in the last decades about pneumonia being limited to an acute episode. Several studies have identified increasing age as a risk factor for long-term mortality after an episode of pneumonia, which is more frequent at the extremes of life. The impact of an aging population has become a major issue of concern. The proportion of US elderly patients is expected to increase from 12% in 2000 to almost 20% in 2030. Immunosenescence is a term to describe a series of physiological changes associated with aging which cause progressive deterioration of the immune system (120).

Due to the growing elderly population, the number of patients being admitted to hospitals has notably increased. In addition, these patients usually have more comorbidities and a poor functional status. It has been suggested that one out of ten hospitalized patients with CAP between 60-79 years of age have an increased risk of mortality. In a recent paper, which CAP patients were compared with a control group, the lowest absolute rate difference for mortality was observed among patients <25 years old while patients >80 years old had the highest absolute rate difference (29). However, the starting risk age is controversial, ranging from 50 years proposed by Hedlund et al. (34) to 70 years proposed by Sligl et al. (36) or 80 proposed in the one-year CAPSI.

The severity of illness has demonstrated an impact on long-term prognosis. Scores such as, PSI, CURB65, or SCAP, initially developed for short-term prognosis, have been also used to assess long-term mortality. All these scores include data from a physical examination and analytics, with two variables that were also included in the one-year CAPSI: BUN >30 mg/dL was weighted with 3 points and RR ≥30 breaths/min with 2 points.

BUN is an important biochemical parameter determined by the complex balance between urea production, urea metabolism, and urea excretion. In addition, BUN can be influenced by several renal and non-renal dependent factors such as glomerular filtration, tubular reabsorbtion of urea, dietary protein intake, parenteral hyperalimentation therapy, catabolism of endogenous proteins, exogenous glucocorticoid dependent catabolism, volume status, and upper gastrointestinal bleeding. BUN levels are well-known to increase with the severity of renal disease. However, increased levels can be also observed in other illnesses, such as pneumonia, myocardial infarction, bone marrow transplant, and esophagectomy (106,121,122,123). Long-term regulation of the urea cycle occurs during adaptation to chronic increases in enteral or parenteral protein intake or to other protein catabolic states, such as starvation or critical illness (124). Whether elevated levels of BUN with normal values of creatinine impact on prognosis have been a matter of concern. Recently, Beier et al. (44) conducted a multicenter observational study among critically ill patients with one year follow-up and concluded that elevated levels of BUN are associated with increased long-term mortality, independent of serum creatinine.

Few authors have tried to explain the relationship between mortality and high BUN levels. The neurohumoral response to arterial underfilling may be responsible for this association. This response involves AVP, the renin-angiotensin-aldosterone system and the sympathetic nervous system (125). High plasma AVP concentrations can result in increased urea reabsorption in the collecting duct, resulting in increased BUN (126). Angiotensin and adrenergic stimulation increase proximal tubular sodium and water reabsorption, decreasing distal fluid delivery, which increases flow-dependent urea reabsorption (127). Such arterial underfilling states are common in cardiac failure and sepsis (128). High BUN levels indicate renal hypoperfusion, and patients with pneumonia are usually dehydrated resulting from increased levels of BUN excretion from the kidneys. Elevations in BUN independent of creatinine may impact on mortality due to the extent of catabolism. Protein catabolism and net negative nitrogen balance are common features of critical illness, and persistent hypercatabolism in critical illness results in decreased immune function (129), which could explain higher long-term mortality. Recently, a new index, named UBMo, was created for in-hospital and one-year mortality among very elderly patients with CAP, by multiplying the uremia by the NT-proBNP plasmatic rate, divided by the monocyte count (130).

It may be more difficult to explain how an acute parameter like RR ≥30 breaths/min was also associated with one-year mortality after a hospitalization for CAP. A high respiratory rate reflects the severity of disease and has been frequently associated with a worse short-term prognosis in patients suffering from CAP. Mortensen et al. (22) assessed long-term mortality among patients enrolled in the PORT cohort after excluding deaths up to 90 days from CAP presentation. The authors identified that the PSI risk class was significantly associated with decreased long-term survival in this cohort with 5.9 years of follow-up. Similarly, Capelastegui et al. (46) showed that the severity of illness measured by CURB was also associated with 90-day mortality after an episode of CAP. Both CURB65 and PSI have been recently assessed for long-term mortality in a six-year follow-up study in patients with CAP (43). Both PSI, which includes comorbidities, and CURB65 showed excellent predictive accuracy. Actually, both scores include RR >30 breaths/min; thus, the impact of a high RR may reflect the impact of severity of illness on long-term prognosis.

Of note, contradictory data have been published concerning the utility of current risk scores for long-term mortality prediction in CAP. Both PSI and CURB65 have been

assessed for long-term mortality, PSI showing the best predictive accuracy (36,37,43). This may be due to the fact that PSI includes comorbidities into the score. However, in the present study, many comorbidities were assessed, and only CHF and dementia showed a great influence on mortality. Recently, other scores such as CURB65 and CRB65 have been compared with the Charlson comorbidity index for one-year mortality prediction after an episode of CAP (50). All the ROC analysis showed a weak and comparable performance leading to the idea that these two easy-to-use indices showed a similar predictive accuracy to a complex comorbidity index. Thus, it seems that CURB65 could be useful in predicting one-year mortality, despite demonstrating a lower predictive accuracy.

In the last decade, substantial evidence has accumulated concerning the association between cardiovascular diseases and pneumonia. Firstly, patients suffering from CAP present higher rates of cardiac complications during hospitalization for CAP, such as acute myocardial infarction, heart failure, or arrhythmia (31,131). This idea was strengthened by Dong et al. (132) in a meta-analysis showing that acute respiratory infections were associated with a higher rate of acute coronary syndromes. Secondly, it has been postulated that suffering from pneumonia increases the risk of developing new-onset heart failure and other cardiovascular diseases in late follow-up (53). Thirdly, patients with CAP that suffer intra-hospital cardiac complications have greater long-term mortality (54).

CHF is included in the one-year CAPSI, and actually has a considerable impact on long-term mortality. Pneumonia leads to an inflammatory storm and factors such as systemic inflammation, coronary artery inflammation, platelet activation and thrombosis, endothelial dysfunction, and the effects of CAP on the heart have been suggested as possible mechanisms for increased cardiovascular events following respiratory infections (133). Thus, pneumonia may reflect an acute state of inflammation while CHF leads to chronic inflammation. Hence, pneumonia may lead to chronic state of inflammation, triggering the onset of new cardiovascular events or an impairment of a previously present inflammatory state.

Cardiovascular diseases have been suggested as causes of long-term mortality after an episode of CAP (30). In fact, cardiovascular events have been postulated to contribute to more than 30% of deaths in long-term follow-up in patients with CAP

(31). More recently, Adamuz et al. (32) determined the causes of death of 1,284 patients discharged after an episode of CAP and observed that infectious diseases were the main reason for one-year mortality, followed by acute cardiovascular events. Moreover, mortality from infectious diseases was higher during the first six months and decreased progressively after that point while cardiovascular causes were stable throughout the follow-up period, which reinforces the idea of chronic persistent inflammation after an episode of CAP. Unfortunately, causes of death could not be obtained in the present study.

Identifying the best prognostic index in any disease is difficult. A good prognostic score should be easily performed in clinical practice. In this sense, it should be taken into account that one-year CAPSI is an easy-to-use index specifically developed to predict one-year mortality among patients admitted for CAP and is based on five easy to remember variables, while PSI is a laborious index, which requires a complex computer program in order to be implemented.

Specific issues should be discussed from the univariate analysis. Not only previously mentioned variables, but also cancer, CVD, confusion, a low hematocrit, a low pO_2, and the use of corticosteroids were significantly associated with one-year mortality in the univariate analysis. Cancer is a clear variable that could impact on mortality. In fact, it has been recently demonstrated that ≤10% of patients hospitalized with CAP are diagnosed with either a primary lung cancer or pulmonary metastasis within several years of admission (134). It should be emphasized that immunosuppressed patients were excluded from the present study and only those with a history of cancer were taken into account. In addition, around 5% of the population had a history of cancer, while more than 10% had a history of cancer in Louisville cohort, as will be discussed later on. Several parameters from the physical examination and analytics have been postulated as risk factors for mortality. It should be mentioned that confusion and dementia are different parameters, the first being of new onset and the latter a chronic cognitive impairment. Low hematocrit has already been described as a risk factor for long-term mortality by Brancati et al. (35) and more recently by Waterer et al. (49). A low hematocrit or albumin usually reflects a poor nutritional status, which could actually mask other diseases.

Another interesting point is the effect of corticosteroids on CAP. The impact of corticosteroids on pneumonia prognosis is controversial. Since it was first suggested in the TORCH study, a higher incidence of pneumonia among patients on inhaled corticosteroids has been published many papers, mostly focusing on short-term prognosis. Recently, in a meta-analysis published in 2015 among hospitalized adults with CAP, systemic corticosteroid therapy turned out to may reduce mortality by approximately 3% and the need for mechanical ventilation by approximately 5% (135). In the present study, non-survivors received corticosteroids more frequently during hospitalization (p=0.06). However, this association did not achieve statistical significance.

Finally, it should be highlighted that TRIPOD statements were used for transparent reporting of the prediction model (105). The score has shown good statistical properties in terms of discrimination, calibration and internal validation Discrimination was measured by the C-index, resulting in 0.75 and 0.72 in the derivation and validation cohorts, respectively, for the one-year CAPSI risk score. Calibration was measured by the GND calibration test for the survival model, and was 0.98 for the derivation cohort and 0.93 for the validation cohort for the one-year CAPSI risk score.

7.2.2. STUDY II: In recent decades, increasing interest has emerged concerning biomarkers. In this sense, this study demonstrates that proADM is associated with the severity of disease measured by severity scores. Hence, patients with more severe disease at diagnosis present higher levels of proADM. After the exclusion of deaths within 15 days, only 24 patients died within one year. Biomarkers showed poor predictive accuracy for one-year mortality and were not able to improve the prediction ability of risk scores for one-year mortality when added to the scores. In a subanalysis carried out including all deaths up to one year, proADM showed the best predictive ability for one-year mortality and, when added to the one-year CAPSI, the prediction ability of the score was significantly improved.

On the other hand, a decrease in proADM from the first 24 hours to 3-5 days, adjusted by proADM value at baseline, was associated with a significantly reduced risk of death at one year. However, once it was adjusted by severity of disease and proADM baseline value, only when all deaths within one year were analyzed was associated with a significantly reduced risk of death at one year, meaning that, based on our sample, its predictive ability is mainly for short-term mortality.

Current risk scores have demonstrated utility for the management of CAP; however, they have several limitations. Firstly, they are vulnerable to bias as they are dependent on differences in terms of the definition of variables. Secondly, they have shown poor predictive accuracy in predicting patients at high risk of dying; hence, they have a high negative predictive value and a low positive predictive value. Thirdly, different scores have used different endpoints like 30-day mortality or ICU admission. Fourthly, scores do not work as well in elderly people. For example, PSI clearly overestimates age, with older people obtaining higher scores while young people are underestimated. Due to the limitations of risk scores, a more accurate approach has been encouraged in order to identify worse outcomes in CAP. In this sense, multiple biomarkers have been studied with good results in the short- and long-term. Considerable efforts have been undertaken in order to assess biomarkers alone or included in current scores. All the scores measure the effect of infection in the host at

the time of diagnosis, but not the inflammatory response mechanisms to the injury, which is undoubtedly crucial to the outcome. The routine use of these biomarkers still remains challenging, probably due to the high cost.

Biomarkers have been assessed for different utilities, such as the severity of disease, etiology, or duration of antibiotic treatment. CRP is a biomarker that has shown benefit in the diagnosis of acute inflammatory responses, including viral and bacterial infections, while PCT is a sensitive and specific marker for the diagnosis of systemic bacterial infection (136). Both biomarkers have demonstrated established evidence in terms of identifying low risk patients, which allow clinicians to send patients home safely. Moreover, increasing interest has emerged concerning the duration of antibiotic treatment (137). A clinical trial carried out by a Swiss group showed that the duration of antibiotic treatment could be safely reduced from 12 days to 5 days using a PCT-guided protocol (74). However, a more recent clinical trial has suggested that treatment reduction could be safely implemented based only on clinical stability criteria (138). Menendez et al. (139) suggested that clinical stability is usually achieved by day three, hence, taking into account IDSA/ATS guidelines, antibiotic treatment could be limited to five days in most patients.

Recently, new cardiovascular biomarkers have been developed with promising results. ProADM is the most stable fragment of adrenomedullin degradation. The importance of this biomarker is mostly focused on its activity as a potent vasodilator and the immunomodulatory regulation of inflammatory processes. It has been promoted as a prognostic biomarker in sepsis as well as a useful marker for risk stratification in patients with CAP (140). However, in terms of discriminating etiology, it has been described as a weak biomarker (73).

In a prospective observational study conducted among 228 patients with CAP, the authors found significantly higher levels of proADM, PCT and CRP as well as higher PSI and CURB65 scores in patients with complications during hospitalization (73). The CAPNETZ group assessed new biomarkers, not only for short-term mortality, but also for 180-day mortality; the authors concluded that proADM was the best predictor of both short- and long-term mortality (71). Bello et al. (73) assessed different biomarkers and showed that proADM was the only one able to distinguish between survivors and non-survivors at one year after an episode of CAP. Of note, the authors did not

exclude in-hospital mortality from analysis, which actually could have had a significant influence on the results.

In our study, three different biomarkers were assessed for one-year mortality, and only proADM showed significantly higher levels among more severe patients, as measured by different risk scores. Surprisingly, patients with higher scores on the one-year CAPSI showed lower levels of CRP, which would support the previously published idea of CRP high levels being protective against complications in patients with CAP (96).

All biomarkers failed to predict one-year mortality. However, it should be taken into account that deaths up to 15 days from diagnosis were excluded; thus, only 24 patients died within one year. Due to the small sample size after the exclusion of deaths within 15 days, a subanalysis was carried out including all deaths up to one year; proADM showed a high predictive ability for one-year mortality. Deaths around the acute episode of CAP could have a great influence when assessing long-term mortality and, ideally, should be excluded from the analysis. However, in this study, proADM was a good predictor of one-year mortality only once all deaths were included. In this sense, future research should focus on obtaining a larger sample size for the study of biomarkers and long-term mortality prediction after a CAP episode, excluding short-term mortality.

Another matter of concern is how much a biomarker could improve the mortality prediction ability of a risk score. España et al. (141) measured proADM levels on admission in a prospective cohort of 491 patients with CAP and observed a significant correlation with severity scores and an improvement in the predictive ability for adverse events when the biomarker was added to the severity score, thus providing an additional margin of safety. In another study carried out among an already well-characterized cohort of patients with CAP from the ProHOSP study, which was first developed to assess antibiotic stewardship, patients were prospectively followed for six years (74). The authors observed a high mortality rate of almost 50% after hospitalization. More interestingly, they described a high predictive accuracy of risk scores, which was actually improved when biomarkers were added.

In our study, the addition of biomarkers failed to improve the predictive accuracy of the scores for mortality. As previously explained, in the subanalysis carried out including

all deaths up to one year, proADM significantly improved the predictive accuracy of one-year CAPSI and CURB65. It would be of great interest to assess this in a bigger cohort, i.e. whether proADM improves the prediction ability of risk scores.

Serial biomarker levels have been assessed by different authors with different aims. A PCT-guided protocol with serial PCT measures carried out in a clinical trial could safely reduce the duration of antibiotic treatment from 12 days to 5 days (84). In our study, the main outcome was one-year mortality, and we strongly believe that inflammation and cardiovascular diseases are related to the increased long-term mortality that patients suffer after an episode of CAP. Hence, we decided to assess serial proADM levels in relation to one-year mortality due to its activity as a potent vasodilator and immunomodulatory regulator of inflammatory processes. Measuring serial proADM levels at follow-up after an episode of CAP could support the hypotheses of chronic persistent inflammation.

In the present study, we could not obtain blood samples at late follow-up, but we were able to obtain biomarkers at 3-5 days after diagnosis. In order to assess the impact of serial biomarker levels on one-year mortality, the proADM changes was estimated by subtracting the proADM value at 3-5 days from the proADM value at the time of diagnosis. ProADM changes failed to significantly predict mortality when deaths within first 15 days were excluded but not when all deaths up to one year were included. Moreover, when patients who died between 15 days and up to one year were excluded, decreases in proADM values were associated with significantly decreased one-year mortality, leading to the idea that, at least in this sample, proADM is related to short-term mortality.

Later on, proADM changes were estimated after adjustment by severity scores and, similarly, proADM changes failed to be protective of one-year mortality. However, when the same analysis was conducted including all deaths up to one year, for each 0.1 nmol/L decrease in proADM, a decrease of 9% in one-year mortality was observed, adjusted by one-year CAPSI. Hence, the greater the reduction in biomarker levels over time, the greater the reduction in one-year mortality. Further analysis excluding those patients who died after 15 days and up to one year showed that decreases in proADM failed to be protective, again leading to the idea that, at least in this sample, proADM is related to short-term mortality. It is of special interest to

measure biomarker levels at admission as well as at follow-up in order to know whether the absence of a decrease is related not only with to increased mortality rate but also to an increased rate of cardiovascular events.

Despite the limitations of the current study results, it seems clear that proADM showed a correlation with the severity of disease. ProADM has been widely studied for long-term mortality, probably due to its cardiovascular effect. As previously mentioned, patients suffering from CAP have a greater probability of suffering from cardiovascular events in the follow-up; moreover, these cardiovascular events seem to be related to the increased mortality rates that these patients suffer at late follow-up. Chronic persistent inflammation could be the underlying issue.

7.2.3. STUDY III: **Long-term mortality was assessed in an external cohort at the Veterans Affairs Medical Center of Louisville, Kentucky. Patients from this study differed from the patients in study I in terms of sociodemographics and comorbidities. Hence, the one-year CAPSI failed to properly validate previous results when applied to this sample. Thus, a specific cohort with different variables from one-year CAPSI was developed for one-year mortality with a high predictive accuracy and based on age ≥75 years, cancer, CHF, dementia, albumin <3.5mg/dL and platelets <100,000 10^9/L or >400,000 10^9/L. However, it seems that predicting mortality on a longer time prediction model is more difficult. In fact, the same score was tested for five-year mortality with a decrease in predictive ability. Another specific score was developed for five-year mortality but the predictive accuracy was not as high as expected.**

In an attempt to assess mortality in an external cohort, 455 patients from the Veterans Affairs Medical Center of Louisville, Kentucky were analyzed. This is a particular cohort including American military veterans. Thus, all patients were male, 70% of patients were hypertensive, and almost half of the cohort were current smokers and suffered from COPD. Despite excluding mortality within 15 days from diagnosis, the one-year mortality rate was as twice high as the one observed in our cohort. One-year CAPSI was applied to this sample and it failed to properly validate the previous results, due to the differences in the sociodemographic and clinical characteristics between both cohorts. Hence, a specific prediction score was developed for one-year mortality.

Under these circumstances, a weighted prediction score was developed based on age ≥75 years, cancer, CHF, dementia, albumin <3.5 and platelets <100,000 or >400,000. Similarly to our cohort, age, CHF, and dementia were included in the score. Moreover, dementia was the second most important variable with 4 points. The most powerful variable was cancer, weighted with 7 points. Although immunosuppressed patients were excluded, still, 12.75% of the cohort had suffered from cancer, while only 5.53% of patients from the Galdakao-Usansolo Hospital had cancer. In addition, low albumin and platelet levels have been related to a poor nutritional status, which actually had a considerable impact on mortality, as previously explained. However, in the Galdakao-

Usansolo Hospital cohort, with a long inclusion period, neither albumin nor platelets could be obtained during the study; thus, these parameters could not be analyzed. The one-year prediction score showed acceptable prediction accuracy. Nevertheless, when the same score was used to assess five-year mortality, accuracy declined.

Five-year mortality was 58% (265 deaths) and a specific prediction score was developed including age, BMI <21, nursing home residence, aspiration, cancer, CHF, and platelets $<100x10^9$/L or $>400x10^9$/L; however, a worse predictive accuracy was shown (AUC 0.69). As explained before, patients with BMI <21, nursing home residence, and aspiration are usually included in HCAP, which had already been suggested as a poor prognosis.

Therefore, it seems that predicting one-year mortality is more feasible than predicting five-year mortality. In this sense, biomarkers could actually become crucial. The addition of cardiovascular biomarkers such as proADM to risk scores has been postulated to improve the predictive accuracy for short- and long-term mortality. On the other hand, it should be taken into account that whenever a score is validated in an external sample, patient similarities in terms of sociodemographics and comorbidities should be tested first. In this study, the sample characteristics differ greatly from those of the first study sample; hence, a specific score was developed for this specific sample.

On the other hand, several issues concerning methodology used for the study carried out in the Veterans Affairs Medical Center of Louisville, Kentucky should be highlighted. Instead of choosing variables significantly related to one-year mortality, an “automatic selection” regression model was used. In order to assess the best fit of the regression model compared to models with different variables, a genetic algorithm was used to identify a best-fit model somewhat automatically using the AIC. This algorithm creates thousands of different regression models, logistic regression in this case, and assesses the model fit based on AIC. This is called an optimization algorithm because it optimizes the model fit given thousands and thousands of different potential variable combinations. When the fit no longer improves by changing the variables around, the algorithm stops and the best model is shown. The genetic algorithm lets us automate much of this process by looking at thousands of models with different variables included and evaluating the AIC of each and comparing them

until it finds an optimum set of variables that minimizes the AIC. This model is then used to weight the variables and create the score.

A key point of this methodology is the fact that the variables included in the score were not necessarily independently associated with the outcome at the p-value cutoff of 0.05. The important thing to consider here is that the objective was not to identify independent predictors of long-term mortality in hospitalized patients with CAP. Indeed, we tried to identify a model that fit the data the best in order to create a composite score that could be able to discriminate between patients who died and those who did not die at one and five years. The fact that some variables were not independently associated with the outcome is not relevant in this situation, as they are to be combined at the end into one variable that then independently predicts the outcome.

7.3 Strengths and limitations

This study has several strengths. The first one is the large sample size of the Galdakao-Usansolo Hospital prospective cohort. More than 2,000 patients with CAP were assessed during hospitalization. In addition, vital status could be obtained from all of them. Deaths within 15 days from diagnosis were excluded in order to avoid the impact an acute episode could have on mortality.

Another strength is that the one-year CAPSI is an easy-to-use score that can accurately predict one-year mortality. Compared to the PSI score, which is complex and difficult to implement in daily clinical practice, the one-year CAPSI includes five easy to determine variables that can easily identify patients at a high risk of death. Furthermore, biomarkers could be assessed, showing a clear correlation with the severity of disease. Biomarker levels could be also assessed at follow-up, which provides a new perspective on the utility of biomarkers. Moreover, a key point of this study is that long-term mortality could be assessed in an external cohort of hospitalized patients with CAP, which strengthens the quality of the scientific research.

This study has also several limitations. Firstly, causes of death could not be obtained in any case, which could have added important information. Secondly, several variables such as tobacco use, albumin, or platelets could not be assessed at the Galdakao-Usansolo Hospital cohort due to missing data. Thirdly, the sample size was notably reduced once deaths within 15 days of diagnosis were excluded, which had a considerable impact, especially in the cohort of section II when biomarkers were analyzed. Hence, due to the small sample size, these data should be cautiously interpreted. Fourthly, when assessing an external cohort, the peculiarities of patients from the Veterans Affairs Medical Center of Louisville, Kentucky limited the results. Fifthly, the study design was retrospective in study III, which could add a limitation. Finally, immunosuppressed patients, those infected by the human immunodeficiency virus, as well as those who had been discharged from an acute care hospital, an onsite subacute care unit, or a palliative care unit within the previous 14 days were excluded from this study. Thus, the data cannot be extrapolated to these patients.

7.4 Potential clinical use and future research

The impact of an aging population has become a major issue of concern. Future research in the area of inflammation is needed. Indeed, inflammation among elderly people should be assessed independently as it probably has a distinctive role. In addition, it seems that persistent chronic inflammation after an episode of CAP could lead to higher long-term mortality rates. Future research should include an assessment of cardiovascular events after hospitalization for CAP, not only at short-term follow-up, but also at long-term. In this sense, it would be of special interest to evaluate in a larger cohort cardiovascular biomarkers levels in the follow-up after hospitalization with CAP in order to demonstrate if patients with less significant decreases over time have higher mortality rates. This would support the idea that persistently elevated levels of biomarkers are associated with an increased risk of cardiovascular events. Moreover, this inflammation could lead to endothelial dysfunction or to a prothrombotic state and, consequently, to a higher rate of cardiovascular events. Indeed, cardiovascular diseases have been postulated as possibly causative of increased mortality in these patients.

This inflammatory storm could lead to the development of new cardiovascular diseases as well as to already established but undiagnosed cardiovascular diseases. Therefore, close monitoring should be encouraged among these patients at high risk of death in order to make an early diagnosis and for the treatment optimization of comorbidities. Additionally, future research should address whether treatment with specific drugs to overcome inflammation favorably impacts long-term mortality.

In conclusion, CAP is an important problem with high morbidity and mortality. In addition, an easy-to use score based on age ≥80, CHF, dementia, BUN >30 mg/dL, and a respiratory rate ≥30 breaths/min can predict one-year mortality with a high predictive accuracy, better than widely known severity scores. Future research should be conducted to clarify the impact of inflammation on CAP prognosis.

8. CONCLUSIONS

STUDY I. One-year mortality prediction among hospitalized patients with CAP in Galdakao-Usansolo Hospital.

1. In this study, 2,351 patients were evaluated to identify one-year mortality predictors, with 250 (10.63%) patients dying within one year. Several variables were identified as predictors of one-year mortality, but five of them could be combined in a single model consisting of age ≥80, CHF, dementia, BUN >30 mg/dL, and a respiratory rate ≥30 breaths/min. Dementia and age ≥80 were the most powerful variables weighted with 6 and 4 points, respectively. BUN >30 mg/dL was weighted with 3 points while CHF and a respiratory rate ≥30 breaths/min were both weighted with 2 points. Recognizing these five variables may be useful for identifying patients with a high probability of dying after an episode of CAP.

2. With these five weighted variables, a new score called the one-year CAPSI was developed to predict one-year mortality among hospitalized patients with CAP. The score showed good statistical properties in terms of discrimination, calibration, and internal validation. Considering one-year CAPSI as a continuous variable, the C-index was 0.76 in the derivation cohort and 0.77 in the validation cohort. In addition, the GND calibration test for the one-year CAPSI was 0.03 for the derivation cohort and 0.23 for the validation cohort.

The previous continuous score was categorized into three risk groups, i.e. minor, moderate, and severe, and was called the one-year CAPSI risk score. This risk score had a C-index of 0.72 and 0.70 in the derivation and validation cohorts, respectively. The GND calibration test for the one-year CAPSI was 0.98 for the derivation cohort and 0.93 for the validation cohort.

For a cut-off point of four on the one-year CAPSI, the results of the statistical measures of performance were: sensitivity 81.40%, specificity 64.47%, PPV 21.56%, and NPV 96.65%, with an accuracy of 66.28% for the derivation cohort. In the validation cohort, sensitivity was 75.63%, specificity 65.09%, PPV 20.27%, and NPV 95.79%, with an accuracy of 66.20%.

3. The one-year CAPSI showed a higher predictive ability than CURB65 and SCAP. In the derivation cohort, the C-index for the one-year CAPSI was 0.76 while for PSI it was 0.73, for CURB65 0.69, and for SCAP 0.70. In the validation cohort, the C-index for the one-year CAPSI was 0.77, while the C-index for PSI was 0.75, for CURB65 0.71, and for SCAP 0.70. Hence, the one-year CAPSI appears to be more useful than current risk scores for the prediction of one-year mortality after a hospitalization for CAP.

STUDY II. Role of biomarkers in one-year mortality prediction among hospitalized patients with CAP in Galdakao-Usansolo Hospital.

1. In this second study, risk scores as well as three biomarkers were assessed for one-year mortality, including CRP, PCT, and proADM. ProADM was the only biomarker with significantly higher levels at admission among more severe patients, while lower levels of CRP were observed among more severe patients measured by the one-year CAPSI. In addition, risk scores showed a high predictive accuracy for one-year mortality. However, biomarkers failed to predict one-year mortality when excluding deaths within 15 days from admission, with a C-index for proADM of 0.64. Once all deaths within one year were included in the analysis, proADM showed a high predictive accuracy for one-year mortality with a C-index of 0.71; based on our sample, its predictive ability is mainly for short-term mortality.

2. Risk scores were able to predict one-year mortality, but not biomarkers. However, as proADM was the only biomarker correlated with the severity of disease, it was added to the current risk scores. ProADM failed to improve the prediction ability of these scores when excluding deaths within 15 days. Once all deaths within one year were included in the analysis, the addition of proADM significantly improved the prediction ability for one-year mortality of CURB65 and one-year CAPSI.

3. When we assessed the role of changes in proADM values from admission to 3-5 days, adjusted by proADM basal values and the risk scores, proADM changes predict one-year mortality; though mainly explain by short-term mortality (<=15 days). Additionally, when proADM changes were adjusted by the one-year CAPSI, a decrease of 0.1 nmol/L in proADM from admission to 3-5 days was associated with a 9% decrease in one-year mortality. Limited sample size and the distribution of the outcome may have influenced the results.

STUDY III. One-year mortality prediction among hospitalized patients with CAP in the Veterans Affairs Medical Center of Louisville, Kentucky.

1. Patients hospitalized for CAP at the Veterans Affairs Medical Center of Louisville, Kentucky differed from patients hospitalized for CAP at the Galdakao-Usansolo Hospital, in terms of sociodemographics and comorbidities. In addition, when the one-year CAPSI was applied to this sample, it failed to properly validate the previous results, due to the differences in the sociodemographic and clinical characteristics of the two cohorts.

2. Taking into account the specific peculiarities of the sample from the Veterans Affairs Medical Center of Louisville, Kentucky, a specific score was developed by a genetic algorithm for one-year mortality. The final multivariate score included age ≥75 years weighted with 2 points, cancer with 7 points, CHF with 1 point, dementia with 4 points, albumin <3.5mg/dL with 2 points, and platelets <100,000 10^9/L or >400,000 10^9/L with 2 points, with an AUC of 0.77. The same score was tested for five-year mortality with a poorer predictive accuracy (AUC 0.70). Thus, predicting long-term mortality after an episode of CAP remains challenging.

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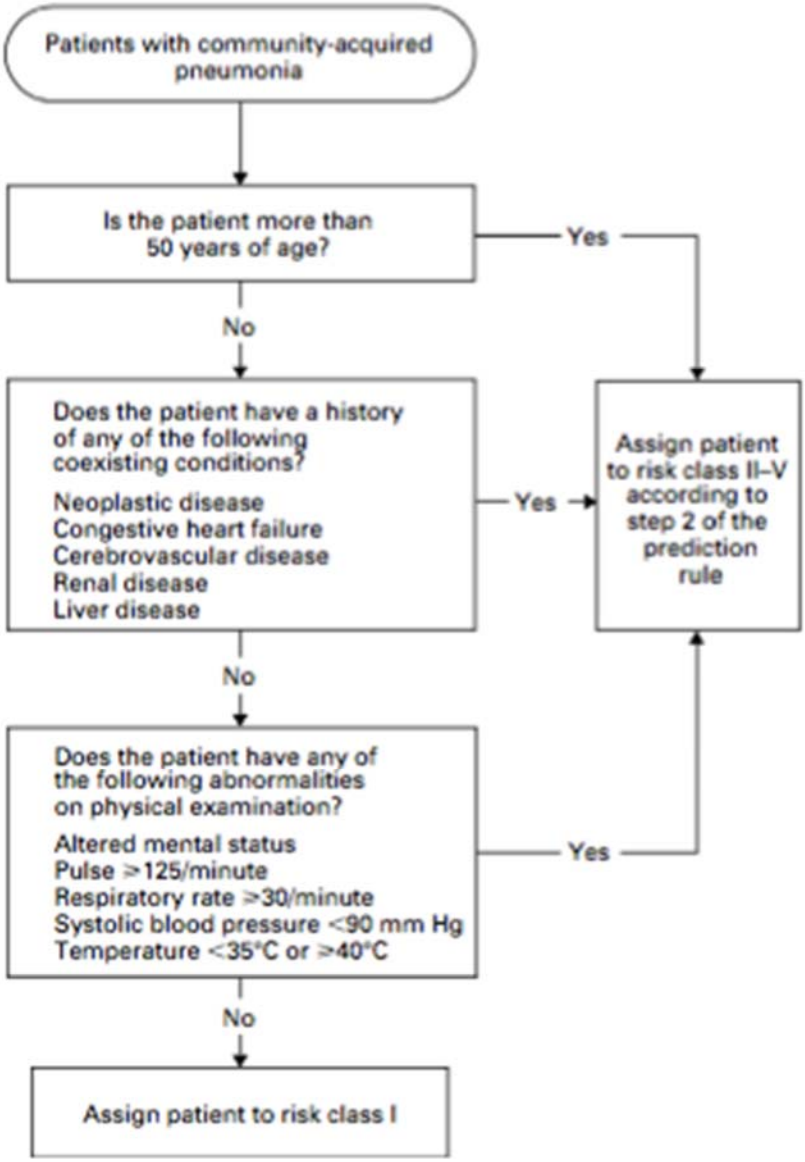
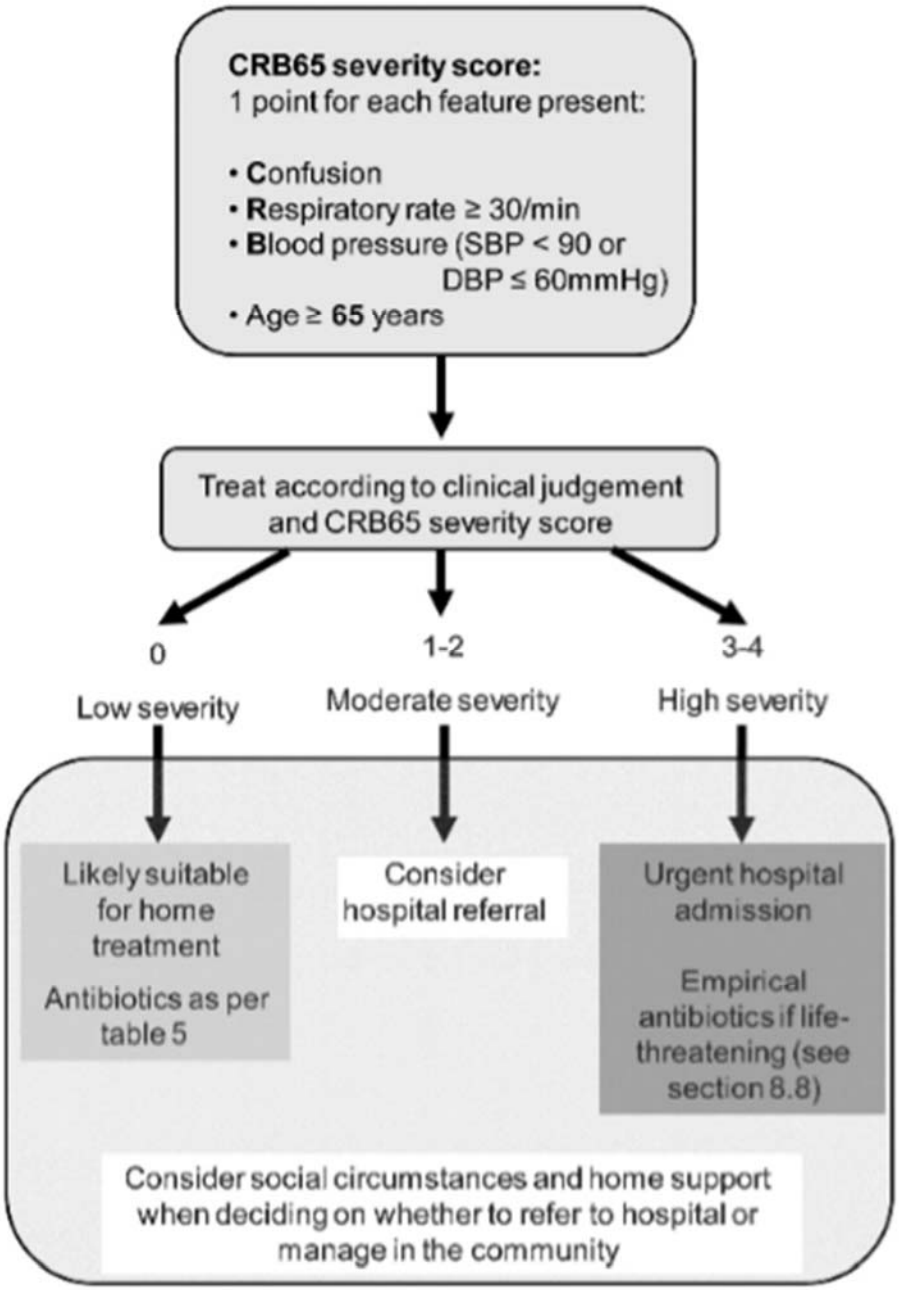
10. APPENDIX

10.1 PSI score.



CHARACTERISTIC	POINTS ASSIGNED*
Demographic factor	
Age	
Men	Age (yr)
Women	Age (yr) − 10
Nursing home resident	+10
Coexisting illnesses†	
Neoplastic disease	+30
Liver disease	+20
Congestive heart failure	+10
Cerebrovascular disease	+10
Renal disease	+10
Physical-examination findings	
Altered mental status‡	+20
Respiratory rate ≥30/min	+20
Systolic blood pressure <90 mm Hg	+20
Temperature <35°C or ≥40°C	+15
Pulse ≥125/min	+10
Laboratory and radiographic findings	
Arterial pH <7.35	+30
Blood urea nitrogen ≥30 mg/dl (11 mmol/liter)	+20
Sodium <130 mmol/liter	+20
Glucose ≥250 mg/dl (14 mmol/liter)	+10
Hematocrit <30%	+10
Partial pressure of arterial oxygen <60 mm Hg§	+10
Pleural effusion	+10

10.2 CURB65 score.



10.3 SCAP score.

Variables	β Parameter	OR (95% CI)	Points	Criteria
Intercept	−4.79			
pH < 7.30	2.38	10.8 (3.5–34.0)	13	Major
Systolic pressure < 90 mm Hg	2.19	8.9 (3.2–25.2)	11	Major
Respiratory rate > 30 breaths/min	1.83	6.3 (3.4–11.7)	9	Minor
Blood urea nitrogen > 30 mg/dl	0.92	2.5 (1.4–4.7)	5	Minor
Altered mental status	0.87	2.4 (1.2–4.6)	5	Minor
Pa_{O_2}/FI_{O_2} < 250 mm Hg	1.12	3.1 (1.7–5.7)	6	Minor
Age ≥ 80 yr	0.86	2.4 (1.3–4.4)	5	Minor
Multilobar/bilateral X-ray	0.68	2.0 (1.1–3.7)	5	Minor

Definition of abbreviations: CI = confidence interval; OR = odds ratio.
The model has an area under the curve of 0.92.