DESARROLLO Y VALIDACION DE MODELOS PREDICTIVOS DE FRACASO RENAL AGUDO INTRAHOSPITALARIO BASADO EN REGISTROS DINÁMICOS DE FACTORES DE RIESGO

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DESARROLLO Y VALIDACION DE MODELOS PREDICTIVOS DE FRACASO RENAL AGUDO INTRAHOSPITALARIO BASADO EN REGISTROS DINÁMICOS DE FACTORES DE RIESGO

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“No temas a las dificultades: lo mejor surge de ellas”

Rita Levi Montalcini

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ABREVIATURAS Y ANGLICISMOS

FRA	Fracaso renal agudo
FRA-H	Fracaso renal agudo intrahospitalario
HA-AKI	Hospital-acquired acute kidney injury
UCI	Unidad de cuidados intensivos
AKIN	Acute Kidney Injury Network
K-DIGO	Kidney Disease Improving Global Outcomes
AINE	Antiinflamatorios no esteroideos
MAKIPS	Madrid Acute Kidney Injury Prediction Score
HA-AKI	Hospital-acquired acute kidney injury
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
CA-AKI	Community-acquired AKI
JIF	The Journal Impact Factor
GFR	Glomerular filtration rate
SD	Standard deviation
AUROC	Area under the receiver operating characteristics curve
IHD	Ischemic heart disease
ICD	Ischemic Cerebrovascular disease

PVD	Ischemic peripheral vascular disease
CCHF	Chronic congestive heart failure
MN	Malnutrition
CPOD	Chronic pulmonary disease
AIDS	Acquired immunodeficiency syndrome
CKD	Chronic Kidney Disease
ARF	Acute respiratory failure
AHF	Acute Hearth failure
SIRS	Patients were considered to suffer from systemic inflammatory response syndrome

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RESUMEN

RESUMEN

El Fracaso renal agudo (FRA) es una complicación frecuente y grave en pacientes hospitalizados. Presentar un episodio de FRA en cualquier momento de la hospitalización conlleva un aumento de la morbimortalidad, estancia y costos hospitalarios. Este problema de salud afecta a todos los centros hospitalarios, independientemente de su nivel de complejidad asistencial. El abordaje es complejo ya que no es posible identificar un solo “actor” que pueda abordar una solución unilateral. Actualmente ningún grupo es "dueño" del problema, de ahí la falta de pensamiento conjunto y de seguimiento asociado a la atención de pacientes de alto riesgo a lo largo del ingreso hospitalario. Sin embargo, hay muchos "actores" que pueden participar en la solución, como farmacéuticos, especialistas en medicina interna, anestesistas, cirujanos, nefrólogos, cardiólogos, radiólogos intervencionistas, asesores hospitalarios y equipos multidisciplinares. La solución para reducir eficazmente la incidencia de FRA intrahospitalario debe contemplar 1: un aumento de la capacidad predictiva y de la sensibilidad de los modelos predictivos 2: intervenciones adecuadas en función de los riesgos individuales.

La hipótesis de esta tesis es que, mediante la combinación de variables demográficas, factores de comorbilidad y variables relacionadas con el estado clínico del paciente, debe ser posible desarrollar modelos predictivos que sean reproducibles y permitan estimar la probabilidad individual de sufrir FRA durante el ingreso hospitalario. Siendo las características demográficas y los factores de comorbilidad variables estables no sujetas a cambio, ambas proporcionan información exclusivamente estática

relacionada con la predisposición individual a sufrir FRA en un determinado contexto clínico. La monitorización secuencial y dinámica de las variables relacionadas con el estado clínico, debería permitir realizar estimaciones más precisas del riesgo y predecir, de forma dinámica los cambios en la probabilidad de sufrir FRA, que se producen cada vez que hay un cambio en el estado clínico del enfermo.

Por ello, hemos desarrollado y validado varios modelos de predicción clínica, modelos que, a diferencia de lo descrito en la literatura hasta la fecha, son dinámicos, con un aprendizaje automático para el desarrollo de FRA durante el ingreso hospitalario en pacientes ingresados en centros de hospitalización no críticos. Su rendimiento ha sido comparado con otros modelos basados en el registro estático de factores de riesgo. Una vez obtenidos y validados los modelos, sus predicciones podrán ser utilizados en la práctica clínica como guía para el diagnóstico y toma de decisiones terapéuticas, y se podrán desarrollar programas de intervención para adecuar la prescripción de fármacos, la exposición a medios de contraste y los procedimientos quirúrgicos, en función de los riesgos individuales de cada uno de nuestros pacientes.

Con los resultados obtenidos podemos concluir que, mediante el uso de registros electrónicos de datos sanitarios, nuestro estudio proporciona un modelo que puede utilizarse en la práctica clínica para obtener una evaluación precisa, dinámica y actualizada del riesgo individual de presentar Fracaso renal agudo intrahospitalario (FRA-H) en pacientes no críticos.

ABSTRACT

Acute renal failure (ARF) is a frequent and serious complication in hospitalized patients, with an incidence of up to 20-25%. An episode of ARF at any time during hospitalization leads to increased morbidity and mortality, hospital stay and hospital costs. This health problem affects all hospitals, regardless of their level of complexity of care. The approach is complex because it is not possible to identify a single "actor" that can address a unilateral solution. Currently, no one group "owns" the problem, hence the lack of joined-up thinking and follow-up associated with the care of high-risk patients throughout hospital admission. However, there are many "players" who can participate in the solution, such as pharmacists, internal medicine specialists, anesthesiologists, surgeons, nephrologists, cardiologists, interventional radiologists, hospital consultants and multidisciplinary teams. The solution to effectively reduce the incidence of in-hospital ARF must contemplate 1: an increase in the predictive capacity and sensitivity of predictive models 2: appropriate interventions according to individual risks.

The hypothesis of this thesis is that, by combining demographic variables, comorbidity factors and variables related to the clinical status of the patient, it should be possible to develop predictive models that are reproducible and allow estimation of the individual probability of suffering ARF during hospital admission. Demographic characteristics and comorbidity factors being stable variables that are not subject to change, both provide exclusively static information related to the individual predisposition to suffer ARF in a given clinical context. The sequential and dynamic monitoring of variables related to clinical status should make it possible to make more

precise risk estimates and dynamically predict the changes in the risk of ARF that occur each time there is a change in the clinical status of the patient.

Therefore, we have developed and validated several clinical prediction models, models that, unlike those described to date, are dynamic, with automatic learning for the development of ARF during hospital admission in patients admitted to non-critical hospitalization centers. Their performance has been compared with other models based on static registration of risk factors. Once the models have been obtained and validated, their predictions can be used in clinical practice as a guide for diagnosis and therapeutic decisions, and intervention programs can be developed to adjust drug prescription, exposure to contrast media and surgical procedures according to the individual risks of the patients.

With the results obtained, we can conclude that, through the use of electronic health records, our study provides a model that can be used in clinical practice to obtain an accurate, dynamic and updated assessment of the individual risk of in-hospital acute renal failure (HA-AKI) in non-critical patients.

1. INTRODUCCIÓN

1.1. FRACASO RENAL AGUDO INTRAHOSPITALARIO

El fracaso renal agudo (FRA) es una complicación frecuente y grave en pacientes hospitalizados, presentando una incidencia que puede llegar hasta un 15-20% según la serie estudiada (1-7). Presentar un episodio de FRA en cualquier momento de la hospitalización conlleva un aumento de la morbimortalidad, estancia y costos hospitalarios (8-12). Además, datos recientes indican que el grado de recuperación de la función renal tras el fracaso renal agudo se asocia con la morbilidad y la mortalidad a largo plazo tras el alta hospitalaria (13,14). La mayoría de los casos de FRA hospitalario (FRA-H) están causados por isquemia o nefrotoxicidad como consecuencia de hipovolemia, hipoxemia, sepsis, exposición a contrastes radiológicos o fármacos nefrotóxicos y estas variables suelen encontrarse asociadas entre sí (15-17). Asimismo, el riesgo de desarrollar FRA tras la exposición a estos factores, depende de las características de los pacientes en cuanto a edad, presencia de enfermedad renal previa, número y tipo de comorbilidades (18,19). Teniendo en cuenta que una gran parte de los episodios de FRA se deben a causas potencialmente evitables, conocer con la mayor exactitud posible el riesgo individual de cada paciente durante todo el tiempo de estancia hospitalaria, podría ayudar a la toma de decisiones y a la aplicación de medidas preventivas para reducir la incidencia de FRA hospitalario (20). Las directrices K-DIGO recomiendan estratificar el riesgo de FRA de los pacientes en el momento del ingreso en función de sus susceptibilidades y tratarlos según las mismas para reducir el riesgo de este (21,22). Revisando la literatura, la mayor parte de los modelos

predictores de FRA se han estudiado y validado en unidades de cuidados intensivos (UCI) (23-28). Sin embargo, estos modelos son difíciles de extrapolar a pacientes no críticos, ya que se han desarrollado para pacientes que se encuentran bajo la influencia de un conjunto de factores de riesgo relacionados con la inestabilidad hemodinámica, el uso de fármacos vasoactivos, la baja oxigenación tisular, la respuesta inflamatoria y los procedimientos invasivos, como la ventilación mecánica, que son exclusivos de este entorno (29-32).

Los estudios que analizan la epidemiología y los factores de riesgo asociados con FRA en pacientes no críticos tienen dos limitaciones principales al momento de identificar con precisión los factores de riesgo asociados al mismo. En primer lugar, todos ellos se basan en características demográficas y comorbilidades que han sido registradas retrospectivamente a partir de los códigos administrativos de alta y, por tanto, están sujetas a un potencial sesgo en la recogida de información codificada (33-39). En segundo lugar, no permiten saber si la exposición a los factores de riesgo precedió o no a la detección del episodio de FRA (40).

1.2. DEFINICIÓN DE FRA

El Fracaso renal agudo se define de acuerdo con las guías K-DIGO como cualquiera de las siguientes situaciones: aumento de la creatinina sérica en ≥0,3 mg/dl (≥26,5 µmol/l) en 48 horas; o aumento de la creatinina sérica hasta X 1,5 veces el valor basal, que se sabe o se presume que se ha producido en los 7 días anteriores; o volumen urinario ≤ 0.5ml/kg/h durante 6 horas (22).

1.3. CLASIFICACIÓN DEL FRA

Existen diversas clasificaciones del fracaso renal agudo, pero en los últimos años la tendencia es a unificar conceptos para poder realizar diagnósticos precoces y precisos. Así, el grupo Acute Kidney Injury Network (AKIN) definió la clasificación AKIN en el 2007, teniendo en cuenta cambios en la creatinina sérica, y en la diuresis, obviando cambios en el filtrado glomerular. En el 2012 se publicaron las guías clínicas Kidney Disease Improving Global Outcomes (K-DIGO), las cuales definen el FRA dependiendo del aumento de la creatinina sérica en el tiempo y los cambios en el volumen de diuresis. De esta forma, se establecen 3 niveles de gravedad del fracaso renal agudo. FRA AKI 1, cuando la creatinina aumenta 1.5-1.9 veces el valor basal, aumento de x 0,3 mg/dl (x 26,5 mmol/l) o volumen de diuresis menor de 0,5 ml/kg/h durante 6-12 horas. AKI 2 si la creatinina aumenta x 2.0-29 veces el valor basal o el volumen de diuresis en menor de 0,5 ml/kg/h por ≥ 12 horas. AKI 3, si la creatinina aumenta > 3 veces su valor basal o ≥ 4mg/dl (353,6 mmol/l), diuresis < 0.3ml/kg/h por ≥ 24 horas o anuria ≥ 12 horas, o se requiere de inicio de tratamiento renal sustitutivo. Y en pacientes menores de 18 años, disminución de la TFGe ≤35 ml/min por 1,73 m^2 (22).

1.4. INCIDENCIA

Dada la dificultad para unir criterios que definan FRA su incidencia es muy variable. Estudios recientes indican que su incidencia puede variar entre 5 y 15% o 30-45

casos/1000 ingresos hospitalarios por año y hasta el 50% de los pacientes ingresados en la unidad de cuidados intensivos (41,42).

1.5. EVALUACIÓN DEL RIESGO

El riesgo de presentar FRA depende de las comorbilidades del paciente y de la exposición a diferentes factores de riesgo (43-51). Es importante conocer estos factores de riesgo para poder actuar según la susceptibilidad de cada uno de nuestros pacientes. Esto es especialmente importante en el ámbito hospitalario, donde la susceptibilidad del paciente puede evaluarse antes de determinadas exposiciones como la cirugía o la administración de agentes potencialmente nefrotóxicos (52-55). En consecuencia, algunos factores pueden modificarse, y las exposiciones contempladas pueden evitarse o adaptarse para reducir el riesgo de FRA. La oportunidad de intervenir, antes de la exposición, es importante, de cara a evitar o minimizar el riesgo de presentarlo (FRA). Asimismo, detectar a este grupo de riesgo susceptible de presentar fracaso renal es de crucial importancia de cara a realizar una vigilancia estrecha en el tratamiento instaurado (56,57).

1.6. ENFOQUE DIAGNÓSTICO, ALERTAS ELECTRÓNICAS

En los últimos años, se ha presentado la tendencia a utilizar alertas electrónicas para el diagnóstico precoz del FRA. Además, existe la suposición de que un mayor reconocimiento del FRA mejorará la atención de estos pacientes con mejores

resultados clínicos, por lo que muchos sistemas de salud en los Estados Unidos y en el Reino Unido han introducido las Alertas electrónicas como parte de la atención clínica de rutina. Pero, los datos sobre la eficacia de estas alertas son limitados y la evidencia definitiva de su beneficio para los resultados de los pacientes ausente. Además, como la lesión renal aguda es una condición heterogénea, una alerta puede provocar acciones que son innecesarias o incluso perjudicial (58-63).

1.7. FRA POST CONTRASTE YODADO

El fracaso renal agudo posterior a la administración de contraste yodado se define por un aumento en la creatinina sérica ≥0.3 mg/dl o ≥ 1,5 veces el nivel en las 48-72 hrs tras su administración (64-70)

1.8. FRA INDUCIDO POR AMINOGLUCÓCIDOS

Los aminoglucósidos son antibióticos bactericidas muy potentes y eficaces contra múltiples patógenos bacterianos gramnegativos y algunos grampositivos. La resistencia antimicrobiana progresiva a otros agentes antimicrobianos y la falta de nuevas alternativas a los antibióticos aminoglucósidos han provocado un aumento reciente de su uso. Los aminoglucósidos tienen muchos atributos favorables, como su notable estabilidad, farmacocinética predecible, baja incidencia de efectos secundarios de origen inmunológico y ausencia de toxicidad hematológica o hepática. La nefrotoxicidad, y en menor grado la ototoxicidad y el bloqueo neuromuscular, siguen siendo las principales toxicidades de los aminoglucósidos que limitan su uso. La

nefrotoxicidad producida por estos fármacos se explica por 3 mecanismos: toxicidad tubular renal, reducción del filtrado glomerular y reducción del flujo sanguíneo renal (71,72).

1.9. FRA INDUCIDO POR ANTIINFLAMATORIOS NO ESTEROIDEOS (AINE)

Los AINE, son fármacos con gran potencial analgésico, en general, no uso no presenta grandes perjuicios en pacientes sin enfermedades renales, jóvenes y sin comorbilidades. Sin embargo, debido a su efecto dosis-dependiente, se debe tener mucha precaución en el uso crónico de estos agentes, ya que aumenta las posibilidades de desarrollar cierta toxicidad y morbilidad. Los agentes AINE, selectivos y no selectivos, interfieren directamente con la función renal debido a la inhibición de la prostaglandina, y pueden causar desde trastornos leves y transitorios a la enfermedad renal crónica. Por lo tanto, la indicación de esta clase de fármacos debe ser bien evaluada, verificando siempre el riesgo-beneficio, además de tomar en consideración al paciente en cuestión y los potenciales efectos causados por su uso (73-75).

2. HIPÓTESIS

El análisis de los datos de los distintos estudios epidemiológicos publicados nos genera la hipótesis que, mediante la combinación de variables demográficas, factores de comorbilidad y variables relacionadas con el estado clínico del paciente, debe ser posible desarrollar modelos predictivos que sean reproducibles y permitan estimar la probabilidad individual de sufrir FRA durante el ingreso hospitalario. Siendo las características demográficas y los factores de comorbilidad variables estables no sujetas a cambio, ambas proporcionan información exclusivamente estática relacionada con la predisposición individual a sufrir FRA en un determinado contexto clínico. La monitorización secuencial y dinámica de las variables relacionadas con el estado clínico, debería permitir realizar estimaciones más precisas del riesgo y predecir, de forma dinámica los cambios en el riesgo de sufrir FRA que se producen cada vez que hay un cambio en el estado clínico del enfermo.

Por otra parte, debe tenerse en cuenta que la mayor parte de los modelos predictivos descritos son útiles para predecir el riesgo de FRA-H, independientemente de su severidad. Ninguno de ellos, es capaz de diferenciar el riesgo individual de sufrir un episodio de FRA-H grave del de sufrir FRA-H leve.

3. OBJETIVOS

Considerando nuestra hipótesis propuesta, los objetivos del estudio son:

3.1. OBJETIVO PRINCIPAL

Desarrollar y validar un modelo predictivo de FRA-H en pacientes no críticos en el que: 1.- los factores de riesgo relacionados con características demográficas, variables de comorbilidad y estado clínico, se obtengan automáticamente mediante la integración de bases de datos de registros electrónicos, 2.- se asegure que la exposición a los factores de riesgo precede a la detección del episodio de FRA-H y 3.- Los episodios de FRA se detecten automáticamente a través de sistemas electrónicos basados en el cálculo de diferencias en los niveles de creatinina.

3.2. OBJETIVOS SECUNDARIOS

1.- Realizar una validación externa del modelo predictivo de FRA MAKIPS, previamente publicado (76).

2.- Desarrollar y validar un modelo predictivo de FRA-H en pacientes no críticos que permita estimar la probabilidad individual de sufrir un episodio de FRA grave.

4. MATERIALES Y MÉTODOS

Para dar respuesta a cada uno de los objetivos planteados, se han realizado 3 estudios independientes. Todos ellos se han publicado en revistas con alto factor de impacto.

- ESTUDIO 1: Publicado en la revista Clinical Kidney Journal JIF 5.860
- ESTUDIO 2: Publicado en la revista Clinical Kidney Journal JIF 5.860
- ESTUDIO 3: Publicado en la revista Journal of Clinical Medicine JIF 4.964

A continuación se describe de manera independiente la metodología de cada uno de los estudios.

4.1. ESTUDIO 1

Validación externa del Score de predicción de Fracaso renal agudo de Madrid

4.1.1. Diseño del estudio

Este estudio observacional retrospectivo de cohorte de validación externa del MAKIPS se realizó en pacientes adultos (18 años) hospitalizados en el Hospital Arnau de Vilanova de Lleida, España, desde abril de 2018 hasta septiembre de 2019. El Hospital Arnau de Vilanova es un centro terciario de alta complejidad que atiende a una población de 430217 habitantes en Lleida que proporciona intervenciones médicas, quirúrgicas y endovasculares guiadas por catéter, con la excepción de la cirugía cardíaca y los servicios de trasplante de pulmón, hígado, riñón o médula ósea. Las comorbilidades, diagnósticos e intervenciones quirúrgicas de los pacientes se obtuvieron de los registros electrónicos de datos médicos y se clasificaron según la Clasificación Internacional de Enfermedades, Novena Revisión, Modificación Clínica (CIE-9-CM), aplicando los mismos códigos utilizados para desarrollar el MAKIPS. Los datos bioquímicos de los pacientes hospitalizados se obtuvieron de bases de datos electrónicas de laboratorios. Los pacientes incluidos fueron adultos, con más de 18 años de edad, que ingresaron al hospital con un tiempo mínimo de 24 horas y a los cuales, se les realizaron al menos dos mediciones de creatinina sérica durante su estancia hospitalaria. Se excluyó a los pacientes que presentaron LRA en las primeras 48 horas de ingreso hospitalario, ya que se consideró que presentaban LRA adquirida en la comunidad. También se excluyó a los pacientes en tratamiento crónico con diálisis.

4.1.2. **Función renal basal**

Nuestro sistema de atención al paciente integra las bases de datos de laboratorio de los registros hospitalarios y de atención primaria de todos los pacientes hospitalizados, siempre que estos datos se hayan registrado previamente en los registros hospitalarios. La función renal basal se obtuvo de los datos de laboratorio del registro de atención primaria y se definió como la tasa de filtración glomerular (TFG) más reciente, estimada según la ecuación de la "Chronic Kidney Disease Epidemiology" (22) en los últimos 12 meses previos al ingreso hospitalario. Para los pacientes sin creatinina sérica en los 12 meses anteriores al ingreso hospitalario, la función renal basal fue el valor más bajo de creatinina sérica tomada durante la hospitalización.

4.1.3. **Definición de FRA**

FRA se definió y clasificó según los estadios de gravedad basándose en la "Kidney Disease: Improving Global Outcomes criteria" (22). FRA-H se definió como un aumento de la creatinina sérica 0,3 mg/dL o >50% por encima del valor basal en las 48h a cualquier momento durante el ingreso hospitalario.

4.1.4. **Detección de FRA**

Se utilizó un programa informático integrado en la base de datos para realizar comparaciones repetidas de todas las mediciones de creatinina sérica creatinina sérica tomadas a cada paciente durante su durante su estancia en el hospital y generó un código de identificación, asignando un «1» cuando se cumplían los criterios de LRA y un «0» cuando no. También asignó el nivel de gravedad del FRA en función de las diferencias máximas en

la creatinina sérica. El número del episodio de ingreso, que es único para cada paciente, se utilizó como filtro para registrar a los pacientes con más de un episodio de FRA durante su estancia hospitalaria. Los miembros del equipo de investigación responsables del análisis de datos anónimos no tuvieron acceso a ningún otro dato. El estudio se realizó de acuerdo con la Declaración de Helsinki y la legislación española y fue aprobado por los comités éticos de los dos centros participantes que consideraron que no era necesario el consentimiento informado para el presente estudio.

4.1.5. **Análisis estadístico**

Los cálculos de incidencia se basaron en el número total de ingresos. Para los pacientes que desarrollaron más de un episodio de FRA durante su estancia hospitalaria, sólo se tuvo en cuenta el episodio más grave. Se consideró que los pacientes que estaban en riesgo y que ingresaron dos o más veces, se incluyeron en los cálculos de cada episodio excepto cuando el reingreso se produjo en los 30 días siguientes al alta hospitalaria. Los resultados se presentan como media, desviación estándar (DE) o como mediana y percentiles 25-75 (P25-P75). Las diferencias en los factores de riesgo entre los grupos se calcularon mediante la prueba de la t de Student no apareada para las variables cuantitativas o la prueba del chi cuadrado para las variables categóricas. Un valor P <0,05 se consideró estadísticamente significativo. El riesgo individual de desarrollar FRA-H se estimó mediante el MAKIPS (83), asignando un valor de cero a la cirugía cardiaca. La discriminación del MAKIPS se evaluó

mediante el estadístico C y el área bajo la curva de característica operática del receptor (AUROC). Se utilizaron diagramas de calibración de ajuste del MAKIPS en la cohorte de validación externa. Los análisis estadísticos se realizaron con el Statistical Package for the

Social Sciences for Windows version 20.0(IBM, Armonk, NY, EE.UU.) y el software R versión 3.6.3 (R Foundation for Statistical Computing, Viena, Austria).

4.2.**ESTUDIO 2**

Integración de registros electrónicos de datos sanitarios para desarrollar y validar un modelo predictivo de fracaso renal agudo adquirido en el hospital en pacientes no críticos

4.2.1. **Diseño del estudio**

Este estudio prospectivo se realizó en dos centros hospitalarios diferentes. El primer centro desarrolló el modelo predictivo (conjunto de estudio) y el segundo centro realizó la validación externa del modelo predictivo (conjunto de validación).

4.2.2.Conjunto de estudio

El conjunto de estudio incluyó a los pacientes ingresados en el Hospital Universitario Vall d'Hebron de enero a diciembre de 2017. Vall d'Hebron es un hospital terciario de alta complejidad que presta asistencia a una población de 500 000 habitantes en Barcelona, España, y proporciona todo tipo de procedimientos médicos y quirúrgicos, incluidos neurocirugía, cirugía cardíaca, procedimientos endovasculares guiados por catéter y programas de trasplante de pulmón, hígado, riñón y médula ósea. Se incluyeron todos los pacientes >18 años de edad que ingresaron en el hospital durante este periodo y no cumplían ninguno de los siguientes criterios de exclusión: ingreso por FRA adquirida en la comunidad; estancia hospitalaria <24 h; ingreso por cirugía cardiaca electiva; ingreso directo desde urgencias a la UCI; ingreso como receptor de un trasplante renal, pulmonar, hepático o de médula ósea; ausencia de mediciones de creatinina sérica realizadas al menos

12 meses después del ingreso hospitalario; tratamiento crónico con hemodiálisis y denegación del consentimiento por escrito para participar en el estudio. El FRA adquirido en la comunidad se diagnosticó siempre que los pacientes cumplían los criterios de FRA en las primeras 24 h del ingreso hospitalario. Los pacientes ingresados inicialmente en salas de hospitalización convencional que posteriormente requirieron ingreso en la UCI sólo se incluyeron si el episodio de FRA se detectó mientras estaban ingresados en salas no críticas antes de su ingreso en la UCI.

4.2.3. **Función renal basal**

Nuestro sistema de atención al paciente integra las bases de datos de laboratorio de los registros hospitalario y de atención primaria, lo que permite obtener datos históricos de todos los pacientes hospitalizados, siempre que estos datos figuren en dichos registros. La función renal basal se obtuvo de los registros electrónicos de datos de laboratorio de atención primaria y se definió como la tasa de filtración glomerular más reciente, estimada mediante la ecuación de la Chronic Kidney Disease Epidemiology Collaboration, dentro de los 12 meses previos al ingreso hospitalario.

4.2.4. **Definición de FRA**

El FRA se definió y clasificó en estadios de gravedad según los criterios KDIGO (22). El FRA-H se definió como un aumento de la creatinina sérica de 0,3 mg/dL o >50% con respecto al valor basal que se produjo desde las primeras 24 h hasta cualquier momento del ingreso hospitalario.

4.2.5. **Detección de FRA**

El programa informático integrado en la base de datos electrónica del laboratorio se utilizó para realizar comparaciones repetidas entre todos los niveles de creatinina sérica disponibles para cada paciente durante la estancia hospitalaria y generó un código de identificación, asignando 1 cuando se cumplían los criterios de FRA y 0 cuando no. También asignó un nivel de gravedad del FRA en función de las diferencias máximas de creatinina sérica detectadas. También se registró la fecha de detección del FRA. El número del episodio de ingreso se utilizó como filtro para que los pacientes con más de un episodio de FRA durante la estancia hospitalaria se introdujeran en la base de datos una sola vez, correspondiendo con el episodio de FRA más grave.

4.2.6. **Evaluación clínica al ingreso hospitalario y durante la estancia hospitalaria**

Al ingreso hospitalario, un equipo de 10 enfermeras formadas y 4 nefrólogos examinó los datos médicos y entrevistó a todos los pacientes para registrar la edad, el sexo, el grupo étnico y la presencia de las siguientes comorbilidades crónicas diabetes mellitus, hipertensión, cardiopatía isquémica (CI), enfermedad cerebrovascular isquémica (ECVI), enfermedad vascular periférica isquémica (EVP), enfermedad digestiva crónica, enfermedad hepática crónica, insuficiencia cardiaca congestiva crónica (ICCC) malnutrición (MN), enfermedad pulmonar obstructiva crónica (EPOC), neoplasia maligna, demencia, enfermedad reumatológica, síndrome de inmunodeficiencia adquirida (SIDA)/virus de inmunodeficiencia humana (VIH), enfermedad urológica o enfermedad renal crónica (ERC). Todas estas variables se registraron en la base de datos general del estudio según los

criterios detallados en las definiciones operativas de los métodos suplementarios. El estado nutricional se evaluó mediante la prueba Nutritional Risk Screening 2002 [77]. La asignación de códigos de comorbilidad a cada paciente se realizó por consenso entre los investigadores clínicos. Todos los pacientes fueron seguidos hasta el alta hospitalaria. Durante la estancia hospitalaria, los datos de seis bases de datos sanitarias electrónicas, a saber, constantes vitales, laboratorio, prescripción farmacéutica, radiología intervencionista, cardiología intervencionista y cirugía, se integraron conjuntamente utilizando el número del episodio de ingreso, que es único para cada paciente y común a todas estas bases de datos. En conjunto, la información extraída de estas seis bases de datos incluía niveles de hemoglobina, recuento de leucocitos, saturación de oxígeno, temperatura corporal, presión arterial, frecuencia cardiaca y respiratoria, así como una lista completa de fármacos nefrotóxicos (detallada en Datos suplementarios, Tabla S1) y exposición a medios de contraste o cirugía mayor. Cada 24 h, la información actualizada de todos estos datos se volcaba en la base de datos general del estudio, que también contenía los datos de comorbilidad y todos los valores disponibles de creatinina sérica de cada paciente. A partir de estos datos, un programa informático generó códigos de clasificación para la anemia, la insuficiencia respiratoria aguda hipoxémica, el síndrome de respuesta inflamatoria sistémica (SRIS), el shock, la exposición a fármacos nefrotóxicos, los medios de contraste y la cirugía mayor. Utilizando estos códigos, la exposición a todos estos factores de riesgo se clasificó como positiva (=1), cuando el sistema detectó al menos una exposición durante la estancia hospitalaria, o negativa (=0), cuando no se detectó ninguna exposición. En todos los casos, el sistema registró el dato de exposición a cada una de estas variables, así como

el número de exposiciones a las mismas. En los pacientes con un código de FRA = 1, la exposición a estos factores de riesgo sólo se clasificó como igual a 1 cuando se produjo en un periodo máximo de tiempo previo a la detección de FRA (48 h para anemia, SIRS y shock, 72 h para medios de contraste y cirugía y 7 días para fármacos nefrotóxicos). La figura 1 muestra de forma esquemática el proceso de interrelación entre las diferentes bases de datos electrónicas realizado para obtener la información de las variables clínicas durante la estancia hospitalaria.

Al ingreso hospitalario (A), las comorbilidades crónicas son comprobadas por el equipo investigador según criterios explícitos y registradas en la base de datos general. Durante la estancia hospitalaria (B), los datos de cinco bases de datos electrónicas de salud diferentes se integran utilizando el número de episodio de ingreso y todas ellas vuelcan la información solicitada en la base de datos general del estudio. La base de datos del laboratorio realiza comparaciones repetidas entre todos los niveles de creatinina sérica y genera un código de identificación, asignando un 1 cuando se cumplen los criterios de FRA y un 0 cuando no. También asigna un nivel de gravedad del FRA en función de las diferencias máximas de creatinina sérica detectadas. También se registra la fecha de detección del FRA. El número de episodio de ingreso se utiliza como filtro para que los pacientes con más de un episodio de FRA durante la estancia hospitalaria se introduzcan en el sistema una sola vez, correspondiendo con el episodio de FRA más grave. El seguimiento de los niveles de hemoglobina se utiliza para generar un código de clasificación de la anemia. El nivel de saturación de oxígeno se utiliza para generar un código de fallo agudo hipoxémico. La información sobre los niveles de leucocitos en sangre, junto con la temperatura y la

frecuencia cardiaca y respiratoria, se integran para generar un código de SIRS y la información sobre la presión arterial, junto con la prescripción de fármacos vasoactivos, se utiliza para generar un código de shock. Se introduce una lista completa de fármacos nefrotóxicos directos en la base de datos de prescripciones farmacéuticas, que genera un código de exposición cada vez que la lista de prescripciones contiene alguno de estos fármacos. Las bases de datos de radiología, angiorradiología y cardiología intervencionista proporcionan información sobre la exposición a medios de contraste y la base de datos de cirugía proporciona información sobre cirugía mayor y anestesia. En todos los casos, el sistema registra los datos de exposición a cada uno de estos factores. En los pacientes con un código de FRA = 1, la exposición a los factores de riesgo se clasifica como igual a 1 sólo cuando se produce dentro de un periodo máximo de tiempo previo a la detección del FRA (48 h para la anemia, el SIRS y el shock, 72 h para los medios de contraste y la cirugía y 7 días para los fármacos nefrotóxicos). En los pacientes con un código de FRA = 0, la exposición a factores de riesgo se clasifica como positiva (=1), cuando el sistema detecta al menos una exposición durante la estancia hospitalaria, o negativa (=0), cuando no se detecta ninguna. En ambos casos (FRA y no FRA), también se registra el número de exposiciones a cada factor de riesgo. A diferencia del nivel de hemoglobina, la saturación arterial de oxígeno, la frecuencia cardiaca, la frecuencia respiratoria y el nivel de presión arterial, al ser variables numéricas que pueden transferirse directamente a la base de datos general, tanto el shock circulatorio como el SIRS son variables complejas que, para ser detectadas automáticamente mediante un código de detección guiado por software, requieren la integración de datos procedentes de diversos registros electrónicos y la

definición de algoritmos de clasificación. En ambos casos, antes de utilizarlos en los análisis estadísticos, analizamos la precisión de los sistemas de detección automática en una muestra de 3426 pacientes. Para ello, a partir de los datos obtenidos de forma ciega por dos investigadores clínicos independientes, se realizó un análisis de concordancia entre la identificación de los casos mediante los sistemas electrónicos de detección y el diagnóstico realizado por los investigadores mediante criterios clínicos, así como un análisis de concordancia inter observador para ambos diagnósticos clínicos. Los resultados de estos análisis se resumen en el apartado Anexos, Datos suplementarios, Estudio 2.

4.2.7. **Conjunto de validación**

El modelo predictivo obtenido en el Hospital Vall d'Hebron fue validado externamente en pacientes ingresados en el Hospital Arnau de Vilanova de Lleida entre junio de 2017 y diciembre de 2018. El Hospital Arnau de Vilanova es un centro docente de alta complejidad que presta asistencia a 490 000 habitantes. Este centro presta actividades similares a las del Hospital Vall d'Hebron con las excepciones de los programas de trasplante y cirugía cardíaca. La selección de los pacientes y los procedimientos del estudio se realizaron de acuerdo con los mismos criterios establecidos para el conjunto del estudio. El estudio de validación externa fue realizado por un equipo de investigación independiente que no participó en el desarrollo del modelo predictivo y se probó únicamente en la historia clínica electrónica del hospital. Se consultó al comité ético del Hospital Arnau de Vilanova, que decidió que no era necesario el consentimiento informado para la validación del modelo, dado que no se realizó ningún tipo de intervención sobre los pacientes.

4.2.8. **Estadística**

Los cálculos de incidencia y prevalencia incluyeron el número total de ingresos. Para los pacientes que desarrollaron más de un episodio de FRA durante el ingreso hospitalario, sólo se incluyó en el estudio el episodio más grave. Se consideró que los pacientes estaban en riesgo cada vez que ingresaban en el hospital y, por lo tanto, los pacientes que ingresaron dos o más veces durante el periodo de estudio se incluyeron en los cálculos en cada ingreso, excepto cuando el reingreso se produjo en los 30 días siguientes al alta hospitalaria. Los resultados se presentan como media ± desviación estándar (DE) o mediana y [intervalo intercuartílico (IQR), percentil 25-75]. Las diferencias en los factores de riesgo entre grupos se calcularon mediante la prueba t de Student no emparejada o la prueba de análisis de la varianza. Las variables cualitativas se compararon mediante la prueba del chi cuadrado. Los análisis de concordancia entre variables cualitativas se realizaron mediante el coeficiente kappa. Los valores $p < 0,05$ se consideraron estadísticamente significativos. Para determinar qué variables se asociaban de forma independiente con el FRA, se realizó un análisis univariante comparando los pacientes con y sin FRA. Todas las variables con un valor $P < 0,1$ en el análisis univariante se introdujeron en el análisis de regresión logística múltiple por pasos con un método de selección hacia delante basado en los cambios de la razón de verosimilitud (RV). Las odds ratio (OR) se calcularon a partir de los coeficientes de regresión como una aproximación al riesgo relativo. El valor predictivo del modelo logístico se evaluó mediante el estadístico C, el R2 de Cox y Snell y el R2 de Nagelgerke.

El sobreajuste del modelo se evitó mediante el criterio de información de Akaike (AIC) (78,79). También se utilizó la prueba de Hosmer-Lemeshow (80) para calcular el poder de

discriminación y la bondad de ajuste del modelo logístico. Los resultados se presentan de acuerdo con las directrices deTransparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis para modelos de predicción de riesgo (81, 82). Una vez obtenido en el conjunto de estudio, el modelo logístico predictivo fue probado ciegamente en el conjunto de validación externa por un grupo independiente de investigadores que no participaron en el desarrollo del modelo predictivo. Los análisis estadísticos se realizaron con el paquete estadístico Statistical Package for the Social Sciences for Windows versión 20.0 (IBM, Armonk, NY, EE. UU.).

4.3.**ESTUDIO 3**

Desarrollo y validación de un modelo de predicción de fracaso renal agudo hospitalario grave en pacientes no críticos

4.3.1. **Diseño del estudio:**

Este estudio prospectivo se realizó en dos centros hospitalarios diferentes. El primer centro desarrolló el modelo predictivo (conjunto de estudio) y el segundo centro realizó la validación externa del modelo predictivo (conjunto de validación).

4.3.2. **Conjunto de estudio**

El conjunto de estudio incluyó a los pacientes ingresados en el Hospital Universitario Vall d'Hebron de enero a diciembre de 2017. Vall d'Hebron es un hospital terciario de alta complejidad que presta asistencia a una población de 500 000 habitantes en Barcelona, España, y proporciona todo tipo de procedimientos médicos y quirúrgicos, incluidos neurocirugía, cirugía cardíaca, procedimientos endovasculares guiados por catéter y programas de trasplante de pulmón, hígado, riñón y médula ósea. Se incluyeron todos los pacientes >18 años de edad que ingresaron en el hospital durante este periodo y no cumplían ninguno de los siguientes criterios de exclusión: ingreso por FRA adquirida en la comunidad; estancia hospitalaria <24 h; ingreso por cirugía cardiaca electiva; ingreso directo desde urgencias a la UCI; ingreso como receptor de un trasplante renal, pulmonar, hepático o de médula ósea; ausencia de mediciones de creatinina sérica realizadas al menos 12 meses después del ingreso hospitalario; tratamiento crónico con hemodiálisis y

denegación del consentimiento por escrito para participar en el estudio. El FRA adquirido en la comunidad se diagnosticó siempre que los pacientes cumplían los criterios de FRA en las primeras 24 h del ingreso hospitalario. Los pacientes ingresados inicialmente en salas de hospitalización convencional que posteriormente requirieron ingreso en la UCI sólo se incluyeron si el episodio de FRA se detectó mientras estaban ingresados en salas no críticas antes de su ingreso en la UCI.

4.3.3. **Función renal basal:**

Nuestro sistema de atención al paciente integra las bases de datos de laboratorio de los registros hospitalario y de atención primaria, lo que permite obtener datos históricos de todos los pacientes hospitalizados, siempre que estos datos figuren en dichos registros. La función renal basal se obtuvo de los registros electrónicos de datos de laboratorio de atención primaria y se definió como la tasa de filtración glomerular más reciente, estimada mediante la ecuación de la Chronic Kidney Disease Epidemiology Collaboration, dentro de los 12 meses previos al ingreso hospitalario.

4.3.4. **Definición de FRA severo**

FRA se definió y clasificó en estadios de gravedad según las directrices de práctica clínica KDIGO (Kidney Disease Improving Global Outcomes) (22). El FRA hospitalario grave (FRA-H grave) se definió como un aumento de la creatinina sérica de al menos 3 sobre el valor basal o 4 mg/dL ocurrido desde las primeras 24 h hasta cualquier momento dentro del ingreso hospitalario.

4.3.5. **Detección de FRA:**

El programa informático integrado en la base de datos electrónica del laboratorio se utilizó para realizar comparaciones repetidas entre todos los niveles de creatinina sérica disponibles para cada paciente durante la estancia hospitalaria y generó un código de identificación, asignando 1 cuando se cumplían los criterios de FRA y 0 cuando no. También asignó un nivel de gravedad del FRA en función de las diferencias máximas de creatinina sérica detectadas. También se registró la fecha de detección del FRA. El número del episodio de ingreso se utilizó como filtro para que los pacientes con más de un episodio de FRA durante la estancia hospitalaria se introdujeran en la base de datos una sola vez, correspondiendo con el episodio de FRA más grave.

4.3.6. **Evaluación clínica al ingreso hospitalario y durante la estancia hospitalaria:**

Las comorbilidades y los códigos de diagnóstico de los pacientes se obtuvieron de los registros electrónicos de datos médicos y se clasificaron según la Novena Clasificación Internacional de Enfermedades, Novena Revisión, Modificación Clínica (CIE-9-CM). Durante la estancia hospitalaria, los datos de seis fuentes clínicas electrónicas de salud, que son, constantes vitales, laboratorio, prescripción farmacéutica, radiología intervencionista, cardiología intervencionista y cirugía, fueron integradas utilizando el número del episodio de ingreso, que es único para cada paciente y común a todas estas bases de datos. En general, la información extraída de estas bases de datos incluía: niveles de hemoglobina, recuento de leucocitos, saturación de oxígeno, temperatura corporal, tensión arterial, frecuencia cardiaca y frecuencia respiratoria, así como una lista completa de fármacos

nefrotóxicos (detallada en la Tabla S1) y exposición contraste yodado o cirugía mayor. Cada 24 h, la información actualizada de todas las bases de datos se volcaba en la base de datos general del estudio, base que contenía también los datos de comorbilidad y todos los valores disponibles de creatinina sérica de cada paciente. A partir de estos datos, un software generaba códigos de clasificación para anemia, insuficiencia respiratoria aguda hipoxémica, síndrome de respuesta inflamatoria sistémica, shock, exposición a fármacos nefrotóxicos, contraste yodado o cirugía mayor. Utilizando estos códigos, la exposición a todos estos factores de riesgo se riesgo se clasificó como positiva = 1, cuando el sistema detectó al menos una exposición hospitalaria, o negativa = 0, cuando no se detectaba ninguna exposición. En todos los casos, el sistema registró los datos de exposición a todas y cada una de estas variables, así como el número de exposiciones a las mismas. En los pacientes con un código de FRA = 1, la exposición a estos factores de riesgo sólo se clasificó como =1 cuando se produjo en un periodo máximo de tiempo previo a la detección del estadio 3 de HA-AKI (48 h para la anemia, el SRIS y el shock, 72 h para los medios de contraste y la cirugía y 7 días para los fármacos nefrotóxicos). Los procedimientos de interrelación entre las distintas bases de datos electrónicas realizadas para obtener la información de las variables clínicas a lo largo de la estancia hospitalaria se han detallado en el estudio 2 (84). A diferencia del nivel de hemoglobina, saturación arterial de oxígeno, frecuencia cardiaca, frecuencia respiratoria o presión arterial, que al ser variables numéricas pueden transferirse directamente a la base de datos general. Tanto el shock como el SIRS como son variables complejas, para ser detectadas automáticamente mediante un código de detección guiado por software, requerían la integración de datos de

diversos registros electrónicos y la definición de algoritmos de clasificación. En ambos casos, antes de utilizarlos en los análisis estadísticos, se analizaron la precisión de los sistemas de detección automática en una muestra de 3426 pacientes, como hemos detallado anteriormente (84).

4.3.7. **Conjunto de validación**

El modelo predictivo obtenido en el conjunto del estudio fue validado externamente en pacientes ingresados en el Hospital Arnau de Vilanova de Lleida entre junio de 2017 y diciembre de 2019. El hospital Arnau de Vilanova es un centro docente de alta complejidad y presta asistencia a 490.000 habitantes. Este centro desarrolla actividades similares a las del conjunto del estudio con las excepciones de los programas de trasplantes y cirugía cardíaca. La selección de pacientes y los procedimientos del estudio se realizaron según los mismos criterios establecidos para el conjunto del estudio. El estudio de validación externa fue realizado por un equipo de investigación independiente que no participó en el desarrollo del modelo predictivo.

4.3.8. **Estadística**

Los cálculos de incidencia y prevalencia incluyeron el número total de ingresos. Para los pacientes que desarrollaron más de un episodio de FRA durante el ingreso hospitalario, sólo se incluyó en el estudio el episodio más grave. Se consideró que los pacientes estaban en riesgo cada vez que ingresaban en el hospital y, por lo tanto, los pacientes que ingresaron dos o más veces durante el periodo de estudio se incluyeron en los cálculos en cada ingreso, excepto cuando el reingreso se produjo en los 30 días siguientes al alta hospitalaria. Los resultados se presentan como media ± desviación estándar (DE) o mediana y [intervalo

intercuartílico (IQR), percentil 25-75]. Las diferencias en los factores de riesgo entre grupos se calcularon mediante las pruebas T no apareada de Student o ANOVA. Las variables cualitativas se compararon mediante la prueba de Chi-cuadrado. Los análisis de concordancia entre variables cualitativas se realizaron mediante el coeficiente kappa. Los valores p <0,05 se consideraron estadísticamente significativos. Para determinar qué variables se asociaban de forma independiente con el FRA, se realizó un análisis univariante comparando los pacientes con y sin FRA. Todas las variables con un valor P < 0,1 en el análisis univariante se introdujeron en el análisis de regresión logística múltiple por pasos con un método de selección hacia delante basado en los cambios de la razón de verosimilitud (RV). Las odds ratio (OR) se calcularon a partir de los coeficientes de regresión como una aproximación al riesgo relativo. El valor predictivo del modelo logístico se evaluó mediante el estadístico C, el R2 de Cox y Snell y el R2 de Nagelgerke.

El sobreajuste del modelo se evitó mediante el criterio de información de Akaike (AIC) (78,79). También se utilizó la prueba de Hosmer-Lemeshow (80) para calcular el poder de discriminación y la bondad de ajuste del modelo logístico. Los resultados se presentan de acuerdo con las directrices deTransparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis para modelos de predicción de riesgo (81, 82). Una vez obtenido en el conjunto de estudio, el modelo logístico predictivo fue probado ciegamente en el conjunto de validación externa por un grupo independiente de investigadores que no participaron en el desarrollo del modelo predictivo. Los análisis estadísticos se realizaron con el paquete estadístico Statistical Package for the Social Sciences for Windows versión 20.0 (IBM, Armonk, NY, EE. UU.).

5. RESULTADOS

5.1 ESTUDIO 1

EXTERNAL VALIDATION OF THE MADRID ACUTE KIDNEY INJURY PREDICTION SCORE

En el primer artículo realizamos la validación externa de un modelo de FRA, publicado en “Madrid Acute Kidney Injury Prediction Score” (83). Obtuvimos una incidencia de Fracaso renal agudo en la cohorte de validación del 5,3%. En comparación con la cohorte MAKIPS (76), la cohorte de validación mostró un mayor porcentaje de hombres, así como una mayor prevalencia de diabetes, hipertensión, enfermedad cardiovascular, enfermedad cerebrovascular, anemia, insuficiencia cardíaca congestiva, enfermedad pulmonar crónica, enfermedades del tejido conectivo y enfermedad renal, mientras que la prevalencia de úlcera péptica, enfermedad hepática, neoplasia maligna, tumores sólidos metastásicos y síndrome de inmunodeficiencia adquirida fue significativamente menor. En la cohorte de validación, el MAKIPS mostró un área bajo la curva de 0,798 (intervalo de confianza del 95%: 0,788–0,809). Los gráficos de calibración mostraron que había una tendencia de los MAKIPS a sobreestimar el riesgo de FRA-H a tasas de probabilidad <0,19 y a subestimar a tasas de probabilidad entre 0,22 y 0,67.

5.2 ESTUDIO 2

INTEGRATING ELECTRONIC HEALTH DATA RECORDS TO DEVELOP AND VALIDATE A PREDICTIVE MODEL OF HOSPITAL-ACQUIRED ACUTE KIDNEY INJURY IN NON-CRITICALLY ILL PATIENTS

Referente al segundo estudio (84) la integración de registros electrónicos de datos sanitarios para desarrollar y validar un modelo predictivo de lesión renal aguda hospitalaria en pacientes no críticos. La incidencia de FRA en el conjunto del estudio fue del 3,9%. Entre las comorbilidades crónicas, las odds ratio (OR) más elevadas correspondieron a la enfermedad renal crónica, la enfermedad urológica y la enfermedad hepática. Entre las complicaciones agudas, las OR más elevadas se asociaron a la insuficiencia respiratoria aguda, la anemia, el síndrome de respuesta inflamatoria sistémica, el shock circulatorio y la cirugía mayor. El modelo mostró un área bajo la curva (AUC) de 0,907 [intervalo de confianza (IC) del 95%: 0,902-0,908], una sensibilidad de 82,7 (IC del 95%: 80,7-84,6) y una especificidad de 84,2 (IC del 95%: 83,9-84,6) para predecir la FRA-H, con una bondad de ajuste adecuada para todas las categorías de riesgo (x^2=6,02, p=0,64). En el conjunto de validación, la prevalencia de FRA fue del 3,2%. El modelo mostró un AUC de 0,905 (IC del 95%: 0,904-0,910), una sensibilidad de 81,2 (IC del 95%: 79,2-83,1) y una especificidad de 82,5 (IC del 95%: 82,2-83) para predecir la FRA-H y tuvo una bondad de ajuste adecuada para todas las categorías de riesgo (x^2=4,2; p=0,83). Existe una herramienta en línea (predaki.amalfianalytics.com) para calcular el riesgo de FRA en otros entornos hospitalarios.

5.3 ESTUDIO 3

DEVELOPMENT AND VALIDATION OF A MODEL TO PREDICT SEVERE HOSPITAL-ACQUIRED ACUTE KIDNEY INJURY IN NON-CRITICALLY ILL PATIENTS

Referente al tercer artículo (85), Desarrollo y validación de un modelo para predecir la lesión renal aguda grave adquirida en el hospital en pacientes no críticos. La incidencia de FRA-H estadio 3 en el conjunto del estudio fue del 0,6%. Entre las comorbilidades crónicas, las odds ratio más elevadas fueron conferidas por la cardiopatía isquémica, la enfermedad cerebrovascular isquémica, la insuficiencia cardiaca congestiva crónica, la enfermedad pulmonar obstructiva crónica, la enfermedad renal crónica y la enfermedad hepática. Entre las complicaciones agudas, las odds ratio más elevadas se asociaron a la insuficiencia respiratoria aguda, la cirugía mayor y la exposición a fármacos nefrotóxicos. El modelo mostró un AUC de 0,906 (IC del 95%: 0,904 a 0,908), una sensibilidad de 89,1 (IC del 95%: 87,0-91,0) y una especificidad de 80,5 (IC del 95%: 80,2-80,7) para predecir el estadio 3 de FRA-H, pero tendía a sobrestimar el riesgo en las categorías de bajo riesgo, con una bondad de ajuste adecuada para todas las categorías de riesgo (Chi^2: 16,4; p: 0,034). En el conjunto de validación, la incidencia de FRA-H estadio 3 fue del 0,62%. El modelo mostró un AUC de 0,861 (IC del 95%: 0,859-0,863), una sensibilidad de 83,0 (IC del 95%: 80,5-85,3) y una especificidad de 76,5 (IC del 95%: 76,2-76,8) para predecir el estadio 3 de FRA-H con una bondad de ajuste adecuada para todas las categorías de riesgo (Chi^2: 15,42; p: 0,052).

6. DISCUSIÓN

Como resultado de los estudios que hemos realizado, hemos dado respuesta a todos los objetivos planteados:

1. En lo que respecta a la validación externa de modelos de predicción de Fracaso renal agudo, hemos realizado la validación externa de un modelo de predicción de Fracaso renal agudo (MAKIPS) ampliamente descrito y conocido en Europa (76). Hemos demostrado que utilizando datos que se pueden obtener fácilmente de los registros electrónicos, este modelo reproducible en un entorno diferente. Cuando un modelo predictivo se valida externamente, se espera que el poder de discriminación sea menor en la cohorte de validación externa debido a un sobreajuste del modelo de derivación (87-89). Los datos obtenidos en nuestro estudio indican que, a pesar de las diferencias mencionadas entre ambos grupos de pacientes, la discriminación de la puntuación MAKIPS en la cohorte de pacientes de validación fue comparable a la descrita en la cohorte original y no se vio afectada por las diferencias en la prevalencia de las variables implicadas en el cálculo del riesgo. Además, la ausencia de una disminución significativa de la discriminación en la cohorte de validación, indica que se realizó un ajuste correcto en la puntuación original para evitar el sobreajuste. La calibración del modelo en la cohorte de validación externa mostró una tendencia similar a la observada en la cohorte de derivación. La puntuación MAKIPS tendió a sobreestimar ligeramente el riesgo de FRA-H en las categorías de riesgo inferiores a 0,19, y a infraestimarlo en las categorías de riesgo comprendidas entre 0,22 y 0,67. En ambos estudios, este comportamiento podría explicarse por el hecho de que el riesgo de desarrollar FRA-H, depende no sólo de los datos demográficos, comorbilidades crónicas y procedimientos quirúrgicos, sino

también de factores de riesgo relacionados con el ambiente inflamatorio, estado hemodinámico, exposición a medios de contraste o fármacos nefrotóxicos durante la estancia hospitalaria, entre otros. Este último conjunto de variables son precipitantes agudos que pueden actuar a lo largo del periodo de hospitalización y pueden dar lugar a cambios relevantes en el perfil de riesgo de los pacientes que no pueden ser identificados con modelos predictivos como MAKIPS, que no los incluyen como predictores. La inclusión de los cambios dinámicos de los posibles precipitantes agudos en los modelos es técnicamente compleja y constituye un reto para futuras investigaciones. Pero su inclusión, podría suponer una mejora significativa en la discriminación de los modelos predictivos y también podría generar modelos predictivos dinámicos capaces de detectar cambios en el perfil de riesgo de los pacientes a lo largo de la estancia hospitalaria. Aun teniendo en cuenta todas estas limitaciones y a la espera de más datos de validación externa procedentes de un mayor número de hospitales que incluyan una casuística más amplia, los datos de nuestra cohorte de validación externa indican que la puntuación MAKIPS puede ser una herramienta útil y fácilmente obtenible a partir de datos de registros electrónicos para predecir FRA-H en hospitales de diferente complejidad.

2. Para dar respuesta a nuestro segundo objetivo, hemos desarrollado y validado el primer modelo descrito hasta el momento que permite obtener una estimación precisa y dinámica de la probabilidad de sufrir FRA en cualquier momento del ingreso hospitalario. Nuestro estudio proporciona un modelo validado externamente basado en datos demográficos, comorbilidades específicas, condiciones clínicas agudas y procedimientos, que puede ser utilizado en la práctica clínica para obtener una

valoración dinámica precisa del riesgo individual de padecer FRA durante todo el periodo de estancia hospitalaria en pacientes ingresados en plantas de hospitalización no crítica. Este modelo es muy versátil y permite realizar una estimación manual repetida del riesgo, utilizando el algoritmo de predicción, o bien realizar una medición automatizada y en tiempo real en aquellos centros en los que sea posible llevar a cabo una integración completa de las bases de datos que contienen la información necesaria. Nuestro estudio sienta las bases a un cambio en la gestión de la insuficiencia renal aguda hospitalaria, al utilizar un modelo dinámico de integración de registros electrónicos con el objetivo de concienciar al médico responsable de estos pacientes de alto riesgo.

3. Por último, dado que el FRA-H severo es el que se asocia con mayor morbilidad y a mayor riesgo de progresión a IRC e incluso necesidad de terapia sustitutiva renal, el tercer estudio realizado, aporta el valor de haber desarrollado y validado el primer modelo que permite predecir de forma dinámica la probabilidad individual de sufrir un episodio de FRA-H grave durante el ingreso hospitalario.

7. CONCLUSIONES

1. Hemos desarrollado y validado el primer modelo descrito hasta el momento que permite obtener una estimación precisa y dinámica de la probabilidad de sufrir FRA-H en cualquier momento del ingreso hospitalario. Nuestro estudio proporciona un modelo validado externamente basado en datos demográficos, comorbilidades específicas, condiciones clínicas agudas y procedimientos, que puede ser utilizado en la práctica clínica para obtener una valoración dinámica y precisa del riesgo individual de padecer FRA durante todo el periodo de estancia hospitalaria en pacientes ingresados en plantas de hospitalización no crítica.

2. Los datos de nuestra cohorte de validación externa indican que la puntuación MAKIPS validan los resultados descritos en la cohorte inicial e indican que dicho modelo predictivo puede ser una herramienta útil y fácilmente obtenible a partir de datos de registros electrónicos para predecir FRA-H en hospitales de diferente complejidad.

3. Hemos desarrollado y validado el primer modelo que permite predecir de forma dinámica y precisa la probabilidad individual de sufrir un episodio de FRA-H grave durante el ingreso hospitalario.

8. LINEAS DE FUTURO

Nuestro modelo está diseñado para ser ampliamente escalable, su diseño permite la adaptación a diferentes entornos hospitalarios dependiendo del sistema informático que cada centro hospitalario cuente.

Nuestra línea de investigación futura es poder integrar nuestro modelo con modelos de “Deep learning”, dado que, a medida que se recopilen más datos clínicos y se desarrollen arquitecturas de redes neuronales más sofisticadas, nuestro modelo integrado podrá identificar patrones complejos en los datos, permitiendo una predicción más precisa y dinámica del riesgo de FRA.

Dado el impacto que nuestro modelo puede tener a nivel clínico y especialmente en el momento de la toma de decisiones para prevenir el establecimiento de un FRA, se requiere investigación futura para aprovechar todo su potencial y traducirlo en mejores resultados para nuestros pacientes.

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10. ANEXOS

10.1. ARTÍCULOS RELACIONADOS CON LA TESIS

10.1.1. ARTÍCULO 1

External validation of the Madrid Acute Kidney Injury Prediction Score

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ORIGINAL ARTICLE

External validation of the Madrid Acute Kidney Injury Prediction Score

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ABSTRACT

Background. The Madrid Acute Kidney Injury Prediction Score (MAKIPS) is a recently described tool capable of performing automatic calculations of the risk of hospital-acquired acute kidney injury (HA-AKI) using data from from electronic clinical records that could be easily implemented in clinical practice. However, to date, it has not been externally validated. The aim of our study was to perform an external validation of the MAKIPS in a hospital with different characteristics and variable case mix.

Methods. This external validation cohort study of the MAKIPS was conducted in patients admitted to a single tertiary hospital between April 2018 and September 2019. Performance was assessed by discrimination using the area under the receiver operating characteristics curve and calibration plots.

Results. A total of 5.3% of the external validation cohort had HA-AKI. When compared with the MAKIPS cohort, the validation cohort showed a higher percentage of men as well as a higher prevalence of diabetes, hypertension, cardiovascular disease, cerebrovascular disease, anaemia, congestive heart failure, chronic pulmonary disease, connective tissue diseases and renal disease, whereas the prevalence of peptic ulcer disease, liver disease, malignancy, metastatic solid tumours and acquired immune deficiency syndrome was significantly lower. In the validation cohort, the MAKIPS showed an area under the curve of 0.798 (95% confidence interval 0.788–0.809). Calibration plots showed that there was a tendency for the MAKIPS to overestimate the risk of HA-AKI at probability rates <0.19 and to underestimate at probability rates between 0.22 and 0.67.

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Conclusions. The MAKIPS can be a useful tool, using data that are easily obtainable from electronic records, to predict the risk of HA-AKI in hospitals with different case mix characteristics.

Keywords: acute kidney injury, external validation, hospital-acquired, prediction, risk score

INTRODUCTION

The incidence of hospital-acquired acute kidney injury (HA-AKI) ranges between 5% and 15%, or 30–45 cases per 1000 hospital admissions per year, but it shows an increasing trend as hospitalized patients are older and subjected to many diagnostic and treatment interventions, as well as exposure to the effects of nephrotoxic drugs [1–3]. HA-AKI is associated with high morbidity and increased mortality rates [4–6]. Since a large majority of HA-AKI episodes are due to potentially avoidable causes, knowing precisely the individual risk of each patient as soon as possible after hospital admission is crucial to the implementation of preventive measures aimed at reducing the incidence of HA-AKI [7–9]. Different models based on demographic data and chronic comorbidities have been developed for this purpose [10–14]. One of the most recently published predictive models is the Madrid Acute Kidney Injury Prediction Score (MAKIPS) [15]. This model can automatically use data from electronic clinical records and can be implemented easily in clinical practice. However, to date, it has not been externally validated. Independent external validation is essential to determine whether the model can be considered as a clinical predictive model by ruling out potential overfitting or deficiencies in statistical modelling in the developing cohort and to evaluate the applicability of the model in different case mix populations [16, 17].

The objective of our study was to perform an external validation of the MAKIPS as a model to predict HA-AKI in a hospital centre with different with different case-mix characteristics.

MATERIALS AND METHODS

This retrospective observational external validation cohort study of the MAKIPS was performed in adult (≥18 years) patients hospitalized in Hospital Arnau de Vilanova in Lleida, Spain, from April 2018 to September 2019. Hospital Arnau de Vilanova is a high-complexity tertiary centre that serves a population of 430 217 inhabitants in Lleida that provides medical, surgical and endovascular catheter-guided interventions, with the exception of cardiac surgery and lung, liver, kidney or bone marrow transplantation services.

Patient comorbidities, diagnoses and procedural interventions were obtained from electronic records of medical data and classified according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), applying the same codes used to develop the MAKIPS. Biochemical data from inpatient settings were obtained from electronic laboratory databases. Patients were included if they were ≥18 years of age, were admitted for at least 24 h in hospital and had at least two serum creatinine measurements during their hospital stay. Patients who had AKI within the first 48 h of hospital admission were excluded, as they were considered to have community-acquired AKI (CA-AKI). Patients on chronic dialysis treatment were also excluded.

Baseline kidney function

Our patient care system integrates the laboratory databases of both hospital and primary care registers, thus allowing historical data to be obtained for all patients who are hospitalized, provided that these data had been previously recorded in those registers. Baseline kidney function was obtained from electronic records of laboratory data from the primary healthcare register and defined as the most recent glomerular filtration rate (GFR), as estimated by the Chronic Kidney Disease Epidemiology Collaboration equation, within the last 12 months prior to hospital admission. For patients with no serum creatinine measurement available within 12 months prior to hospitalization, the baseline kidney function was the lowest serum creatinine measurement taken during hospitalization.

Definition of AKI

AKI was defined and classified according to severity stages based on the Kidney Disease: Improving Global Outcomes criteria [18]. HA-AKI was defined as an increase in serum creatinine ≥0.3 mg/dL or >50% above the baseline occurring within the first 48 h to any time during hospital admission.

AKI detection

Software integrated into the hospital electronic laboratory database was used to perform repeat comparisons of all serum creatinine measurements taken for each patient during their hospital stay and generated an identification code, with '1' assigned when AKI criteria were met and '0' assigned when not. It also assigned the level of AKI severity according to the maximum differences in serum creatinine levels detected. The number of the admission episode, which is unique for each patient, was used as a filter so that patients with more than one AKI episode during their hospital stay were recorded on the database only once, with the entry corresponding to the more severe AKI episode.

The research team members responsible for data analysis had access to anonymized data only and were blinded to any other data. The study was conducted in accordance with the Declaration of Helsinki and Spanish law and was approved by the ethics committees of the two participating centres, which considered that informed consent was not necessary.

Statistics

The incidence calculations were based on the total number of admissions. For patients who developed more than one AKI episode during their hospital stay, only the most severe episode was included in the study. Patients were considered to be at risk on each hospital admission and therefore patients who, during the study period, were admitted two or more times, were included in the calculations for each admission, except when readmission occurred within 30 days after hospital discharge. Results are given as the mean ± standard deviation (SD) or as the median and 25th–75th percentiles (P25–P75). Differences in risk factors between groups were calculated using the unpaired

Student's t-test for quantitative variables or the chi-squared test for categorical variables. A P-value <0.05 was considered statistically significant. The individual risk of developing HA-AKI was estimated by the MAKIPS [15], assigning a value of zero to cardiac surgery. Discrimination of the MAKIPS was evaluated using the C statistic and the area under the receiver operating characteristics curve (AUROC). Calibration diagrams were used to calculate the goodness-of-fit of the MAKIPS in the external validation cohort. Statistical analyses were performed using the Statistical Package for the Social Sciences for Windows version 20.0 (IBM, Armonk, NY, USA) and R software version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Clinical and biochemical characteristics of patients

During the study period there were 26 362 hospital discharges. Figure 1 shows the flow chart of patient selection. The final study group comprised 21 787 patients. Of this cohort, 1155 patients (5.3%) developed AKI, with an incidence of 53 AKI episodes per 1000 hospital admissions. Distributions by AKI stages were as follows: stage 1, $n = 785$ (68%); stage 2, $n = 219$ (19%); and stage 3, $n = 151$ (13%).

Table 1 summarizes the demographic, clinical and admission characteristics of the study group and those of the MAKIPS cohort of patients. When compared with the MAKIPS cohort, patients from our study group showed a higher percentage of men as well as significantly higher prevalence of diabetes, hypertension, cardiovascular disease, cerebrovascular disease, anaemia, congestive heart failure, chronic pulmonary disease, connective tissue diseases and renal disease, whereas the prevalence of peptic ulcer disease, liver disease, malignancy, metastatic solid tumours and acquired immune deficiency syndrome (AIDS) was significantly lower. The percentages of both surgical patients and urgent admissions were significantly higher in our cohort of patients.

Table 2 summarizes the demographic characteristics and comorbidities of the external validation cohort of patients classified according to the presence of HA-AKI. Patients with HA-AKI were older and predominantly male compared with non-AKI patients. Comorbidities, including diabetes, cardiovascular disease, anaemia, hemiplegia, congestive heart failure, liver disease, malignancy and renal disease, were more frequent in AKI patients. Patients with AKI also showed significantly higher rates of urgent and surgical admissions. AKI patients had higher levels of uric acid, urea, glucose and potassium, as well as higher leucocyte counts, compared with non-AKI patients.

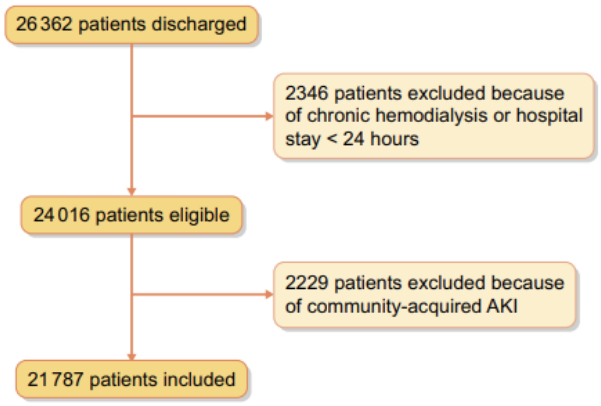


FIGURE 1: Flow chart showing patient selection.

Predictive value and goodness-of-fit of the MAKIPS algorithm in the external validation cohort

The MAKIPS showed an AUROC of 0.798 [95% confidence interval (CI) 0.788–0.809] (Figure 2).

Calibration plots for the association between predicted probabilities and observed event rates showed that with a 95% CI there was a tendency for the MAKIPS to overestimate the observed risk of HA-AKI at probability rates <0.21 and to underestimate at probability rates between 0.22 and 0.67 (Figure 3).

DISCUSSION

In this study we have carried out the first external validation of the MAKIPS score in a hospital that, in relation to the center where the original model was performed, lacks cardiac surgery and presents differential characteristics, both in the clinical profile and in the distribution of patients when compared with the hospital studied when developing the original model.

The overall incidence of HA-AKI reported in different studies varies, depending on the definition criteria of CA-AKI and the percentage of patients who come from intensive care units (ICUs), with an incidence of ~50% in the latter [13, 19–22]. The percentage of patients with CA-AKI in our study was very similar to that described in the MAKIPS cohort [15]. On the other hand, although the proportion of admissions to ICUs was significantly higher in our cohort, these patients represented only a small percentage of the total in both centres. Therefore the incidence of HA-AKI, in both cases, was very similar to previous reports in non-critically ill patients [23]. When comparing our cohort of patients with the MAKIPS cohort, we observed statistically significant differences in the prevalence of most of the chronic comorbidities analysed, in spite of the fact that in both cohorts the same ICD-9 codes were applied when classifying clinical conditions. These differences may be due to dissimilarities in the case mix between the hospitals, but may also be due to biases associated with potential discrepancies in assigning administrative codes to clinical conditions [24, 25]. There were also between-group differences in other variables involved in the calculation of the risk of HA-AKI, such as the total percentage of urgent or surgical admissions and the type of surgical intervention performed in each centre. Although not the only one, the most notable difference was related to exposure to cardiac surgery, since this intervention was not performed in the external validation centre.

External validation of a predictive model involves quantifying the model's discrimination and calibration performance using an external source of data that were not used to develop the model [26]. Discrimination is the ability of a model to differentiate between patients with different outcomes and is usually measured by the AUROC and C statistic. Calibration analyses the agreement between predicted and observed risks, and can be visualized by plotting observed against predicted risks across categories of predicted risk, using a calibration plot with a smooth, non-linear curve [17, 27]. When a predictive model is externally validated, the discrimination power is expected to be lower in the external validation cohort due to overfitting from derivation modelling [28]. Data obtained in our study indicate that, despite the aforementioned differences between both cohorts of patients, the discrimination of the MAKIPS in the

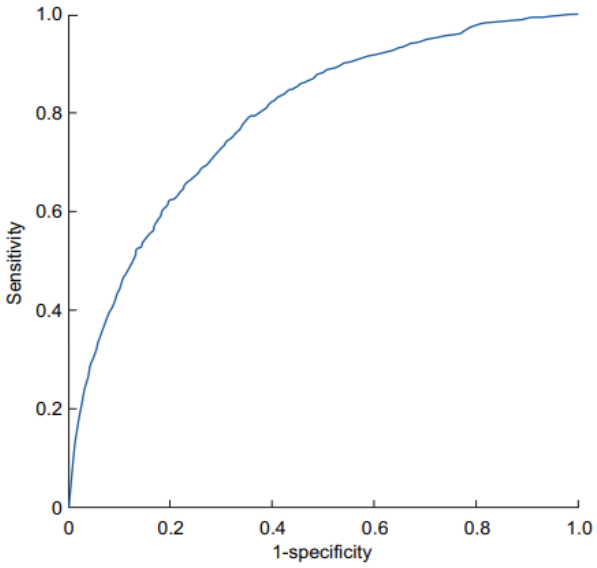
Table 1. Comorbidity and admission characteristics of the external validation and MAKIPS cohorts

Variables	External validation cohort	MAKIPS cohort	P-value
Patients, *n*	21 787	47 466	
Men, % (*n*)	46 (9932)	43.5 (20 647)	<0.0001
Mean age (years), mean (SD)	60.1 (19.7)	62.1 (20.1)	nd
Diabetes, % (*n*)	13.2 (2876)	12.2 (5786)	0.0002
Hypertension, % (*n*)	32 (6972)	30.3 (14 392)	<0.0001
Cardiovascular disease, % (*n*)	8.1 (1765)	7.6 (3596)	0.0167
Cerebrovascular disease, % (*n*)	6.9 (1486)	6 (2842)	<0.0001
Anaemia, % (*n*)	12 (2614)	11 (5205)	0.0035
Myocardial infarction, % (*n*)	3 (654)	2.8 (1363)	0.0888
Congestive heart failure, % (*n*)	7.5 (1634)	6.7 (3222)	0.0007
Peripheral vascular disease, % (*n*)	4 (851)	3.9 (1867)	0.8675
Dementia, % (*n*)	0.8 (172)	0.6 (319)	0.0967
Chronic pulmonary disease, % (*n*)	14.4 (3102)	13.4 (6385)	0.0052
Connective tissue disease, % (*n*)	3.6 (790)	1.7 (809)	<0.0001
Peptic ulcer disease, % (*n*)	0.38 (83)	0.5 (265)	<0.0001
Liver disease, % (*n*)	4.2 (915)	5.3 (2535)	<0.0001
Hemiplegia, % (*n*)	1.1 (240)	1.0 (506)	0.6700
Renal disease, % (*n*)	8 (1743)	6.0 (2849)	<0.0001
Malignancy, % (*n*)	14.3 (3115)	15.0 (7142)	0.0103
Metastatic solid tumour, % (*n*)	4 (871)	6.5 (3107)	<0.0001
AIDS/HIV, % (*n*)	0.4 (86)	0.6 (294)	0.0003
Urgent admission, % (*n*)	66.3 (14 445)	54.6 (25 916)	<0.0001
Surgical admission, % (*n*)	49 (10 675)	45.6 (21 633)	<0.0001
Admission department			<0.0001
Intensive care unit, % (*n*)	4.5 (980)	0.78 (372)	–
Nephrology, % (*n*)	1.5 (372)	0.42 (200)	–
Cardiology, % (*n*)	10.7 (2340)	6.3 (2986)	–
Cardiac surgery, % (*n*)	0	0.48 (228)	–
Vascular surgery, % (*n*)	3.6 (792)	1.8 (854)	–
Urology, % (*n*)	8.8 (1918)	6 (2835)	–
General surgery, % (*n*)	22.8 (4982)	11.8 (5596)	–
Other, % (*n*)	47.9 (10 449)	72.4 (34 395)	–

HIV, human immunodeficiency virus.

Table 2. Demographic and clinical characteristics of the external validation cohort, classified according to the presence or absence of HA-AKI

Variables	Total	AKI	Non-AKI	P-value
Patients, *n* (%)	21 787	1155 (5.3)	20 632 (94.7)	
Male, *n* (%)	10 022 (46.0)	647 (56.0)	9375 (45.4)	<0.0001
Age (years), mean (SD)	55.8 (21.3)	75.4 (24.1)	54.7 (20.3)	<0.0001
Diabetes, *n* (%)	2876 (13.2)	316 (27.4)	2560 (12.4)	<0.0001
Cardiovascular disease, *n* (%)	1.765 (8.1)	231 (20.0)	1534 (7.4)	<0.0001
Anaemia, *n* (%)	2614 (12.0)	312 (27.0)	2302 (11.1)	<0.0001
Hemiplegia, *n* (%)	240 (1.1)	29 (2.5)	211 (1.0)	<0.0001
Congestive heart failure, *n* (%)	1634 (7.5)	323 (28.0)	1311 (6.3)	<0.0001
Liver disease, *n* (%)	915 (4.2)	127 (11.0)	788 (3.8)	<0.0001
Malignancy, *n* (%)	3115 (14.3)	283 (24.5)	2832 (13.7)	<0.0001
Renal disease, *n* (%)	1743 (8.0)	337 (29.2)	1406 (6.8)	<0.0001
Urgent admission, *n* (%)	14.445 (66.3)	901 (78.0)	13 544 (65.6)	<0.0001
Surgical admission, *n* (%)	10 675 (49.0)	665 (57.5)	10 010 (48.5)	<0.0001
Estimated GFR (mL/min/1.73 m^2), median (P25–P75)	94.1 (75–114.6)	76.2 (51–98.3)	95.4 (77–1189)	<0.0001
Uric acid (mg/dL), median (P25–P75)	4.9 (3.7–6.8)	6.1 (4.7–7.6)	4 (3.5–4.6)	<0.0001
Urea (mg/dL), median (P25–P75)	39 (31.0–45.0)	50 (41.0–72.0)	39 (28.0-55.0)	<0.0001
Calcium (mg/dL), median (P25–P75)	9.1 (8.4–9.6)	8.8 (8.1–9.4)	9.3 (8.2–9.5)	<0.0001
Glucose (mg/dL), median (P25–P75)	94 (83.0–124.0)	114 (98.0–155.0)	93 (82.0–116.0)	<0.0001
Sodium (mEq/L), median (P25–P75)	138 (136.0–141.0)	137 (135.0–142.0)	139 (134.0–143.0)	<0.0001
Potassium (mEq/L), median (P25–P75)	4.2 (3.7–4.6)	4.3 (3.9–4.7)	4.1 (3.8–4.4)	<0.0001
Leucocytes (n/μL), median (P25–P75)	8.23 (5.1–11.9)	10.7 (6.6–12.3)	8.6 (5.8–10.9)	<0.0001



Area	Standard error	Asymptotic sig.	Asymptotic 95% CI Lower bound	Asymptotic 95% CI Upper bound
0.798	0.009	0	0.788	0.809

FIGURE 2: AUROC of the MAKIPS to predict HA-AKI in the external validation cohort.

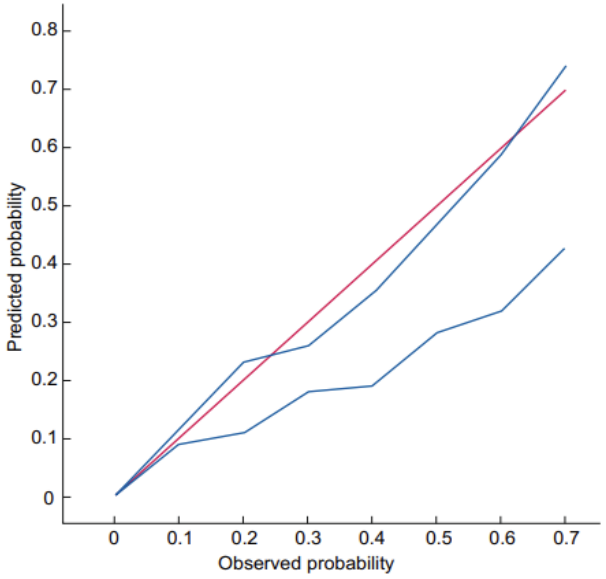


FIGURE 3: Calibration plot of the MAKIPS in the external validation cohort (n = 21 787). Calibration plots for the association between predicted probabilities and observed event rates showed that with a 95% CI, there was a tendency for the MAKIPS to overestimate the observed risk of HA-AKI at probability rates <0.21 and underestimate at probability rates between 0.22 and 0.67.

external validation cohort was comparable to that reported in the original cohort and was not affected by differences in the prevalence of the variables involved in risk calculation. Moreover, the absence of a significant decrease in discrimination in the external validation cohort indicates that correct adjustment was made to the original score to avoid overfitting.

Calibration of the model in the external validation cohort showed a similar trend to that observed in the derivation cohort. There was a tendency for the MAKIPS to overestimate slightly the risk of HA-AKI at category risks <0.19 and to underestimate the risk at category risks between 0.22 and 0.67. In both studies, this overestimating and underestimating tendency could be explained by the fact that the risk of developing HA-AKI depends not only on demographic data, chronic comorbidities and surgical procedures, but also on risk factors related to the inflammatory environment, haemodynamic status and exposure to contrast media or nephrotoxic drugs during the hospital stay, among others [29–31]. This last set of variables involves acute precipitants and may arise throughout the hospitalization period and can lead to relevant changes in the risk profile of patients that cannot be identified with predictive models such as the MAKIPS, which do not include these variables as predictors. The inclusion of dynamic changes of potential acute precipitants into predictive models is technically complex and is a challenge for future research. It could lead to a significant improvement in the discrimination of predictive models and could also generate dynamic predictive models capable of detecting changes in the risk profile of patients throughout their hospital stay.

Notwithstanding all these limitations and with more external validation data still awaited from more hospitals, including wider case mix scenarios, the data from our external validation cohort indicate that the MAKIPS can be a useful tool using data that are easily obtainable from electronic records to predict HA-AKI in hospitals with different case-mix populations.

CONFLICT OF INTEREST STATEMENT

None declared.

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10.1.2. ARTÍCULO 2

INTEGRATING ELECTRONIC HEALTH DATA RECORDS TO DEVELOP AND VALIDATE A PREDICTIVE MODEL OF HOSPITAL-ACQUIRED ACUTE KIDNEY INJURY IN NON-CRITICALLY ILL PATIENTS

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ORIGINAL ARTICLE

Integrating electronic health data records to develop and validate a predictive model of hospital-acquired acute kidney injury in non-critically ill patients

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ABSTRACT

Background. Models developed to predict hospital-acquired acute kidney injury (HA-AKI) in non-critically ill patients have a low sensitivity, do not include dynamic changes of risk factors and do not allow the establishment of a time relationship between exposure to risk factors and AKI. We developed and externally validated a predictive model of HA-AKI integrating electronic health databases and recording the exposure to risk factors prior to the detection of AKI.

Methods. The study set was 36 852 non-critically ill hospitalized patients admitted from January to December 2017. Using stepwise logistic analyses, including demography, chronic comorbidities and exposure to risk factors prior to AKI detection, we developed a multivariate model to predict HA-AKI. This model was then externally validated in 21 545 non-critical patients admitted to the validation centre in the period from June 2017 to December 2018.

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Results. The incidence of AKI in the study set was 3.9%. Among chronic comorbidities, the highest odds ratios (ORs) were conferred by chronic kidney disease, urologic disease and liver disease. Among acute complications, the highest ORs were associated with acute respiratory failure, anaemia, systemic inflammatory response syndrome, circulatory shock and major surgery. The model showed an area under the curve (AUC) of 0.907 [95% confidence interval (CI) 0.902–0.908), a sensitivity of 82.7 (95% CI 80.7–84.6) and a specificity of 84.2 (95% CI 83.9–84.6) to predict HA-AKI, with an adequate goodness-of-fit for all risk categories ($\chi^2 = 6.02$, P = 0.64). In the validation set, the prevalence of AKI was 3.2%. The model showed an AUC of 0.905 (95% CI 0.904–0.910), a sensitivity of 81.2 (95% CI 79.2–83.1) and a specificity of 82.5 (95% CI 82.2–83) to predict HA-AKI and had an adequate goodness-of-fit for all risk categories ($\chi^2 = 4.2$, P = 0.83). An online tool (predaki.amalfianalytics.com) is available to calculate the risk of AKI in other hospital environments.

Conclusions. By using electronic health data records, our study provides a model that can be used in clinical practice to obtain an accurate dynamic and updated assessment of the individual risk of HA-AKI during the hospital admission period in non-critically ill patients.

Keywords: acute kidney injury, electronic health data records, hospital-acquired, prediction, risk score

INTRODUCTION

Acute kidney injury (AKI) is a frequent and serious complication in hospitalized patients [1–3]. In addition, AKI has been associated with long-term morbidity and mortality after hospital discharge [4, 5].

Most cases of AKI in hospitalized patients are caused by ischaemia or nephrotoxicity [6–8]. The risk of developing AKI depends on the characteristics of the patient in terms of age, presence of previous kidney disease and number and types of comorbidities [9]. Since a large part of the AKI episodes are due to potentially avoidable causes, knowing as accurately as possible the individual risk at any time of the hospital stay could help decision making and implementation of preventive measures to reduce the incidence of hospital AKI [10]. The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend that patients be stratified for risk of AKI at admission and managed according to their susceptibilities and exposures to reduce the risk of AKI [11]. The incidence and risk factors associated with AKI in patients admitted to intensive care units (ICUs) have been extensively analysed [12, 13]. However, these models are difficult to extrapolate to non-critically ill patients since they have been developed for patients that are under the influence of a cluster of risk factors related to haemodynamic instability, use of vasoactive drugs, low tissue oxygenation, inflammatory response and invasive procedures such as mechanical ventilation that are unique to this environment [14]. The few studies analysing the epidemiology and risk factors associated with AKI in non-critically ill patients have two main limitations to identify accurately the risk factors associated with AKI. First, all of them are based on demographic characteristics and comorbidities that have been registered retrospectively from the discharge administrative codes and therefore are subject to a potential bias in the collection of coded information [15–20]. Second, they do not allow us to know whether the exposure to risk factors preceded the detection of the AKI episode [21].

The aim of our study was to develop and validate a predictive model of hospital-acquired AKI (HA-AKI) in non-critically ill patients in which risk factors are automatically obtained by integrating electronic health databases, it is ensured that the exposure to risk factors precedes the detection of the AKI episode and AKI episodes are automatically detected through electronic systems based on the calculation of differences in creatinine levels.

MATERIALS AND METHODS

This prospective study was performed at two different hospital centres. The first centre developed the predictive model (study set) and the second centre performed the external validation of the predictive model (validation set).

Study set

The study set included patients admitted to the Vall d'Hebron University Hospital from January to December 2017. Vall d'Hebron is a tertiary, high-complexity hospital that provides assistance to a population of 500 000 habitants in Barcelona, Spain and provides all kinds of medical and surgical procedures, including neurosurgery, cardiac surgery, endovascular catheter-guided procedures and lung, liver, kidney and bone marrow transplantation programmes. We included all patients >18 years of age who were admitted to the hospital during this period and did not meet any of the following exclusion criteria: admission for community-acquired AKI; hospital stay <24 h; admission for elective heart surgery; direct admission from the emergency room to the ICU; admission as a recipient of a renal, lung, liver or bone marrow transplant; absence of serum creatinine measurements done at least 12 months after hospital admission; chronic haemodialysis treatment and denial of written consent to participate in the study. Community-acquired AKI was diagnosed whenever patients met the AKI criteria within the first 24 h of hospital admission. Patients initially admitted to conventional hospitalization wards who afterwards required admission to the ICU were only included if the AKI episode was detected while they were admitted in non-critically ill wards prior to their admission to the ICU.

Baseline kidney function

Our patient care system integrates the laboratory databases of the hospital and primary care registers, thus allowing historical data to be obtained for all patients who are hospitalized, provided that these data appear in those registers. Baseline kidney function was obtained from the electronic laboratory data records of primary healthcare and defined as the most recent glomerular filtration rate, estimated by the Chronic Kidney Disease Epidemiology Collaboration equation, within the 12 months prior to hospital admission.

Definition of AKI

AKI was defined and classified in severity stages according to the KDIGO criteria [11]. HA-AKI was defined as an increase in serum creatinine ≥0.3 mg/dL or >50% over the baseline occurring from the first 24 h to any time within the hospital admission.

AKI detection

The software integrated into the electronic laboratory database was used to perform repeated comparisons among all serum creatinine levels available for each patient during the hospital stay and generated an identification code, assigning 1 when the AKI criteria were met and 0 when not. It also assigned a level of AKI severity according to the maximum differences in serum creatinine detected. The date of AKI detection was also recorded. The number of the admission episode was used as a filter so that patients with more than one AKI episode during the hospital stay were entered into the database only once, corresponding with the more severe episode of AKI.

Clinical evaluation at hospital admission and during hospital stay

At hospital admission, a team of 10 trained nurses and 4 nephrologists examined the medical data and interviewed all patients to record age, gender, ethnic group and the presence of the following chronic comorbidities: diabetes mellitus, hypertension, ischaemic heart disease (IHD), ischaemic cerebrovascular disease (ICD), ischaemic peripheral vascular disease (PVD), chronic digestive disease, chronic liver disease, chronic congestive heart failure (CCHF), malnutrition (MN), chronic obstructive pulmonary disease (COPD), malignancy, dementia, rheumatologic disease, acquired immunodeficiency syndrome (AIDS)/human immunodeficiency virus (HIV), urologic disease or chronic kidney disease (CKD). All these variables were recorded in the general study database according to the criteria detailed in the Supplementary methods operational definitions. Nutritional status was assessed using theNutritional Risk Screening 2002 test [22]. The allocation of comorbidity codes to each patient was carried out by consensus among clinical researchers. All patients were followed up until hospital discharge. During the hospital stay, the data of six electronic health databases, i.e. vital signs, laboratory, pharmacy prescription, interventional radiology, interventional cardiology and surgery, were integrated together using the number of the admission episode, which is unique for each patient and common to all these databases. Overall, the information extracted from these six databases included haemoglobin levels, leucocyte count, oxygen saturation, body temperature, blood pressure, heart rate and respiratory rate, as well as a complete list of nephrotoxic drugs (detailed in Supplementary data, Table S1) and exposure to contrast dyes or major surgery. Every 24 h, updated information from all these data was dumped into the general study database, which also contained the comorbidity data and all available values of serum creatinine for each patient. From these data, software generated classification codes for anaemia, hypoxaemic acute respiratory failure, systemic inflammatory response syndrome (SIRS), shock, exposure to nephrotoxic drugs, contrast dyes and major surgery. Using these codes, the exposure to all these risk factors was classified as positive (=1), when the system detected at least one exposure during the hospital stay, or negative (=0), when no exposure was detected. In all cases, the system recorded the data of exposure to each of these variables as well as the number of exposures to them. In patients with a code of AKI = 1, the exposure to these risk factors only was classified as equal to 1 when it occurred within a maximum period of time prior to AKI detection (48 h for anaemia, SIRS and shock, 72 h for contrast dyes and surgery and 7 days for nephrotoxic drugs). Figure 1 shows a schematic view of the interrelation process among the different electronic databases carried out to obtain the information on the clinical variables during the hospital stay.

At hospital admission (A), chronic comorbidities are checked by the research team according to explicit criteria and recorded in the general database. During the hospital stay (B), the data of five different electronic health databases are integrated using the admission episode number and all of them dump the requested information into the general study database. The laboratory database performs repeated comparisons among all serum creatinine levels and generates an identification code, assigning a 1 when the AKI criteria are met and a 0 when not. It also assigns a level of AKI severity according to the maximum differences in serum creatinine detected. The date of AKI detection is also recorded. The admission episode number is used as a filter so that patients with more than one AKI episode during the hospital stay are entered into the system only once, corresponding with the more severe episode of AKI. The follow-up of haemoglobin levels is used to generate a classification code of anaemia. The level of oxygen saturation is used to generate a code of hypoxaemic acute failure. Information on blood leucocyte levels, together with temperature, heart and respiratory rate, are integrated to generate a code for SIRS and information on blood pressure, together with the prescription of vasoactive drugs, is used to generate a code for shock. A complete list of direct nephrotoxic drugs is introduced in the pharmacy prescription database, which generates a code of exposure every time the prescription list contains any of these drugs. The databases of radiology, angioradiology and interventional cardiology provide information about the exposure to contrast dyes and the database of surgery provides information about major surgery and anaesthesia. In all cases, the system records the data for exposure to each one of these factors. In patients with a code of AKI = 1, the exposure to risk factors is classified as equal to 1 only when it occurs within a maximum period of time prior to AKI detection (48 h for anaemia, SIRS and shock, 72 h for contrast dyes and surgery and 7 days for nephrotoxic drugs). In patients with a code of AKI = 0, the exposure to risk factors is classified as positive (=1), when the system detects at least one exposure during the hospital stay, or negative (=0), when none is detected. In both cases (AKI and no AKI), the number of exposures to each risk factor is also recorded.

Unlike the haemoglobin level, arterial oxygen saturation, heart rate, respiratory rate and blood pressure level, being numerical variables that can be directly transferred into the general database, both circulatory shock and SIRS are complex variables that, to be automatically detected using a software-guided detection code, require the integration of data from various electronic records and the definition of classification algorithms. In both cases, before using them in statistical analyses, we analysed the accuracy of the automatic detection systems in a sample of 3426 patients. To do this, using data blindly obtained by two independent clinical investigators, we performed a concordance analysis between the identification of cases using electronic detection systems and the diagnosis made by the investigators using clinical criteria, as well as an analysis of interobserver agreement for both clinical diagnoses. The results of these analyses are summarized in Supplementary data, Table S2.

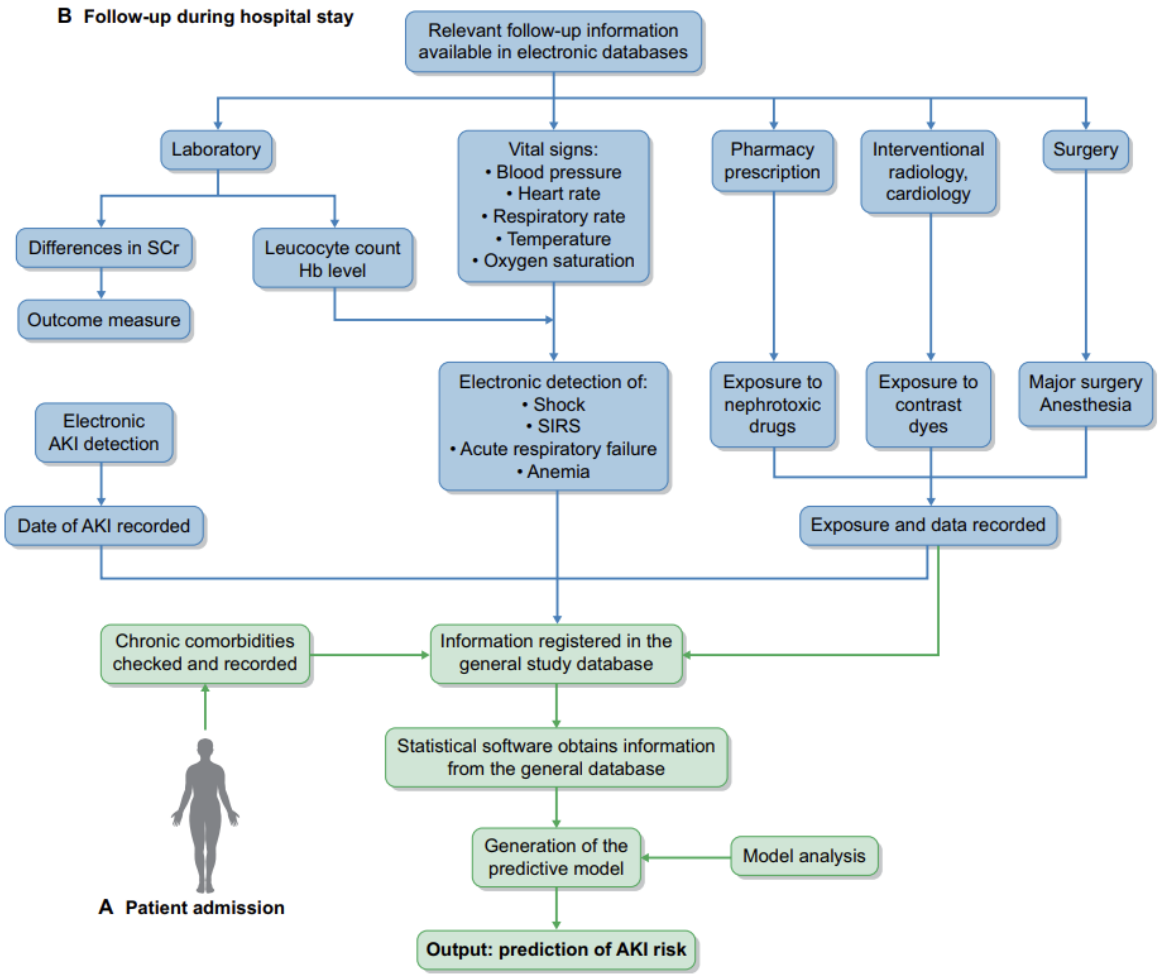

FIGURE 1: Schematic representation of the interrelation between electronic databases performed to obtain updated clinical information during the hospital stay.

Validation set

The predictive model obtained at the Vall d'Hebron Hospital was externally validated in patients admitted to the Arnau de Vilanova Hospital of Lleida between June 2017 and December 2018. Arnau de Vilanova Hospital is a high-complexity teaching centre that provides assistance to 490 000 habitants. This centre provides similar activities as the Hospital Vall d'Hebron with the exceptions of transplant programmes and cardiac surgery. The selection of patients and the study procedures were done according to the same criteria stated for the study set. The external validation study was performed by an independent research team that did not participate in the development of the predictive model and it was tested in the hospital electronic health record only.

The ethics committee of the Arnau de Vilanova Hospital was consulted and they decided that informed consent was not necessary for the validation of the model, given that no type of intervention was carried out on the patients.

Statistics

The incidence and prevalence calculations included the total number of admissions. For patients who developed more than one AKI episode during the hospital admission, only the most severe episode was included in the study. Patients were considered to be at risk each time they were admitted to the hospital and therefore patients who were admitted two or more times during the study period were included in the calculations on each admission, except when readmission occurred within 30 days after hospital discharge. Results are given as the mean ± standard deviation (SD) or median and [interquartile range (IQR), 25th percentile–75th percentile]. Differences in risk factors between groups were calculated by the Student's unpaired *t*-test oranalysis of variance test. Qualitative variables were compared using the chi-squared test. Concordance analyses between qualitative variables were done by the kappa coefficient. P-values <0.05 were considered statistically significant. To determine which variables were independently associated with AKI, we carried out a univariate analysis comparing patients with and without AKI. All the variables with a P-value <0.1 in the univariate analysis were entered into stepwise multiple logistic regression analysis with a forward selection method based on changes in the likelihood ratio (LR). Odds ratios (ORs) were calculated from the regression coefficients as an approximation of the relative risk. The predictive value of the logistic model was evaluated using the C statistic, Cox and Snell R^2 and Nagelgerke R^2. Model overfitting was prevented using the

Akaike information criterion (AIC) [23, 24]. The Hosmer–Lemeshow test [25] was used as well to calculate the discrimination power and goodness-of-fit of the logistic model. Results are presented according to theTransparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis guidelines for risk prediction models [26, 27]. Once obtained in the study set, the predictive logistic model was blindly tested on the external validation set by an independent group of researchers who did not participate in the development of the predictive model. Statistical analyses were performed with the Statistical Package for the Social Sciences for Windows version 20.0 (IBM, Armonk, NY, USA).

RESULTS

Study set

During the study period there were 42 449 hospital discharges. Figure 2 shows the flow chart for patient selection. The final study group comprised 36 852 patients. Of this cohort, 1453 (3.9%) developed AKI, with an incidence of 39 AKI episodes/1000 hospital admissions. Distribution by AKI stages was Stage 1, n = 1069 (73.5%); Stage 2, n = 258 (17.8%) and Stage 3, n = 126 (8.7%).

Table 1 summarizes the demographic characteristics, comorbidities, clinical events and procedures during the hospital stay in the study group, classified according to the presence of AKI. AKI patients were older and more frequently male than non-AKI patients. Comorbidities including IHD, ICD, ischaemic PVD, chronic liver disease, CCHF, MN, COPD, malignancy, urologic disease and CKD stages were also more frequent in AKI patients. The AKI risk increased linearly as glomerular filtration rate decreased. Patients with AKI also showed significantly higher rates of urgent admission, anaemia, acute respiratory failure, SIRS, shock, major surgery and exposure to contrast dyes and nephrotoxic drugs.

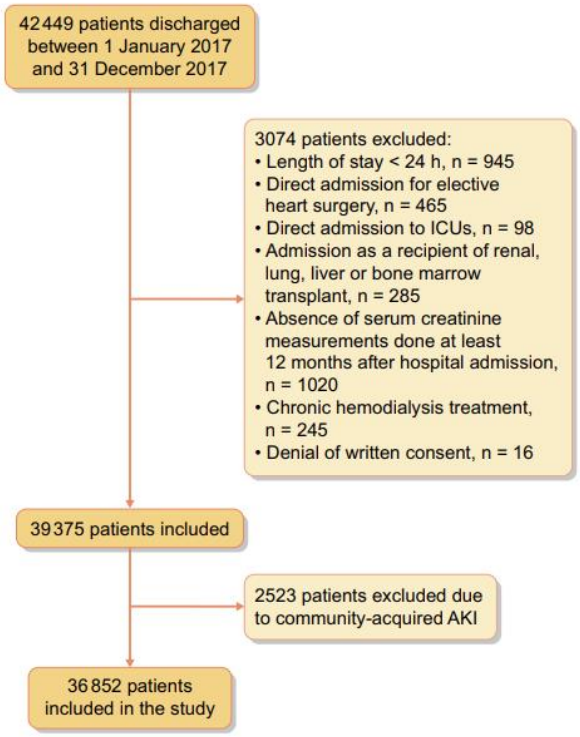

FIGURE 2: Flow chart for patient selection.

The results of the logistic model to predict AKI are summarized in Table 2. The highest ORs were associated with advanced stages of CKD, shock, acute respiratory failure and SIRS. The model showed an AUC of 0.907 (95% CI 0.902–0.908), with a sensitivity of 82.7 (95% CI 80.7–84.6) and a specificity of 84.2 (95% CI 83.9–84.6) to predict HA-AKI and showed an adequate goodness-of-fit for all risk categories (Table 3; $\chi^2 = 6.02$, P = 0.64).

Supplementary data, Table S3 summarizes the results of the stepwise forward procedures done to develop the final logistic model, including changes in the LRs, Cox and Snell R^2, Nagelkerke R^2 and AIC.

Validation set

The demographic characteristics, comorbidities and clinical parameters of the study and external validation cohorts are summarized in Table 4.

When compared with the study set, patients of the validation set showed significantly lower prevalences of major surgery and patients with AIDS/HIV. There was as well a significant difference in the distribution of CKD stages between the two centres. In the validation set, 807/21 545 (3.7%) developed HA-AKI, with an incidence of 37.4 AKI episodes/1000 hospital admissions. Distribution by AKI stages was Stage 1, n = 605 (75%); Stage 2, n = 129 (16%) and Stage 3, n = 736 (9%), with no significant differences between the study set and validation set. When the predictive model was tested in the validation set, it showed an AUC of 0.905 (95% CI 0.904–0.910), with a sensitivity of 81.2 (95% CI 79.2–83.1) and a specificity of 82.5 (95% CI 82.2–83) to predict HA-AKI and an adequate goodness-of-fit for all risk categories ($\chi^2 = 4.2$,P = 0.83; Table 5).

There were no significant differences between the AUC obtained in the study set and that obtained in the validation set (Figures 3 and 4).

DISCUSSION

In this study we integrated the information of six electronic health databases commonly used in clinical practice to develop and externally validate a predictive dynamic model that allows one to accurately estimate the individual likelihood of suffering AKI at any time during a hospital stay in non-critically ill patients. In the study group, the final logistic model identified two sets of risk factors. The first set included the demographic data and the patient's chronic comorbidities. The second included a set of risk factors related to the patient's clinical status and to the exposure to major surgery, contrast media or nephrotoxic drugs during the hospital stay. This model showed a high sensitivity and specificity to predict hospital AKI and showed an adequate calibration for all risk categories, both in the study group and in the validation group. When compared with previously published risk models, our model differs at various points. First, unlike previous studies, our study provides a model that allows estimating the risk of HA-AKI tailored to patients admitted to non-critical hospital wards. Moreover, in order to obtain a predictive model that could be exportable to hospitals with different characteristics and complexities, patients who were admitted for programmes and/or procedures such as cardiac surgery or solid organ or bone marrow transplantation that are not commonly available at all hospital centres were deliberately excluded. This potential scalability to less complex centres could be demonstrated as the model had the same performance

Table 1. Demographic characteristics, chronic comorbidities, clinical events and procedures during the hospital admission and univariate logistic analysis of variables associated with HA-AKI in the study group

Variables	Total	AKI	Non-AKI	OR (95 % CI)
Patients, *n* (%)	36 852 (100)	1453 (3.9)	35 399 (96)	
Gender (male), *n* (%)	16 782 (45.5)	879 (60.5)	15 903 (44.9)	1.76 (1.59–1.96)
Age (years), mean (SD)	54.9 (20.6)	73 (15.0)	54 (20.5)	1.065 (1.061–1.070)
Chronic comorbidities, *n* (%)				
Diabetes	6837 (18.6)	574 (39.5)	6263 (17.7)	3.04 (2.73–3.39)
Hypertension	14 507 (39.4)	990 (68.1)	13 517 (38.2)	3.46 (3.09–3.87)
IHD	2728 (7.4)	194 (13.4)	2534 (7.2)	2.00 (1.71–2.34)
ICD	2560 (6.9)	181 (12.5)	2379 (6.7)	1.98 (1.68–2.32)
Ischaemic PVD	1924 (5.2)	138 (9.5)	1786 (5.0)	1.98(1.65–2.37)
Chronic digestive disease	2132 (5.8)	70 (4.8)	2062 (5.8)	0.82 (0.64–1.05)
Chronic liver disease	1277 (3.5)	123 (8.5)	1154 (3.3)	2.74 (2.26–3.33)
CCHF	2988 (8.1)	225 (15.5)	2763 (7.8)	2.16 (1.87–2.51)
MN	8524 (23.1)	766 (52.7)	7758 (21.9)	3.97 (3.57–4.42)
COPD	5383 (14.6)	537 (37.0)	4846 (13.7)	3.7 (3.10–4.30)
Malignancy	5278 (14.3)	496 (34.1)	4782 (13.5)	3.32 (2.97–3.71)
Dementia	332 (0.9)	14 (1.0)	318 (0.9)	1.07 (0.63–1.84)
Rheumatologic disease	1543 (4.2)	58 (4.0)	1486 (4.2)	0.95 (0.73–1.24)
AIDS/HIV	293 (0.8)	28 (1.9)	265 (0.7)	2.61 (0.76–3.86)
Urologic disease	2731 (7.4)	172 (11.8)	2559 (7.2)	1.72 (1.46–2.07)
CKD stages, *n* (%)				
0 + 1	30 260 (82.1)	879 (60.5)	29 381 (83.0)	Reference
2	3654 (9.9)	192 (13.2)	3462 (9.8)	1.85 (1.58–2.18)
3	2171(5.9)	231 (15.9)	1940 (5.5)	3.98 (3.42–4.63)
4	767 (2.1)	151 (10.4)	616 (1.7)	8.19 (6.77–9.91)
Clinical variables during hospital admission, *n* (%)				
Urgent admission	24 441 (66.3)	1282 (88.2)	23 159 (65.4)	3.96 (3.37–4.66)
Anaemia	5417 (14.7)	528 (36.3)	4889 (13.8)	3.56 (3.19–3.98)
Acute respiratory failure	1827 (5.0)	286 (19.7)	1541 (4.4)	5.39 (4.69–6.19)
SIRS	658 (1.8)	271 (18.7)	387 (1.1)	20.74 (17.58–24.48)
Circulatory shock	650 (1.8)	300 (20.6)	350 (1.0)	26 (22.09–30.73)
Major surgery	12 127 (32.9)	594 (40.9)	11 533 (32.6)	1.43 (1.29–1.59)
Exposure to contrast media	3353 (9.1)	303 (20.9)	3050 (8.6)	2.80 (2.45–3.19)
Exposure to nephrotoxic drugs	19 145 (52.0)	1011 (69.6)	18 134 (51.2)	2.18 (1.94–2.44)

in the validation set as in the study set. Second, in our study, comorbidities were not obtained through the administrative discharge codes but were checked case by case. Moreover, the classification of comorbidities was performed using explicit and objective definition criteria. In this way, biases related to discrepancies in assigning administrative codes to clinical conditions or to the lack of coding of certain comorbidities were minimized as much as possible. As proof of this, the prevalences of certain comorbidities observed in our cohort of patients are higher than those reported from administrative discharge codes in previous studies [28, 29]. Additionally, in our cohort, the prevalence of comorbidities such as MN, which are barely recorded in the diagnostic codes of discharge, showed similar figures than those described in studies specifically designed to analyse its prevalence [30]. Overall, these differences are in agreement with previously published data that demonstrate the variability and limitations of administrative data to define co-morbidities and clinical conditions [31]. Third, comorbidities were considered separately, which allowed assigning a risk to each of them and identifying independent predictors of AKI risk such as MN, which are not described in previous models. In addition, our model allowed stratifying the risk associated with renal function in greater detail than that provided by the dichotomous classification, depending on the presence or absence of chronic renal failure. Fourth, the main novelty of our study is the prospective monitoring of the evolution of the clinical data of the patients through integration and cross-talk between the different electronic databases containing all these data. This procedure allowed us to analyse the dynamic exposure to risk factors related to the clinical status of patients during the hospital stay, such as hypoxaemia, haemoglobin level, blood pressure changes, contrast dyes or nephrotoxic drugs, prior to the detection of the AKI episode. This integration allowed as well to perform an accurate transformation of single variables such as blood pressure, heart rate, arterial oxygen saturation, prescription of vasoactive drugs or blood leucocyte counts into more complex variables defining specific syndromes such as SIRS and circulatory shock. Electronic records also allowed us to record the exposure to the same variables and risk factors in patients who did not develop AKI during the hospital admission. This approach made it possible to estimate the individual risk, based on the actual exposure to each risk factor. Lastly, since our predictive model was developed from the values of risk factors assessed prior to AKI detection, our model allows one perform dynamic monitoring of risk and even to predict the changes in the individual risk that are expected to happen every time the values of different predictive risk factors change.

Our group recently performed external validation of one of the most recent predictive models of acute renal failure, the

Table 2. Final multivariate model selected by forward stepwise logistic regression to predict HA-AKI

Variables	β	Standard error	Wald	OR (95% CI)	P-value
Gender (male), *n* (%)	0.21	0.069	9.63	1.29 (1.08–1.42)	0.002
Age (years), mean (SD)	0.05	0.003	218.25	1.05 (1.04–1.05)	<0.001
Chronic comorbidities					
Diabetes	0.48	0.085	31.67	1.61 (1.36–1.90)	<0.001
Hypertension	0.17	0.073	5.76	1.19 (1.03–1.37)	0.016
Ischaemic heart disease	0.32	0.101	10.02	1.38 (1.13–1.67)	0.002
Ischaemic peripheral vascular disease	0.41	0.123	11.31	1.51 (1.19–1.93)	0.001
Chronic liver disease	1.04	0.126	68.95	2.84 (2.22–3.63)	<0.001
CCHF	0.48	0.079	37.05	1.61 (1.38–1.88)	<0.001
MN	0.25	0.078	10.23	1.29 (1.10–1.50)	0.001
COPD	0.32	0.085	14.03	1.37 (1.16–1.62)	<0.001
Malignancy	0.59	0.089	40.27	1.76 (1.48–2.10)	<0.001
Chronic urologic disease	0.96	0.117	67.02	2.60 (2.07–3.27)	<0.001
CKD stages					
0 + 1					Reference
2	0.89	0.096	84.42	2.42 (2.01–2.93)	<0.001
3	1.38	0.098	198.25	3.98 (3.28–4.82)	<0.001
4	2.04	0.125	265.63	7.67 (5.99–9.78)	<0.001
Clinical variables during hospital admission					
Urgent admission	0.79	0.097	66.42	2.21 (1.83–2.67)	<0.001
Anaemia	0.78	0.069	125.61	2.18 (1.90–2.49)	<0.001
Acute respiratory failure	1.26	0.097	169.11	3.53 (2.92–4.27)	<0.001
Acute heart failure	0.69	0.095	53.24	2.00 (1.66–2.41)	<0.001
SIRS	1.25	0.129	94.88	3.50 (2.72–4.5)	<0.001
Circulatory shock	1.82	0.127	205.48	6.16 (4.80–7.89)	<0.001
Major surgery	0.99	0.076	169.43	2.70 (2.32–3.13)	<0.001
Exposure to contrast media	0.52	0.087	36.52	1.69 (1.43–2.00)	<0.001
Exposure to nephrotoxic drugs	0.57	0.070	67.04	1.77 (1.54–2.03)	<0.001

Table 3. Hosmer–Lemeshow's goodness-of-fit of the logistic predictive model in the study group

	AKI = 0		AKI = 1		
Risk deciles	Observed	Expected	Observed	Expected	Total
<0.0008504	3684	3683.9	2	2.1	3686
0.0085041–0.0016950	3678	3680.7	8	5.3	3686
0.0016951–0.0031772	3675	3675.8	11	10.1	3686
0.0031773–0.0053733	3663	3660.6	15	17.3	3678
0.0053733–0.0087714	3655	3656.7	30	28.2	3685
0.0087715–0.0140660	3644	3641.7	42	44.2	3686
0.0140661–0.0228354	3628	3615.7	56	68.2	3684
0.0228355–0.0394850	3586	3575.0	100	110.9	3686
0.0394851–0.0850955	3471	3477.2	214	207.7	3685
>0.0850955	2715	2731.0	974	957.9	3689

$\chi^2 = 6.01$. P = 0.645.

Madrid Acute Kidney Injury Prediction Score (MAKIPS) [32]. This model can be calculated automatically from electronic medical records and could be easily implemented in clinical practice. With our validation, we conclude that the MAKIPS can be a useful tool, easily obtainable from electronic records data, to predict AKI in hospitals of different complexity. However, this model, as well as many others described, has the main limitation that it does not include dynamic factors. The inclusion of dynamic changes of possible acute precipitants in the models is technically complex and constitutes a challenge for future research. It could lead to a significant improvement in the discrimination of predictive models and could also generate dynamic predictive models capable of detecting changes in the risk profile of patients throughout the hospital stay.

Our model has some limitations that affect neither its predictive capacity nor its calibration but must be highlighted. First, the record of clinical variables such as blood pressure, heart rate, respiratory rate or oxygen saturation were automatically dumped into the study database; however, these values are not without potential error related to the variability in the manual introduction of these variables into their corresponding databases. Second, although the model allows AKI to be accurately predicted, it does not predict its severity stage. Third, our data indicate that integrating data from different electronic databases make it possible to obtain a reliable prediction of the risk of AKI. However, the model obtained in our study is not the only one that can be obtained with the combination of these data. As exposure to each of the acute complications or

Table 4. Comparison of demographic characteristics, comorbidities and clinical variables between the study set and the external validation set

Variables	Study set	Validation set	P-value
Patients, *n*	36 852	21 545	–
Gender (male), *n* (%)	16 782 (45.5)	9932 (46)	0.19
Age (years), mean (SD)	549 (20.6)	60.1 ± 19.7	0.38
Chronic comorbidities, *n* (%)			
Diabetes	6837 (18.6)	3942 (18.3)	0.44
Hypertension	14 507 (39.4)	8389 (38.9)	0.27
IHD	2728 (7.4)	1573 (7.3)	0.66
ICD	2560 (6.9)	1486 (6.9)	0.83
Ischaemic PVD	1924 (5.2)	1163 (5.4)	0.36
Chronic digestive disease	2132 (5.8)	1228 (5.7)	0.68
Chronic liver disease	1277 (3.5)	775 (3.6)	0.41
CCHF	2988 (8.1)	1659 (7.7)	0.08
MN	8524 (23.1)	4869 (22.6)	0.14
COPD	5383 (14.6)	3102 (14.4)	0.49
Malignancy	5278 (14.3)	3038 (14.1)	0.47
Dementia	332 (0.9)	172 (0.8)	0.1
Rheumatologic disease	1543 (4.2)	851 (4)	0.56
AIDS/HIV	293 (0.8)	86 (0.4)	<0.0001
Urologic disease	2731 (7.4)	1573 (7.3)	0.63
CKD stages, *n* (%)			
0 + 1	30 260 (82.1)	17 731 (82.3)	0.015
2	3654 (9.9)	2198 (10.2)	–
3	2171 (5.9)	1142 (5.3)	–
4	767 (2.1)	474 (2.2)	–
Clinical variables during the hospital admission, *n* (%)			
Urgent admission	24 441 (66.3)	14 422 (66.9)	0.13
Anaemia	5417 (14.7)	3189 (14.8)	0.74
Acute respiratory failure	1827 (5)	1120 (0.5)	0.19
SIRS	658 (1.8)	383 (1.8)	0.97
Circulatory shock	650 (1.8)	370 (1.72)	0.68
Major surgery	12 127 (32.9)	6753 (31.3)	<0.0001
Exposure to contrast media	3353 (9.1)	2068 (9.6)	0.6
Exposure to nephrotoxic drugs	19 145 (52)	11 144 (51.7)	0.59

Table 5. Hosmer–Lemeshow's goodness-of-fit of the logistic predictive model in the validation group

	AKI = 0		AKI = 1		Total
Deciles of risk	Observed	Expected	Observed	Expected	
<0.0009026	2154	2153.6	1	1.4	2155
0.0009027–0.0018699	2151	2149.9	2	3.1	2153
0.0018700–0.0032362	2150	2149.5	5	5.4	2155
0.0032363–0.0054175	2143	2145.2	11	8.7	2154
0.0054176–0.0085382	2144	2140.2	10	13.8	2154
0.0085383–0.0127563	2134	2131.9	20	22.1	2154
0.0127564–0.0214063	2121	2118.3	33	35.6	2154
0.0214064–0.0391575	2093	2092.6	61	61.3	2154
0.0391575–0.0874214	2034	2035.0	120	118.9	2154
>0.0874214	1612	1623.3	546	533.6	2158

$\chi^2 = 4.2$. P = 0.836.

nephrotoxic agents can occur at different times after hospital admission, in order to relate the exposure to them with the development of AKI it was necessary to define a maximum period of time between exposure and detection of AKI. In our study, the duration of this period of time was defined by consensus of the research group using pathophysiological criteria. The definition of other periods of time, based on alternative criteria, would modify the prevalence of exposure to these risk factors and consequently the magnitude of the associations found between these variables and AKI.

In conclusion, our study provides an externally validated model based on demographic data, specific comorbidities, acute clinical conditions and procedures that can be used in clinical practice to obtain an accurate dynamic assessment of the individual risk of suffering AKI during the entire hospital stay period in patients admitted into non-critical hospitalization

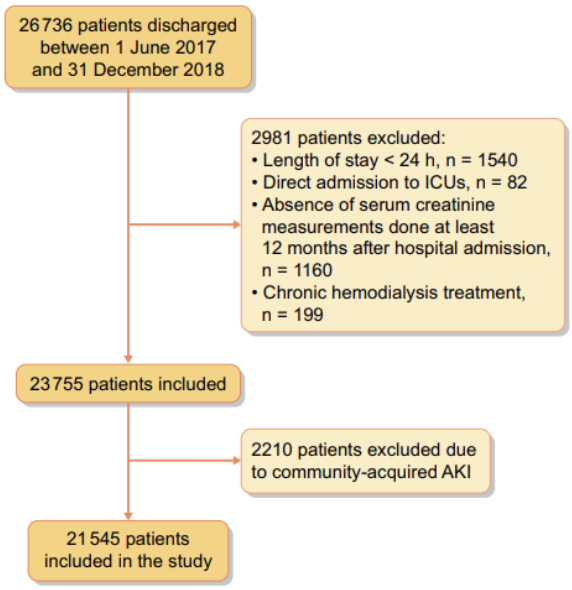

FIGURE 3: Flow chart for patient selection.

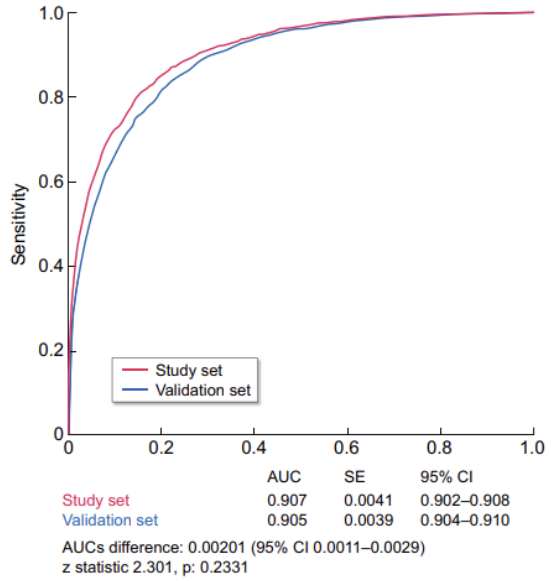

FIGURE 4: Comparison of AUCs obtained in the study set and in the validation set.

wards. This model is highly versatile and allows for performing repeated manual risk estimation, using the prediction algorithm, to provide an automatic risk measure updated in real time in those centres where it is possible to carry out a complete integration of the healthcare databases containing the necessary information.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

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CONFLICT OF INTEREST STATEMENT

None declared.

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10.1.3. **ARTICULO 3**

DEVELOPMENT AND VALIDATION OF A MODEL TO PREDICT SEVERE HOSPITAL-ACQUIRED ACUTE KIDNEY INJURY IN NON-CRITICALLY ILL PATIENTS

Jacqueline Del Carpio, Maria Paz Marco, Maria Luisa Martin, Natalia Ramos, Judith de la Torre, Joana Prat, Maria J. Torres, Bruno Montoro, Mercedes Ibarz, Silvia Pico, Gloria Falcon, Marina Marina Canales, Elisard Huertas, Iñaki Romero, Nacho Nieto, Ricard Gavaldà and Alfons Segarra.

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Development and Validation of a Model to Predict Severe Hospital-Acquired Acute Kidney Injury in Non-Critically Ill Patients

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Abstract: Background. The current models developed to predict hospital-acquired AKI (HA-AKI) in non-critically ill fail to identify the patients at risk of severe HA-AKI stage 3. Objective. To develop and externally validate a model to predict the individual probability of developing HA-AKI stage 3 through the integration of electronic health databases. Methods. Study set: 165,893 non-critically ill hospitalized patients. Using stepwise logistic regression analyses, including demography, chronic comorbidities, and exposure to risk factors prior to AKI detection, we developed a multivariate model to predict HA-AKI stage 3. This model was then externally validated in 43,569 non-critical patients admitted to the validation center. Results. The incidence of HA-AKI stage 3 in the study set was 0.6%. Among chronic comorbidities, the highest odds ratios were conferred by ischemic heart disease, ischemic cerebrovascular disease, chronic congestive heart failure, chronic obstructive pulmonary disease, chronic kidney disease and liver disease. Among acute complications, the highest odd ratios were associated with acute respiratory failure, major surgery and exposure to nephrotoxic drugs. The model showed an AUC of 0.906 (95% CI 0.904 to 0.908), a sensitivity of 89.1 (95% CI 87.0–91.0) and a specificity of 80.5 (95% CI 80.2–80.7) to predict HA-AKI stage 3, but tended to overestimate the risk at low-risk categories with an adequate goodness-of-fit for all risk categories (Chi^2: 16.4, *p*: 0.034). In the validation set, incidence of HA-AKI stage 3 was 0.62%. The model showed an AUC of 0.861 (95% CI 0.859–0.863), a sensitivity of 83.0 (95% CI 80.5–85.3) and a specificity of 76.5 (95% CI 76.2–76.8) to predict HA-AKI stage 3 with an adequate goodness of fit for all risk categories (Chi^2: 15.42, *p*: 0.052). Conclusions. Our study provides a model that can be used in clinical practice

to obtain an accurate dynamic assessment of the individual risk of HA-AKI stage 3 along the hospital stay period in non-critically ill patients.

Keywords: acute kidney injury; hospital-acquired; electronic health data records; risk score

1. Introduction

Acute kidney injury (AKI) is a global concern with a high incidence among hospitalized patients [1,2]. The incidence of hospital-acquired AKI (HA-AKI) ranges between 5 and 15% or 30–45 cases/1000 hospital admissions/year but shows an increasing trend as hospitalized patients are older and subjected to more interventional diagnostic and treatment techniques, and exposed to the effects of nephrotoxic drugs [3–5]. In addition, AKI has been associated with significant increases in health care resource utilization and costs in patients who are hospitalized, and with long-term morbidity and mortality after hospital discharge [6–11]. Numerous studies on AKI have been published in patients admitted to intensive care units, in which the causes, risk factors, mortality, and the influence of different treatment strategies have been identified [12–17]. The epidemiology of acute renal failure in patients admitted to conventional hospitalization wards is much less known [18]. Since a large part of the AKI episodes are due to potentially avoidable causes, knowing as accurately as possible the individual risk at any time of hospital stay could help decision making and implementation of preventive measures to reduce the incidence of hospital AKI [19,20]. The diagnostic approach to in-hospital AKI has undergone a significant change over time. The old detection models were based on the communication of the cases at the time of the diagnosis, by conventional analytical controls, and were subject to the influence of multiple sources of error that motivated avoidable delays in the identification of cases and in the adoption of treatment measures [21]. With the appearance of electronic laboratory data records, electronic alert systems were designed. These systems allow the detection of all cases at an early stage, but they do not allow to adopt preventive measures since they detect the problem once it has occurred [22]. The evolution of the management systems of the in-hospital AKI has gone in the direction of the development of predictive models of individual risk, whose purpose is to be able to anticipate the episode of AKI and to carry out prevention measures appropriate to the particular situation of each patient [23]. In recent years, several models have been developed and validated to allow the estimation of the risk of suffering AKI during hospitalization, but the results of early diagnosis and intensive interventions in terms of reduction of morbidity and mortality have been discordant and inconclusive [24]. The studies analyzing the epidemiology and risk factors associated with AKI in non-critically ill patients have two main limitations to identify accurately the risk factors associated with HA-AKI. First, most of them are based on demographic characteristics and comorbidities that have been registered retrospectively, from the discharge administrative codes, and therefore, are subject to a potential bias in the collection of coded information [25]. Secondly, they do not allow to know whether the exposure to risk factors preceded or not the detection of the AKI episode [26]. Thirdly, they do not allow to identify the categories of severe AKI. Wu L. et al. recently published an article where the risk factors that predict the presentation of severe AKI were defined, but they included both ICU and non-ICU patients and no external validation was performed [27]. Our group recently developed a model that overcame some of those limitations and provides an accurate dynamic assessment of the individual risk of suffering AKI along the whole hospital stay period in patients admitted into non-critical hospitalization wards [28]. However, although this model allows AKI to be accurately predicted, because of a lack of statistical power, it does not allow to detect the risk of developing AKI-3 severity stage, which is the one associated with greater morbidity, related to the severity of complications and, in many cases, to the need for replacement of kidney function. The aim of our study

was to develop and externally validate a model to predict the risk of HA-AKI stage 3 in hospital-acquired AKI in non-critically ill patients.

2. Methods

This study was performed at two different hospital centers. The first center developed the predictive model (study set) and the second center performed the external validation of the predictive model (validation set).

2.1. Study Set

The study set included patients admitted to the Vall d'Hebron hospital from January 2011 to December 2017. Vall d'Hebron is a tertiary hospital that provides assistance to a population of 500,000 habitants in Barcelona, Spain, and develops all kinds of medical and surgical procedures, including neurosurgery, cardiac surgery, endovascular catheter-guided procedures as well as lung, liver, kidney and bone marrow transplantation programs. We included all patients >18 years of age who were admitted to hospital along this period and did not meet any of the following exclusion criteria: 1.- admission for community-acquired AKI, 2.- hospital stay < 24 h, 3.- admission for elective heart surgery, 4.- direct admission from the emergency room to the intensive care units (ICUs), 5.- admission as a recipient of renal, lung, liver or bone marrow transplant, 6.- absence of serum creatinine measurements done at least 12 months after hospital admission, 7.- chronic hemodialysis treatment and 8.- denial to give a written consent to participate in the study. Community-acquired AKI was diagnosed whenever patients met the AKI criteria within the first 24 h of hospital admission. Patients initially admitted to conventional hospitalization wards who afterwards required admission into ICUs were only included if the AKI episode was detected while they were admitted in non-critically ill wards, prior to their admission into the ICUs.

2.2. Baseline Kidney Function

Our patient care system integrates the laboratory databases of the hospital and primary care registers, thus allowing historical data to be obtained for all patients who are hospitalized, provided that these data appear in those registers. Baseline kidney function was obtained from the electronic laboratory data records of primary health care and defined as the most recent glomerular filtration rate, estimated by the CKD-EPI equation, within the 12 months prior to hospital admission.

2.3. Definition of AKI Severe

AKI was defined and classified in severity stages according to the KDIGO (Kidney Disease Improving Global Outcomes) clinical practice guidelines [29]. Severe AKI HA-AKI was defined as an increase serum creatinine of at least $\times 3$ over the baseline or ≥ 4 mg/dL, occurring from the first 24 h to any time within hospital admission.

2.4. AKI Detection

A software integrated into the electronic laboratory database was used to perform repeated comparisons among all serum creatinine levels available for each patient during hospital stay and generated an identification code, assigning a 1 when the HA-AKI stage 3 criteria were met and a 0 when not. The date of HA-AKI stage 3 detection was also recorded. The number of the admission episode was used as a filter so that patients with more than one HA-AKI stage 3 episode during hospital stay were entered into the database only once, corresponding with the more severe episode.

2.5. Clinical Evaluation at Hospital Admission and during Hospital Stay

Patient comorbidities and diagnosis codes were obtained from the electronic medical data records and classified according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). During hospital stay, the data of six electronic

health databases, namely, vital signs, laboratory, pharmacy prescription, interventional radiology, interventional cardiology and surgery, were integrated together using the number of the admission episode, which is unique for each patient and common to all these databases. Overall, the information extracted from these databases included: hemoglobin levels, leukocyte count, oxygen saturation, body temperature, blood pressure, heart rate and respiratory rate as well as a complete list of nephrotoxic drugs (detailed in Table S1), and exposure to contrast dyes or major surgery. Every 24 h, updated information of all these data was dumped into the general study database which contained as well the comorbidity data and all available values of serum creatinine of each patient. From these data, a software generated classification codes for anemia, hypoxemic acute respiratory failure, Systemic Inflammatory Response Syndrome, shock, exposure to nephrotoxic drugs, contrast dyes or major surgery. Using these codes, the exposure to all these risk factors was classified as positive = 1, when the system detected at least one exposure during hospital stay, or negative = 0 when no exposure was detected. In all cases, the system recorded the data of exposure to each and one of these variables as well as the number of exposures to them. In patients with a code of AKI = 1, the exposure to these risk factors only was classified as =1 when it occurred within a maximum period of time prior to HA-AKI stage 3 detection (48 h for anemia, SIRS and shock, 72 h for contrast dyes and surgery and 7 days for nephrotoxic drugs). The procedures for the interrelation among the different electronic databases carried out to obtain the information on the clinical variables along hospital stay have been detailed in a previous report [28]. Unlike the hemoglobin level, arterial oxygen saturation, heart rate, respiratory rate or blood pressure level, that being numerical variables could be directly transferred to the general database, both circulatory shock and SIRS are complex variables that, to be automatically detected using a software-guided detection code, required the integration of data from various electronic records and the definition of classification algorithms. In both cases, before using them in statistical analyses, we analyzed the accuracy of the automatic detection systems in a sample of 3426 patients, as previously detailed [28].

2.6. Validation Set

The predictive model obtained at study set was externally validated in patients admitted at Arnau de Vilanova Hospital of Lleida between June 2017 and December 2019. Arnau de Vilanova hospital is a high-complexity teaching center and provides assistance to 490,000 habitants. This center develops similar activities as the study set with the exceptions of transplant programs and cardiac surgery. The selection of patients and the study procedures were done according to the same criteria stated for the study set. The external validation study was performed by an independent research team that did not participate in the development of the predictive model.

2.7. Statistics

The incidence and prevalence calculations were referred the total number of admissions. For patients who developed more than one AKI episode along hospital admission, only the most severe episode was included in the study. Patients were considered to be at risk each time they were admitted to the hospital and, therefore, patients who during the study period were admitted two or more times were included in the calculations on each admission, except when readmission occurred within the 30 days after hospital discharge. Results are given as the mean ± SD or median and [P_{25}–P_{75}]. Differences in risk factors between groups were calculated by the Student's unpaired T or ANOVA tests. Qualitative variables were compared using the Chi-squared test. Concordance analyses between qualitative variables was done by the Kappa coefficient. A p value of less than 0.05 was considered statistically significant. To determine which variables were independently associated with AKI, we carried out a univariate analysis comparing patients with and without AKI. All the variables with p values under 0.1 in the univariate analysis were entered into stepwise multiple logistic regression analysis with a forward selection method

based on changes in the likelihood ratio (LR). Odds ratios (OR) were calculated from the regression coefficients as an approximation of the relative risk. The predictive value of the logistic model was evaluated using the C statistic, Cox & Snell R^2 and Nagelgerkes' R^2. Model over-fitting was prevented using the Akaike Information Criterion (AIC) [30,31]. The Hosmer–Lemeshow's test [32] was used as well to calculate the discrimination power and goodness of fit of the logistic model. Results are presented according to the TRIPOD guidelines for risk-prediction models [33,34]. Once obtained in the study set, the predictive logistic model was blindly tested on the external validation set by an independent group of researchers who did not participate in the development of the predictive model. Statistical analyses were performed with the Statistical Package for the Social Sciences for Windows 20.0.

3. Results

3.1. Study Set

Along the study period, there were 192,435 hospital discharges. Figure 1 shows the chart flow for patient selection. The final study group comprised 165,893 patients. Out of this cohort, 995 (0.60 %) developed HA-AKI stage 3.

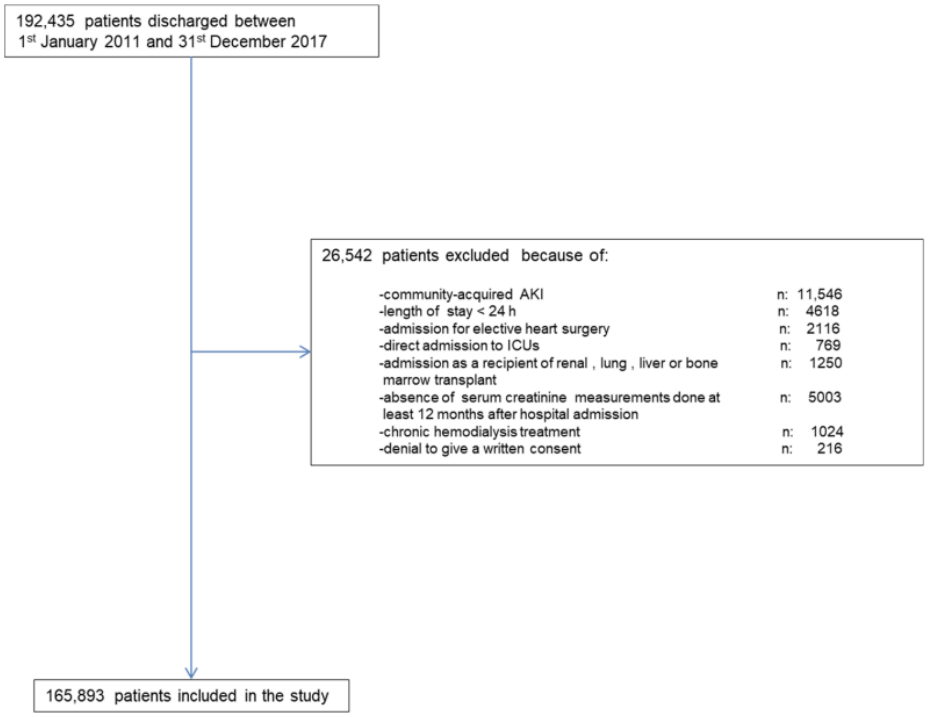


Figure 1. Flow-chart for patient's selection.

Table 1 summarizes the demographic characteristics, comorbidities, clinical events and procedures along hospital stay in the study group, classified according to the presence of HA-AKI stage 3. HA-AKI stage 3 patients were older and more frequently male than non-AKI patients. Comorbidities including diabetes, hypertension, ischemic heart disease, ischemic peripheral vascular disease, chronic liver disease, chronic congestive heart failure, chronic obstructive pulmonary disease, malignancy, urologic disease and chronic kidney disease stages were also more frequent in AKI patients. The AKI risk increased linearly as glomerular filtration decreased. Patients with HA-AKI stage 3 showed also significantly

higher rates of urgent admission, anaemia, acute respiratory failure, SIRS, shock, major surgery, and exposure to contrast dyes and to nephrotoxic drugs.

Table 1. Demographic characteristics, chronic comorbidities, clinical events and procedures along hospital admission, and univariate analysis of variables associated with HA-AKI stage 3 in the study group.

Variables	Total	Stage 3 AKI	Non-Stage 3 AKI	Sig
n	165,893	995 (0.6)	164,898 (99.4)	
Gender: Men. (*n*) %	74,962 (45.2)	517 (52.0)	74,445 (45.1)	<0.001
Age (years). mean (SD)	54.9 (20.6)	67.1 (21)	53.9 (19.9)	<0.001
Chronic comorbidities				
Diabetes. (*n*) %	30,357 (18.3)	450 (45.2)	29,907 (18.1)	<0.001
Hypertension. (*n*) %	65,554 (39.5)	707 (71.1)	64,847 (39.3)	<0.001
Ischemic Heart Disease. (*n*) %	12,428 (7.5)	169 (17.1)	12,259 (7.4)	<0.001
Ischemic Cerebrovascular disease. (*n*) %	11,446 (6.9)	78 (7.8)	11,368 (6.9)	0.136
Ischemic Peripheral vascular disease. (n) %	8706 (5.2)	93 (9.3)	8613 (5.2)	<0.001
Chronic digestive disease. (*n*) %	9627 (5.8)	51 (5.1)	9576 (5.8)	0.198
Chronic liver disease. (*n*) %	5667 (3.4)	105 (10.6)	5562 (3.4)	<0.001
Chronic congestive heart failure. (*n*) %	14,344 (8.6)	256 (25.7)	14,088 (8.5)	<0.001
Chronic obstructive pulmonary disease. (*n*) %	23,272 (14.0)	424 (42.6)	22,848 (13.9)	<0.001
Malignancy. (*n*) %	23,504 (14.2)	304 (30.6)	23,200 (14.1)	<0.001
Rheumatologic disease. (*n*) %	6828 (4.1)	41 (4.1)	6787 (4.1)	0.529
Urologic disease. (*n*) %	11,926 (7.2)	148 (14.9)	11,778 (7.1)	<0.001
Chronic Kidney disease stages				<0.001
0 + I	137,385 (82.8)	583 (58.6)	136,802 (83)	
II	16,252 (9.8)	109 (11.0)	16,143 (9.8)	
III	9265 (5.6)	175 (17.6)	9090 (5.5)	
IV	2991 (1.8)	128 (12.9)	2863 (1.7)	
Clinical variables along hospital admission				
Urgent admission. (*n*) %	108,577 (65.5)	947 (95.2)	107,630 (65.3)	<0.001
Anaemia. (*n*) %	23,291 (14.0)	379 (38.1)	22,912 (13.9)	<0.001
Acute respiratory failure. (*n*) %	7803 (4.7)	308 (31.0)	7495 (4.5)	<0.001
Acute Hearth failure (*n*) %	6204 (3.7)	241 (24.2)	5963 (3.6)	<0.001
SIRS. (*n*) %	2358 (1.4)	235 (23.6)	2123 (1.3)	<0.001
Circulatory shock. (*n*) %	2018 (1.2)	280 (28.1)	1738 (1.1)	<0.001
Major surgery. (*n*) %	61,583 (37.1)	408 (41.0)	61,675 (37.4)	<0.001
Exposure to contrast media. (*n*) %	14,698 (8.9)	280 (28.1)	14,418 (8.7)	<0.001
Exposure to nephrotoxic drugs. (*n*) %	85,863 (51.8)	677 (68.0)	85,186 (51.7)	<0.001

The results of the logistic model to predict HA-AKI stage 3 are summarized in Table 2. The variables that had the strongest association with HA-AKI stage 3 were stage 3 of chronic kidney disease, diabetes mellitus and urological diseases, among chronic comorbidities, shock, acute respiratory failure, shock and urgent admission status, among acute complications, and major surgical procedures among the procedures performed.

Table 2. Variables independently associated with HA-AKI stage 3 in the logistic regression analysis.

Variable	B	S.E.	Wald	OR	95% CI	*p*-Value
Age	0.024	0.003	91.2	1.03	1.02–1.03	0.000
Hypertension	0.539	0.084	41.1	1.71	1.45–2.02	0.000
Diabetes	1.184	0.079	223.5	3.27	2.79–3.81	0.000
Peripheral vascular disease	0.597	0.135	19.7	1.82	1.39–2.37	0.000
Anaemia	0.664	0.075	78.0	1.94	1.67–2.25	0.000
Chronic congestive hearth failure	0.405	0.085	22.5	1.50	1.27–1.77	0.000
Ischemic hearth disease	0.653	0.107	37.6	1.92	1.56–2.37	0.000
Chronic obstructive pulmonary disease	0.469	0.096	23.9	1.60	1.32–1.93	0.000
Chronic liver disease	1.013	0.133	58.1	2.75	2.12–3.57	0.000
Chronic urologic disease	1.309	0.118	123.9	3.70	2.94–4.66	0.000

Table 2. *Cont.*

Variable	B	S.E.	Wald	OR	95% CI	*p*-Value
CKD_stage			469.9			0.000
CKD_stage(1)	0.582	0.122	22.7	1.79	1.41–2.27	0.000
CKD_stage(2)	1.425	0.1	204.0	4.16	3.49–5.05	0.000
CKD_stage(3)	2.187	0.119	339.8	8.91	7.06–11.24	0.000
SIRS	0.698	0.128	29.6	2.01	1.56–2.59	0.000
Shock	2.055	0.122	286.1	7.81	6.15–9.9	0.000
Acute Hearth Failure	0.801	0.096	69.9	2.23	1.84–2.69	0.000
Major_surgery	1.213	0.083	211.8	3.36	2.85–3.96	0.000
Acute respiratory failure	1.283	0.106	147.4	3.61	2.93–4.44	0.000
Nephrotoxic drugs	0.345	0.078	19.8	1.41	1.21–1.64	0.000
Exposure to contrast dyes	0.931	0.085	119.5	2,53	2.15–2.99	0.000
Urgent_admission	1.899	0.161	139.0	6.68	4.87–9.15	0.000
Constant	−11.211	0.237	2239.0	0.00		

The model showed an AUC of 0.906 (95% CI 0.904 to 0.908), with a sensitivity of 89.1 (95% CI 87.0–91.0) and a specificity of 80.5 (95% CI 80.2–80.7) to predict HA-AKI stage 3 and showed an adequate calibration for high- and medium-risk categories but over-estimated the risk for low-risk categories. Table 3 (Chi^2: 16.4, *p*: 0.034).

Table 3. Hosmer and Lemeshow's goodness of fit of the logistic predictive model in the study group.

Risk Deciles	Acute Kidney Injury = 0		Acute Kidney INJURY = 1		Total
	Observed	Expected	Observed	Expected	
<0.0001702	16,514	16,512.6	0	1.4	16,514
0.0001702–0.0003350	16,587	16,586.0	2	3.0	16,589
0.0003351–0.0004798	16,584	16,580.2	1	4.8	16,585
0.0004799–0.0007357	16,577	16,581.0	12	8.0	16,589
0.0007358–0.0011664	16,549	16,558.2	22	12.8	16,571
0.0011665–0.0016138	16,556	16,554.0	19	21.0	16,575
0.0016139–0.0027321	16,557	16,554.9	32	34.1	16,589
0.0027322–0.0044384	16,527	16,526.5	56	56.5	16,583
0.0044385–0.0098603	16,463	16,478.8	126	110.2	16,589
>0.0098603	15,984	15,965.7	725	743.3	16,709

Chi-square: 16.4, *p*: 0.034.

The results of the stepwise forward procedures done to develop the final logistic model, including changes in the likelihood ratios, Cox and Snell R^2, Nagelkerke R^2 and AIC are summarized in the previous report [28].

3.2. Validation SET

Along the study period there were 49,971 hospital discharges. Figure 2 shows the chart flow for patient selection. The final validation group comprised 43,569 patients.

The demographic characteristics, comorbidities and clinical parameters of the study and external validation cohorts are summarized in Table 4.

Figure 2. Shows the chart flow for patient selection.

Table 4. Comparison of demographic characteristics, comorbidities and clinical variables between the study set and the external validation set.

Variables	Study Set	Validation Set	*p*-Value
n	165,893	43,569	
HA-AKI Stage 3	995 (0.60)	271 (0.62)	0.594
Gender: Men. (*n*) %	74,962 (45.2)	19,606 (44.9)	0.105
Age (years). mean (SD)	54.9 (20.6)	55.7 (22.1)	0.389
Chronic comorbidities			
Diabetes (*n*) %	30,357 (18.3)	7840 (17.9)	0.048
Hypertension (*n*) %	65,554 (39.5)	16,991 (38.9)	0.059
Ischemic Heart Disease (*n*) %	12,428 (7.5)	3033 (6.9)	<0.001
Ischemic Cerebrovascular disease (*n*) %	11,446 (6.9)	2614 (6.0)	<0.001
Ischemic Peripheral vascular disease (*n*) %	8706 (5.2)	2396 (5.5)	0.037
Chronic digestive disease (*n*) %	9627 (5.8)	2483 (5.7)	0.407
Chronic liver disease (*n*) %	5667 (3.4)	1307 (3.0)	<0.001
Chronic congestive heart failure (*n*) %	14,344 (8.6)	3267 (7.5)	<0.001
Chronic obstructive pulmonary disease (*n*) %	23,272 (14)	6535 (15.0)	<0.001
Malignancy (*n*) %	23,504 (14.2)	6317 (14.5)	0.081
Rheumatologic disease (*n*) %	6828 (4.1)	1743 (4.0)	0.285
Urologic disease (*n*) %	11,926 (7.2)	3135 (7.1)	0.971

Table 4. *Cont.*

Variables	Study Set	Validation Set	*p*-Value
Chronic Kidney Disease stages			0.2758
0 + I	137,385 (82.8)	36,162 (83.0)	
II	16,252 (9.8)	4182 (9.6)	
III	9265 (5.6)	2396 (5.5)	
IV	2991 (1.8)	829 (1.9)	
Clinical variables along hospital admission			
Urgent admission (*n*) %	108,577 (65.5)	28,319 (65.0)	0.077
Anaemia (*n*) %	23,291 (14.0)	6186 (14.2)	0.397
Acute respiratory failure (*n*) %	7803 (4.7)	2178 (5.0)	0.011
Acute Hearth failure (*n*) %	6204 (3.7)	1655 (3.8)	0.565
SIRS (*n*) %	2358 (1.4)	653 (1.5)	0.227
Circulatory shock (*n*) %	2018 (1.2)	566 (1.3)	0.167
Major surgery (*n*) %	61,583 (37.1)	13,942 (32.0)	<0.001
Exposure to contrast dyes (*n*) %	14,698 (8.9)	3.921 (9.0)	0.36
Exposure to nephrotoxic drugs (*n*) %	85,863 (51.8)	23,135 (53.1)	<0.001

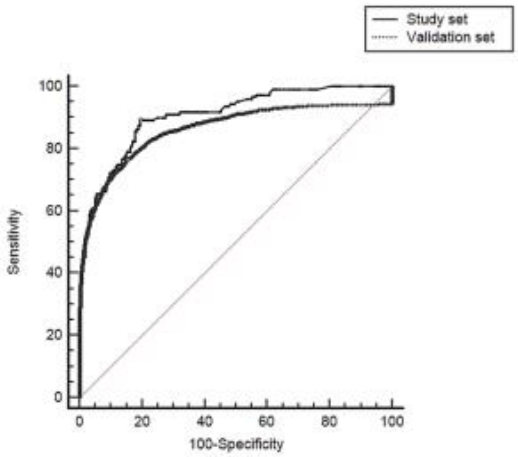
When compared with the study set, patients of the validation set showed significantly lower prevalence of ischemic heart disease, ischemic cerebrovascular disease, chronic congestive heart failure, liver disease and major surgery. There was as well a significant difference in the distribution of chronic kidney disease stages between the two centers. In the validation set, 270 (0.62%) developed HA-AKI stage 3, with no significant differences between the study set and validation set. When the predictive model was tested in the validation set, it showed an AUC of 0.861 (95% CI 0.859–0.863) with a sensitivity of 83.0 (95% CI 80.5–85.3) and a specificity of 76.5 (95% CI 76.2–76.8) to predict HA-AKI and an adequate goodness of fit for all risk categories (Chi^2: 15.42, *p*: 0.052). Table 5.

Table 5. Hosmer and Lemeshow's goodness of fit of the logistic predictive model in the validation group.

	Acute Kidney Injury = 0		Acute Kidney Injury = 1		Total
Risk Deciles	Observed	Expected	Observed	Expected	
<0.0001486	4342	4343.4	2	0.58	4344
0.0001486–0.0002375	4347	4347.7	2	1.30	4349
0.0002376–0.0003818	4374	4371.8	0	2.12	4374
0.0003819–0.0006162	4353	4355.7	6	3.23	4359
0.0006163–0.0009573	4351	4352.3	6	4.70	4357
0.0009574–0.0015601	4345	4351.2	9	6.74	4358
0.0015602–0.0025301	4347	4345.1	8	9.86	4355
0.0025302–0.0044511	4349	4341.6	8	15.3	4357
0.0044512–0.0101964	4327	4329.1	31	28.8	4358
>0.0101964	4159	4157.7	199	200.24	4358

Chi-square: 15.416, *p*: 0.052.

The AUC was significantly lower than that observed in the study. Difference between AUC 0.0449, SD 0.00404 (95% CI 0.036–0.052), z 11.107 and $p < 0.001$) (Figure 3).



	AUC	SE	95% CI
Study set	0.906	0.00499	0.904–0.908
Validation set	0.861	0.00814	0.859–0.863
AUCs difference	0.0449	0.00404	0.0369–0.0528
z stadistic	11.107, $p < 0.0001$		

Figure 3. Comparison between AUCs obtained in the study set and in the validation set.

4. Discussion

In our study, we integrated the information of six electronic health databases, commonly used in the clinical practice, and we were able to develop the first predictive dynamic model that allows to estimate accurately, in non-critically ill patients, the individual likelihood of suffering HA-AKI stage 3 at any time during hospital stay. The final logistic model included the demographic data and the patient's chronic comorbidities as well as a set of risk factors related to the patients' clinical status and to the exposure to major surgery, contrast media or nephrotoxic drugs along hospital stay. In univariable analysis, those who developed HA-AKI stage 3 tended to be older and male. With respect to chronic comorbidities, diabetes, hypertension, ischemic heart disease, ischemic peripheral vascular disease, chronic liver disease, chronic congestive heart failure, chronic obstructive pulmonary disease, malignancy, urologic and chronic kidney disease were significantly more prevalent in patients who developed HA-AKI stage 3. All clinical variables evaluated, namely, anaemia, acute respiratory failure, acute heart failure, SIRS, circulatory shock, major surgery, and exposure to nephrotoxic drugs and to contrast media, were more prevalent in patients who developed HA-AKI stage 3. This model showed a high sensitivity and specificity to predict HA-AKI stage 3 and showed an adequate calibration for all, except for the lowest-risk categories for which it tended to over-estimate slightly the risk. This misclassification, however, affected only a few numbers of patients located at the lowest-risk categories. When compared with those previously published so far [35,36], the main novelty of our model is that it is the first one that predicts accurately the likelihood of suffering HA-AKI stage 3 along the whole hospital stay in non-critically ill patients rather than predicting the occurrence of AKI, regardless of its stage. Hence, it allows to estimate the individual likelihood of suffering severe AKI during hospitalization. The prospective monitoring of clinical data, through integration and cross-talk between different electronic databases, allowed us to analyze the dynamic exposure to risk factors related to the clinical status of patients along hospital stay, such as hypoxemia, hemoglobin level, blood pressure changes, contrast dyes or nephrotoxic drugs, prior to the detection of the HA-AKI stage 3 episode.

This integration allowed as well to perform an accurate and reliable transformation of single variables such as blood pressure, heart rate, arterial oxygen saturation, prescription of vasoactive drugs or blood leukocyte counts into more complex variables defining specific syndromes such as SIRS and circulatory shock. Electronic records also permitted us to record the exposure to the same variables and risk factors in patients who did not develop HA-AKI stage 3 during hospital admission. This approach made it possible to estimate the individual risk, based on the actual exposure to each and one of risk factors. Since our predictive model was developed from the values of risk factors assessed prior to HA-AKI stage 3 detection, it allows to perform a dynamic monitoring of risk and even to predict the changes in the individual risk that are expected to happen every time the value of the different predictive risk factors changes. In order to obtain a predictive model that could be exportable to hospitals with different case-mix, patients who were admitted for programs and/or procedures such as cardiac surgery, solid organ or bone marrow transplantation, that are not commonly available to all hospital centers, were deliberately excluded from the study set. When comparing the study and the validation sets, we still observed statistically significant differences in the prevalence of several chronic comorbidities, in spite of the fact that, in both cohorts, we used the same ICD-9 codes to classy them. These differences may be due to dissimilarities in the case mix between both hospitals, but may also be caused by biases associated with potential discrepancies in assigning administrative codes to clinical conditions [37]. There were also between-group differences in other variables involved in the calculation of the risk of HA-AKI stage 3, such as the total percentage of urgent or surgical admissions. The discrimination ability of the model in the validation cohort was slightly but significantly lower than that observed in the original cohort. These differences are expected to be found when a predictive model is externally validated, and may be partially attributable to some degree of overfitting of the derivation modeling [38,39]. The calibration of the model in the external validation cohort showed a similar trend to that observed in the derivation cohort. Overall, the differences in the performance of the model between the study set and the validation set were small, which supports the potential scalability of the predictive model to fewer complex centers.

Our model has some limitations that must be highlighted. First, the record of clinical variables such as blood pressure, heart rate, respiratory rate or oxygen saturation were automatically dumped into the study database; however, these values are not without potential error related to the variability in the manual introduction of these variables into their corresponding databases. Second, the model obtained in our study is not the only one that can be obtained with the combination of data obtained from electronic records. As exposure to each of the acute complications or nephrotoxic agents can occur at different times after hospital admission, in order to relate the exposure to them with the development of HA-AKI stage 3, it was necessary to define a maximum period of time between exposure and detection of HA-AKI stage 3. In our study, the duration of this period of time was defined by consensus of the research group, using pathophysiological criteria. The definition of other periods of time, based on alternative criteria, would modify the prevalence of exposure to these risk factors and, consequently, the magnitude of the associations found between these variables and HA-AKI stage 3.

In conclusion, our study provides the first model, based on demographic data, specific comorbidities, acute clinical conditions and procedures, that can be used in clinical practice to obtain an accurate dynamic assessment of the individual risk of suffering HA-AKI stage 3 along the whole hospital stay period in patients admitted into non-critical hospitalization wards. This model allows from performing a repeated manual risk estimation, using the prediction algorithm, to providing an automatic risk measure updated in real time, in those centers where it is possible to carry out a complete integration among the health databases containing the necessary information. We anticipate that our study sets the cornerstone to a change in the management of hospital acute renal failure, by using a dynamic model of integration of electronic records with the aim of awareness of the physician in charge

to these patients at high risk for AKI 3. It should be the aim to take special care to these patients at high risk to prevent acute renal failure and thus avoid fatal outcomes.

The anonymized database is available for reproduction as long as the requestor attaches a document endorsed by an ethical committee.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/jcm10173959/s1, Table S1: List of nephrotoxic drugs included.

Author Contributions: A.S.: Principal investigator. J.D.C.: correspondence author. A.S. and J.D.C. conceptualized and performed the tests and wrote the manuscript. The rest of authors supervised and reviewed the manuscript. All authors have read and agreed to the published version of the manuscript.

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Informed Consent Statement: Not applicable.

Data Availability Statement: The anonymized database is available for reproduction as long as the requestor attaches a document endorsed by an ethical committee.

Conflicts of Interest: The authors declare no conflict of interest.

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10.2 MATERIAL SUPLEMENTARIO ARTÍCULO 2

10.2.1 Datos suplementarios- Definición operativa y criterios de clasificación

1. Diabetes: patients were considered diabetic if this diagnosis was recorded in their medical cards, they were treated with oral hypoglycemic agents, insulin or both.
2. Hypertension: patients were classified as hypertensive if this diagnosis was recorded in the clinical cards of primary health care or they followed chronic treatment with at least one antihypertensive drug, documented in the clinical records of primary care system.
3. Ischemic heart disease (IHD): was defined as evidence of a history of previous admissions for demonstrated acute myocardial infarction or clinical evidence of previous angina episodes, accompanied by typical electrocardiographic abnormalities and/or compatible conventional stress, sonographic or stress scintigraphy tests, after reviewing records of previous hospital admissions and primary care.
4. Ischemic Cerebrovascular disease (ICD): was diagnosed when there was documented evidence of transient ischemic attacks, ischemic or hemorrhagic stroke, or diagnostic tests indicative of atheromatous disease of intra or extracranial arteries, treated or not by surgery or endovascular procedures.

5. Ischemic peripheral vascular disease (PVD): was diagnosed when there was evidence of previous amputations, surgical or non-invasive revascularization techniques, clinical intermittent claudication or a documented ankle brachial pathological index (<0.9), according to the criteria described by Hirsch. [1]
6. Chronic digestive disease: was diagnosed when documented evidence in the clinical cards of chronic non-malignant diseases with esophageal, gastric or intestinal involvement.
7. Chronic Liver disease was defined according to the Child – Pugh classification. [2]
8. Chronic congestive heart failure (CCHF): this diagnostic was obtained from primary care or hospital clinical cards.
9. Malnutrition (MN): was defined according to the NRS ~~2020~~ 2002 criteria. (reference cited in main body).
10. Chronic pulmonary disease (CPOD): Diagnosis was confirmed using the GOLD criteria, reviewing the electronic records of previous hospitalizations and primary care.[3]
11. Malignancy: documented evidence of active hematologic or solid organ neoplastic processes undergoing chemotherapy, radiotherapy, or palliative care.
12. Dementia: Patients were considered with dementia when this diagnosis was recorded in either hospital or primary care clinical cards.
13. Rheumatologic disease: documented evidence of any chronic rheumatological or connective tissue disease, including rheumatoid arthritis, systemic lupus

erythematous, systemic sclerosis, mixed connective tissue disease, overlap syndromes, vasculitis or seronegative spondyloarthropathies.

14. Acquired immunodeficiency syndrome (AIDS)/human immunodeficiency virus (HIV): when this diagnosis was recorded in either hospital or primary care clinical cards.
15. Urologic diseases: documented evidence in the clinical cards of any non-malignant chronic disease of urological tract including unilateral nephrectomy, obstructive uropathy, urolithiasis, ureteral or urethral stenosis, vesical reflux, or benign prostatic hypertrophy.
16. The CKD classification was based exclusively on glomerular filtration following the KDIGO guidelines without taking into account pathological albuminuria. Thus, the stages were: Stage 1 ≥ 90 ml/min/1.73 m2, Stage 2: 60 - 89 ml/min/1.73 m2, Stage 3: 30 -59 ml/min/1.73 m2, Stage 4: 15 – 29 ml/min/1.73 m2, Stage 5: < 15 ml/min/1.73 m2.
17. Anaemia: was defined according to the criteria described in WHO. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. Vitamin and Mineral Nutrition Information System. [5]
18. Acute respiratory failure (ARF) was defined according to Campbell's classical criteria. [6]
19. Acute Hearth failure (AHF) was defined as a new onset or rapid change in heart failure signs and symptoms resulting in a need for urgent therapy. [7,8]

20. Patients were considered to suffer from systemic inflammatory response syndrome (SIRS) if they presented at least one of the following: temperature> 38°C or <36°C; heart rate> 90 beats/min; respiratory rate>20 breaths/min; or leukocyte count> 12,000 or <4000 cells /mm^3. [9]
21. The diagnosis of circulatory shock was based on clinical criteria, requiring the evidence of a systolic blood pressure < 90 mm Hg with associated tachycardia >100 beats/min, clinical signs of tissue hypoperfusion and administration of vasoactive drugs, documented in the electronic record of vital signs and in the pharmacologic prescription records. [10]
22. Major surgery was defined as any surgical procedure involving total anesthesia and respiratory assistance and included lung, urologic and abdominal surgery.
23. Exposure to contrast dyes was obtained from the electronic database of radiology and interventional radiology. Exposure was recorded as a categorical variable, assigning a value of 1 when contrast dyes had been administered, regardless of whether one or more procedures were performed or 0 otherwise. The dose and type of contrast dye administered, were not recorded.
24. Exposure to nephrotoxic drugs: Our study restricted the term nephrotoxic drug exposure to drugs related with acute tubular toxicity. To classify medications as nephrotoxic, the medication had to be referred as associated with inducing acute tubular toxicity in the literature. Drugs whose potential for nephrotoxicity arose from a different mechanism or drugs causing idiosyncratic acute interstitial nephritis, were excluded. The exposure was defined as 1 if

medication was administered. Information on drug administration was obtained from the electronic records of hospital pharmacy. These records allow to identification the medications that have actually been administered as well as the data and time of administration. [11-13]

NOTE: the criteria for diabetes, hypertension, ischemic heart disease, ischemic cerebrovascular disease and chronic congestive heart failure were obtained from the information in the medical history and reference-guided criteria were not used.

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10.2.2 Datos suplementarios Tabla 1. Lista de fármacos nefrotóxicos

Non-steroidal anti-inflammatory drugs	Antibiotics	Antiviral agents	Antifungal agents	Immunosuppressors	Chemotherapy	Others
All	Vancomycin Aminoglycosides: amikacin, gentamicin, netilmicin Sulfadiazine	Nucleosidic inhibitors: acyclovir, adefovir, cidofovir, tenofovir, indinavir Foscarnet	Amphotericin B Caspofungin Voriconazole	Cyclosporin Tacrolimus Everolimus Temsirolimus Immunoglobulins containing sucrose	Cisplatin, Carboplatin Gemcitabine Ifosfamide Mitramicin Pemetrexed Linalidomide Venetoclax Pentostatine Imatininib, Dasatininb Methotrexate (high dose > 10 g/m2) VEGF inhibitors Ibrutinib	Mannitol Lithium Zoledronic acid

10.2.3 Datos suplementarios Table 2

1. Weighted Kapa concordance correlation coefficients between the electronic codes and the clinical diagnosis of shock or SIRS made by the two independent researchers.

Clinical diagnosis of shock Observer 1	Electronic code for shock		
	0	1	
0	3356	21	3377 (98.6%)
1	0	49	49 (1.4%)
	3356 (98.0%)	70 (2.0%)	3426

Weighted Kappa[a]	0.821
Standard error	0.038
95% CI	0.745 to 0.896

Clinical diagnosis of shock Observer 1	Electronic code for shock		
	0	1	
0	3356	20	3376 (98.5%)
1	0	50	50 (1.5%)
	3356 (98.0%)	70 (2.0%)	3426

Weighted Kappa[a]	0.830
Standard error	0.037
95% CI	0.757 to 0.903

Clinical diagnosis of SIRS Observer 1	Electronic code for SIRS		
	0	1	
0	3333	8	3341 (97.5%)
1	30	55	85 (2.5%)
	3363 (98.2%)	63 (1.8%)	3426

Weighted Kappa[a]	0.738
Standard error	0.041
95% CI	0.658 to 0.818

Clinical diagnosis of SIRS Observer 2	Electronic code for SIRS		
	0	1	
0	3346	8	3354 (97.9%)
1	17	55	72 (2.1%)
	3363 (98.2%)	63 (1.8%)	3426

Weighted Kappa[a]	0.811
Standard error	0.037
95% CI	0.739 to 0.884

2. Inter-rater agreement between the clinical diagnosis of shock or SIRS made by the two independent researchers

Clinical diagnosis of shock Observer 2	Clinical diagnosis of shock Observer 1		
	0	1	
0	3363	6	3369 (98.3%)
1	0	57	57 (1.7%)
	3363 (98.2%)	63 (1.8%)	3426

Weighted Kappa[a]	0.949
Standard error	0.021
95% CI	0.908 to 0.990

Clinical diagnosis of SIRS Observer 2	Clinical diagnosis of SIRS Observer 1		
	0	1	
0	3334	20	3354 (97.9%)
1	7	65	72 (2.1%)
	3341 (97.5%)	85 (2.5%)	3426

Weighted Kappa[a]	0.824
Standard error	0.033
95% CI	0.759 to 0.889

10.2.4 Datos suplementarios Tabla 3

Number of variables in the model	New variable added to the model	- 2LR	Cox & Snell R^2	Nagelkerke R^2	AIC
1	Shock	11,635.3	0.028	0.105	-11,633.3
2	Age	10,992.5	0.033	0.118	-10,990.5
3	Acute respiratory failure	9,724.5	0.066	0.234	-9,720.5
4	Malnutrition	9,279.4	0.077	0.273	-9,273.4
5	CKD stages	8,884.9	0.087	0.308	-8,876.9
6	Chronic obstructive pulmonary disease	8,709.9	0.091	0.323	-8,699.9
7	Hypertension	8,606.8	0.094	0.332	-8,594.8
8	Anemia	8,493.3	0.097	0.342	-8,479.3
9	Malignancy	8,415.5	0.099	0.349	-8,399.5
10	Diabetes	8,282.3	0.102	0.361	-8,264.3
11	Chronic congestive heart failure	8,195.8	0.104	0.368	-8,175.8
12	Urgent admission	8,078.1	0.107	0.378	-8,054.1
13	SIRS	8,046.2	0.108	0.381	-8,020.2
14	Nephrotoxics	8,014.7	0.109	0.384	-7,986.7
15	Gender	7,985.4	0.109	0.386	-7,955.4
16	Chronic liver disease	7,963.9	0.110	0.388	-7,931.9
17	Contrast media	7,948.9	0.110	0.389	-7,914.9
18	Cerebrovascular disease	7,938.2	0.110	0.390	-7,902.2
19	Ischaemic heart disease	7,929.6	0.110	0.397	-7,891.6
20	Peripheral vascular disease	7,922.4	0.111	0.399	-7,882.4
21	Chronic urologic disease	7,916.4	0.111	0.402	-7,874.4
22	Major surgery	7,911.0	0.111	0.419	-7,867.0