External validation of the Madrid Acute Kidney Injury Prediction Score (MAKIPS)

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ABSTRACT

Background. The Madrid Acute Kidney Injury Prediction Score (MAKIPS) is a recently described tool able to do an automatic calculation of the risk of hospital-acquired AKI (HA-AKI) from electronic clinical records and could easily be implemented in clinical practice but, to date, it has not been externally validated. The objective of our study was to perform an external validation of the MAKIPS score in a hospital with different characteristics and case-mix.

Methods. External validation cohort study of the MAKIPS score, performed on patients hospitalized at a single tertiary hospital between April 2018 and September 2019. Performance was assessed by discrimination using area under the receiver operating characteristic curves (AUCROC) and calibration plots.

Results. HA-AKI in the external validation cohort was 5.3%. When compared to the MAKIPS cohort, the validation cohort showed a higher prevalence of men, diabetes, hypertension, cardiovascular disease, cerebrovascular disease, anaemia, congestive heart failure, chronic pulmonary disease, connective tissue diseases and renal disease, whereas, the prevalences of peptic ulcer disease, liver disease, malignancy, metastatic solid tumours and AIDS were significantly lower. In the validation cohort, the MAKIPS score showed an AUC of 0.798 (95% CI 0.788 -0.809). Calibration plots showed that at probability rates below 0.19, the score tended to overestimate, and at probability rates between 0.22 and 0.67, rates the score tended to underestimate the risk of HA-AKI.

Conclusions. The MAKIPS score can be a useful tool, easily obtainable from electronic records, to predict 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 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 [1-3]. HA-AKI is associated with severe morbidity and increased mortality rates [4-6]. Since a large part of the HA-AKI episodes are due to potentially avoidable causes, knowing accurately the individual risk of each patient as soon as possible after hospital admission is crucial for the implementation of preventive measures aimed to reduce its incidence [7-9]. Different models based on demographic data and chronic comorbidities have been developed so far for this purpose [10-14]. One of the most recent predictive models published is the Madrid Acute Kidney Injury Prediction Score (MAKIPS) [15]. This model can be automatically calculated from electronic clinical records and could easily implemented in the clinical practice, but to date, has not externally validated. Independent external validation is essential before considering whether to use a clinical prediction model, in order to rule out potential overfitting or deficiencies in the statistical modelling in the developing cohort and to evaluate the transportability of the model in different case-mix populations [16, 17].

The objective of our study is to perform an external validation of the behavior of the Madrid Acute Kidney Injury Prediction Score (MAKIPS) in predicting HA-AKI in a hospital center with different characteristics and complexity level.

MATERIALS AND METHODS

This retrospective observational external validation cohort study of the MAKIPS score was performed on the adult (≤18 years) hospitalized patients of Hospital Arnau de Vilanova, Lleida, Spain, for the period of April 2018 to September 2019. Hospital Arnau de Vilanova hospital is a tertiary high-complexity hospital that provides assistance to a population of 430,217 habitants in Lleida, Spain and develops all kind of medical, surgical and
endovascular catheter-guided procedures, with the exception of cardiac surgery and lung, liver, kidney or bone marrow transplantation programs.

Patient comorbidities, diagnosis and procedures were obtained from the electronic medical data records and classified according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) with the same codes used to develop the MAKIPS score. Biochemical data from inpatient settings were obtained from the electronic laboratory databases. Patients were included if they were ≥ 18 years of age, stayed at least 24h at hospital and had at least two serum creatinine measurements during hospital stay. Patients who had AKI within the first 48 h of hospital admission were excluded as they were considered to suffer from 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 the hospital and primary care registers, thus allowing historical data to be obtained for all patients who are hospitalized, provided that these data have been previously recorded 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. For patients with no serum creatinine available within 12 months prior to hospitalization, the baseline was the lowest serum creatinine during hospitalization.

**Definition of AKI**

AKI was defined and classified in severity stages according to the KDIGO criteria [18]. Hospital-acquired AKI was defined as an increase in serum creatinine ≥ 0.3 mg/dL or >50% over the baseline occurring from the first 48 h to any time within hospital admission.
AKI detection

A software integrated into the hospital 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 AKI criteria were met and a 0 when not. It also assigned a level of AKI severity according to the maximum differences in serum creatinine detected. The number of the admission episode, that is unique for each patient, was used as a filter so that patients with more than one AKI episode during hospital stay were registered into the database only once, corresponding with the more severe episode of AKI.

The research team members responsible for data analysis had access only to the anonymized database and were blinded to any other data.

The study complied with the Declaration of Helsinki and Spanish law, and was approved by the ethics Committees of the two participating centers which considered that informed consent was no necessary.

Statistics

The incidence calculations were referred to the total number of admissions. For patients who developed more than one AKI episode along hospital stay, 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 [P25-P75]. Differences in risk factors between groups were calculated by the Student’s unpaired T test for quantitative variables or the Chi-squared test for categorical variables. A p value of less than 0.05 was considered statistically significant.

The individual risk to develop HA-AKI was estimated by the MAKIPS score [15], assigning a value of 0 to cardiac surgery. The discrimination of the MAKIPS score was evaluated using
the C statistic and the area under the ROC curve (AUROC). The calibration diagrams were used to calculate the goodness of fit of the MAKIPS score in the external validation cohort. Statistical analyses were performed with the Statistical Package for the Social Sciences for Windows 20.0 and R software version 3.6.3

RESULTS

1.- Clinical and biochemical characteristics of patients.

Along the study period there were 26,362 hospital discharges. Figure 1 shows the flow chart for patient selection. The final study group, comprised 21,787 patients. Out of this cohort, 1,155 (5.3%) developed AKI, with an incidence of 53 AKI episodes/1000 hospital admissions. Distribution by AKI stages were: n: 785 (68%) stage I, n: 219 (19%) stage II, and n: 151 (13%) stage III.

**FIGURE 1:** Flow chart for patient selection.

Table 1, summarizes the demographic, clinical and admission characteristics of the study group and those of the MAKIPS cohort of patients. When compared to the MAKIPS cohort, patients from our study group showed a higher percentage of men a 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 prevalences of peptic ulcer disease, liver disease, malignancy, metastatic solid tumours and AIDS were significantly lower. The percentages of surgical patients and urgent admissions were, both, significantly higher in our cohort of patients.

Table 1. Comorbidity and admission characteristics of the study and MAKIPS cohort

| Variables                        | EXTERNAL VALIDATION COHORT | MAKIPS COHORT | P-value   |
|----------------------------------|-----------------------------|---------------|-----------|
| n                                | 21 787                      | 47 466        | <0.0001   |
| Men, % (n)                       | 46 (9 932)                  | 43.5 (20 647) |           |
| Mean age (years), mean (SD)      | 60.1 (19.7)                 | 62.1 (20.1)   |           |
| Diabetes, % (n)                  | 13.2 (2 876)                | 12.2 (5 786)  | 0.0002    |
| Hypertension, % (n)              | 32 (6 972)                  | 30.3 (14 392) | <0.0001   |
| Cardiovascular disease, % (n)    | 8.1 (1 765)                 | 7.6 (3 596)   | 0.0167    |
| Cerebrovascular disease, % (n)   | 6.9 (1 486)                 | 6.2 (2 842)   | <0.0001   |
| Anaemia, % (n)                   | 12 (2 614)                  | 11 (5 205)    | 0.0035    |
| Myocardial infarction, % (n)     | 3.6 (654)                   | 2.8 (1 363)   | 0.0888    |
| Congestive heart failure, % (n)  | 7.5 (1 634)                 | 6.7 (3 222)   | 0.007     |
| Peripheral vascular disease, % (n)| 4.8 (851)                  | 3.9 (1 867)   | 0.8675    |
| Dementia, % (n)                  | 0.8 (172)                   | 0.6 (319)     | 0.0967    |
| Chronic pulmonary disease, % (n) | 14.4 (3 102)                | 13.4 (6 385)  | 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 (2 535)   | <0.0001   |
| Hemiplegia, % (n)                | 1.1 (240)                   | 1.0 (506)     | 0.6700    |
| Renal disease, % (n)             | 8 (1 743)                   | 6.0 (2 849)   | <0.0001   |
| Malignancy, % (n)                | 14.3 (3 115)                | 15.0 (7 142)  | 0.0103    |
| Metastatic solid tumour, % (n)   | 4.8 (871)                   | 6.5 (3 107)   | <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

|                         | nd: not done |
|-------------------------|--------------|
| Intensive care unit % (n)| 4.5 (980)    |
| Nephrology % (n)        | 1.5 (372)    |
| Cardiology % (n)        | 10.7 (2 340) |
| Cardiac surgery % (n)   | 0            |
| Vascular surgery % (n)  | 3.6 (792)    |
| Urology % (n)           | 8.8 (1 918)  |
| General surgery % (n)   | 22.8 (4 982) |
| Other % (n)             | 47.9 (10 449)|

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 more frequently male than 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 showed also
significantly higher rates of urgent and surgical admission. AKI patients had higher uric acid, urea, glucose potassium and leucocytes than non-AKI patients.

Table 2. Demographic and clinical characteristics of the external validation cohort, classified according to the presence or not of HA-AKI.

Quantitative variables are expressed as median and (IQR 25-75))

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

The MAKIPS prediction score showed an AUROC of 0.798 (95% CI 0.788-0.809), Figure 2.
Figure 2. Area under de ROC curve of the MAKIPS score to predict HA-AKI in the external validation cohort.

Calibration plots for the association between predicted probabilities and observed event rates showed that, with a 95% confidence interval, at probability rates below 0.21, the score tended to overestimate, and at probability rates comprised between 0.22 and 0.67, the score tended to underestimate the observed risk of HA-AKI, Figure 3.
Figure 3. Calibration plot of the MAKIPS score 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% confidence interval, at probability rates below 0.21, the score tended to overestimate, and at probability rates comprised between 0.22 and 0.67, the score tended to underestimate the observed risk of HA-AKI.

DISCUSSION

In this study, we have carried out the first external validation of the MAKIPS score in a hospital that lacks of cardiac surgery and shows differential characteristics both in the clinical profile and in the distribution of the source of the patients, in relation to the hospital in which the original model was developed.

The overall incidence of HA-AKI described in different studies varies depending on the definition criteria of CA-AKI and the percentage of patients who come from intensive care units, in which the incidence is around 50% [19-23]. 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 intensive care units was significantly higher in our cohort, the contribution of these patients to the total was small in both centers. Therefore, the incidence of HA-AKI, in both cases, was very similar to that described in the few studies that focus on patients admitted to non-critically ill patients [24]. When comparing our cohort of patients with the MAKIPS cohort, we observed statistically significant differences in the prevalence of most of the chronic comorbidities analyzed, in spite of the fact that, in both studies, the same ICD-9 codes were used to record them. These differences may be due to dissimilarities in the case-mix between both hospitals, but may also be caused to biases associated to potential discrepancies in assigning administrative codes to clinical conditions [25,26]. 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 activity performed in each center. Although not the only one, the most notable difference was the exposure to cardiac surgery since this procedure was not performed in the validation center. The external validation of a prediction model involves quantifying the model’s discrimination and calibration performance using an external source of data that were not used to develop the model [27]. The discrimination is the ability of the model to differentiate between patients with different outcomes and is usually measured by the area under the ROC curve (AUROC) and the C statistics. The calibration, analyzes the agreement between the predicted and the observed risks, and can visualized by plotting observed versus predicted risks across categories of predicted risk, using a calibration plot with a smoothed non-linear curve [28,29]. When a predictive model is externally validated, it is expected the discrimination power to be lower in the external validation cohort due to an overfitting from derivation modeling [30]. The data obtained in our study indicate that, despite the aforementioned differences between both groups of patients, the discrimination of the MAKIPS score in the validation cohort of patients was comparable to that described in the original cohort and was not affected by the differences in the prevalence

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of the variables involved in risk calculation. Moreover, the absence of a significant decrease of discrimination in the validation cohort, indicates that a correct adjustment was made in the original score to avoid overfitting. The calibration of the model in the external validation cohort, showed a similar trend to that observed in the derivation cohort. The MAKIPS score tended to overestimate slightly the risk of HA-AKI at category risks below 0.19, and to underestimate it at risk categories comprised between 0.22 and 0.67. In both studies, this behavior could be explained by the fact that the risk of developing HA-AKI, depends not only on the demographic data, chronic comorbidities and surgical procedures but also on risk factors related to the inflammatory environment, hemodynamic status, exposure to contrast media or nephrotoxic drugs during hospital stay, among others [31-33]. These last set of variables are acute precipitants which may act 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 MAKIPS, which do not include them as predictors. The inclusion of dynamic changes of potential acute precipitants into the 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 able to detect changes in the risk profile of patients throughout hospital stay.

Even considering all these limitations and waiting for more external validation data coming from a greater number of hospitals, including wider case-mix scenarios, the data from our external validation cohort indicate that the MAKIPS score can be a useful tool, easily obtainable from data of electronic records, to predict HA-AKI in hospitals with different complexity.

**CONFLICT OF INTEREST STATEMENT**

None declared.
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26,362 patients discharged

- 2346 patients excluded because of chronic hemodialysis or hospital stay < 24 hours

24,016 patients eligible

- 2229 patients excluded because of community-acquired AKI

21,787 patients included
87x251mm (300 x 300 DPI)
| Area    | Standard error | Asymptotic sig. | Asymptotic 95% CI Lower bound | Asymptotic 95% CI Upper bound |
|---------|----------------|-----------------|-------------------------------|-------------------------------|
| 0.798   | 0.009          | 0               | 0.788                         | 0.809                         |
Predicted probability

Observed probability
