External validation study of a laboratory-based perioperative prediction model for acute kidney injury after cardiac surgery.

Protocol version: October 2023

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1.General Information

1.1 Title: External Validation Study of a Laboratory-Based Perioperative Prediction Model for Acute Kidney Injury after Cardiac Surgery

1.2 Protocol version

3.0

1.3 Sponsor of the study

1.4 Coordinating researcher

1.5 Methodology of the study

1.6 Coordination and monitoring of the study

1.8 Scientific Committee

1.8 Clinical Research Ethics Committee

The Clinical Research Ethics Committee of the Principality of Asturias approved version 1.0: CEImPA Code 2023.111

1.9 Participating Centres

All anaesthesia services and intensive care units of all European hospitals with cardiac surgery services will be invited to participate, most of them belonging to the Spanish group of renal dysfunction in cardiac surgery (GEDRCC2).

2. Background and current status of the issue

Acute *Kidney Injury* (AKI) is a major complication of cardiac surgery and its most severe forms are associated with significant morbidity and mortality[1][2] .

Identification of patients at risk may facilitate early use of management protocoolos recommended by KDIGO (Kidney Disease: Improving Global Outcomes), such as haemodynamic and volume optimisation, monitoring of renal function and discontinuation or reduction of nephrotoxic drugs[3][4] . The rate associated with cardiac surgery varies according to its different historical definitions, from 0.3% to 29.7%[5][6] . Cases requiring renal replacement therapy (RRT) occur between 1 .2%-3.0% in the studied cardiac surgery cohorts and their presence is a n independent predictor of mortality.

Because AKI still lacks effective treatments in addition to support and elimination of the cause, early and specific diagnosis is an unmet but critical need f o r successful and personalised patient management. [8][9][10]

Creatinine, urea and urine output have been and are the main ways to diagnose and treat renal failure. Other types of biomarkers that seem to be related to risk of postoperative AKI are currently under study. Although more research is needed, they may eventually become predictive diagnostic tools. Several studies have indicated that the urinary level of NGAL[11][12] excreted intraoperatively and after surgery is effective in predicting AKI in both adult and paediatric populations. Similar results have been obtained with other urinary biomarkers, such as the cell cycle arrest biomarkers TIMP-2 and IGFBP7)[11] KIM-1, NAG, IL-18 and L-FAP[12] . The major limitation of these biomarkers is that they are not easily accessible in all hospitals and clinical settings. Recently Demirjian et al[13] developed a predictive model in which they observed that perioperative change in serum creatinine and postoperative blood urea nitrogen, serum sodium, potassium, bicarbonate and albumin from the first metabolic panel after cardiac surgery show good predictive value for moderate to severe AKI within 72 hours and 14 days after the surgical procedure.

3. Hypothesis

The score developed by Demirjian et al has a good predictive ability for moderate to severe AKI after cardiac surgery in the European population.

4. Objectives

4.1 Main

- Confirm the usefulness and externally validate the scale.

- Compare this scale with other models of AKI prediction after cardiac surgery: Thakar, Mehta, ISR, Callejas, Leicester, CRATE.

4.2 Secondary

- Identify new risk factors for Acute Kidney Injury (AKI)

- Understanding the incidence of AKI after cardiac surgery in Europe

- Validating a model for predicting discharge dialysis after cardiac surgery

- Investigate the performance of these models in specific surgeries: coronary surgery without cardiopulmonary bypass and heart transplantation.

- Assess the performance of other scales and compare them.

- Determine the prevalence and risk factors for Acute Kidney Disease (AKD) (renal injury beyond 7 days, up to 90 days).

- Determine the prevalence and risk factors for new Chronic Kidney Disease (CKD) (follow-up for 120 days or 4 months).

- Determine the prevalence and risk factors for CKD progression, defined by a one-stage progression in patients with pre-existing CKD. Follow-up for 120 days (4 months).

5. Methodology

5.1 Design: descriptive, observational, prospective, multicentre, prospective study.

5.2 Study population: patients undergoing cardiac surgery.

5.3 Ethical aspects: the study has been approved for assessment by the Ethical Committee for Research with Medicines of the Principality of Asturias.

5.4 Inclusion criteria: All patients over 18 years of age undergoing cardiac surgery.

5.5 Exclusion criteria

- Exitus in the first 48h postoperative period

- Patient undergoing renal replacement therapy or preoperative dialysis

- Minor" cardiac surgery (sternal dehiscence, MCP removal or implantation, pericardial window)

5.6 Study variables

Hospital

Age

Sex

Male

Female

Race

Asian

Black

Multiracial

White

Weight (kg)

Height(cm)

BMI

Comorbidities

Hypertension
Insulin-dependent diabetes
Non-insulin-dependent diabetes
Congestive heart failure
Coronary artery disease
Tripple Vessel coronary artery disease
Chronic obstructive pulmonary disease
Poor mobility (musculoskeletal, neurological)
Chronic kidney disease
Peripheral vascular disease
Atrial fibrillation
Liver disease

NYHA (New York Heart Association Functional Classification)

Left ventricular ejection fraction (LVEF) %
Pulmonary systolic pressure (mmHg)

Unstable angina

Recent miocardial infarction (90 days)

Smoker YES/NO/Ex-smoker

Receives iSGLT2 (dapagliflozin, canaglifozin, empagliflozin...)

Receives GLP1 agonists (liraglutide, semaglutide, dulaglutide...)

Receives calcium antagonists (verapamil, nifedipine, amlodipine...)

Preoperative values

Serum creatinine (mg/dL)

FGe by Cockroft-Gault mL/min/1.73 m^2

FGe by EPI CKD ml/min

eGFR by MDRD ml/min/

Serum Albumin (mg/dL)

Serum Urea (mg/dL) or Serum BUN (mg/dL)

Serum sodium (mmol/L)

Serum potassium (mmol/L)

Serum bicarbonate (mmol/L)

Haemoglobin (mg/dL)

Platelets

Bilirubin (mg/dL)

Surgery

On-pump CABG

Off-pump CABG

Valvular

Aortic

Combined (coronary+valvular)

Other, multiple procedures (>2)

Heart transplant

Previous heart surgery

YES/NO

Euroscore II

Classification Surgery

Emergent

Urgent

Elective

Salvage (pre-operative cardiopulmonary resuscitation)

Catheter to surgery

Within 24 h

>24 h this admission

>24 h previous admission

No catheter prior to surgery

Pre-operative critical status (IABP, mechanical ventilation, VT, CRP, amines, renal failure)

YES/NO

Endocarditis at the time of surgery

YES/NO

Preoperative cardiogenic shock

YES/NO

Use of IABP prior to surgery

YES/NO

Intraoperative variables

CPB (cardiopulmonary bypass) time min

Aorta cross-clamp time (min)

Vasopressors YES/NO

Inotropes YES/NO

Red blood cell transfusion YES/NO

Number of red cell concentrates transfused

Platelet transfusion YES/NO

Fresh Frozen Plasma Transfusion YES/NO

Intraoperative diuresis (ml)

Nadir hemoglobin (lowest intraoperative in mg/dL)

Antibiotic (Gentamicin, Vancomycin, Cefazolin...)

Immediate postoperative values

Time from end of surgery to first analytical panel (hours)

Serum creatinine (mg/dL)

Serum albumin (mg/dL)

Urea (mg/dL) or BUN (mg/dL)

Serum sodium (mmol/L)

Serum potassium (mmol/L)

Serum chlorine (mmol/L)

Serum bicarbonate (mmol/L)

Lactate (mmol/L)

Urgent re-intervention first 24h

YES/NO

Length of hospital stay (days)

Discharge status

Discharge

Éxitus

Need for dialysis at discharge

YES/NO

Postoperative renal failure

Creatinine at ICU admission
Creatinine at 24h
Creatinine at 48h
Creatinine at 72h

Peak creatine 4th to 7th day
Peak creatine 7th to 14th day

Last creatinine at hospital discharge

Does the patient develops Stage 1 AKI in the first 14 days?

*Stage 1 AKI: (↑) Creatinine 1.5-1.9 times baseline or ≥0.3 mg/dL increase

If yes, which day?

Does the patient develops Stage 2 AKI in the first 14 days?

*Stage 2 AKI: (↑) Creatinine 2-2.9 times baseline

If yes, which day?

Does the patient develops severe AKI in the first 14 days?

* Stage 3 AKI : (↑) Creatinine ≥3 times baseline or ≥ 4 mg/dLincrease or dialysis.

If yes, which day?

Does the patient requires renal replacement therapy within the first 14 days?

If yes, which day?

5.7 **Sample size estimation**: Taking into account an incidence of moderate severe AKI in Spain of 9% according to previous studies and using the

Wilcoxon test, 1045 patients are needed to detect a difference of 0.1 in aROC with a power of 80% and an alpha error of 0.05. Assuming a 10% loss to follow-up, 1150 patients would be needed.

5.8 **Data collection**: a data collection notebook will be used to carry out the study. The researcher will include in it the sample of patients, without any data that would allow their identification.

5.9 **Analysis of results**: the results will be analysed using the statistical package IBM-SPSS 20.0 for Mac OS and RStudio version 1.1.463. The basic statistics of centralisation and dispersion will be used to describe the results. For comparison of means, t-tests for independent data or Mann-Whitney U-tests will be used in those cases where the conditions for their application are violated. Chi-square tests shall be used for comparison of proportions. Bonferroni correction shall be applied for multiple contrasts. To study the predictive ability, 2 measures will be studied, the discrimination ability by means of the area under the ROC curve and the calibration by means of the Hoshmer Lemeshow Test. The areas under the ROC curve will be compared using the Mann-Whitney U test.

5.10 Limitations of the study

Those due to the prospective study design and those arising from the impossibility of reviewing the patients included in the database.

5.11 Timeline

- Completion of the project protocol and application to the ethics committee: February-March 2023
- Completion of the database: from obtaining the ethics committee to completing the sample size:

6-12 months

- Statistical analysis: 2 months
- Project drafting: 6-12 months

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6. Ethical aspects

This study will follow the ethical principles set out in the Declaration of Helsinki, the Council of Europe Convention on Human Rights and Biomedicine and the Unesco Universal Declaration on the Human Genome and Human Rights. In addition, it will comply with the requirements of Spanish legislation in relation to biomedical research, personal data protection and bioethics. To ensure its approval, it will be submitted to the Research Ethics Committee (EC) and only patients who have signed an informed consent form will be included. Confidentiality and data security will be maintained in the following areas

The research manager will be responsible for maintaining the records at each site and determining the publication policy.

7. Dissemination of research results and substudies

The Scientific Committee will appoint an Editorial Committee to prepare the scientific report(s) of this research, which will be disseminated in due course. A number of secondary analyses are expected to be carried out, the conduct of which will be prioritised by the investigators and they will be encouraged to carry them out. Participation in these analyses will be based on the contribution to the study in their respective fields. The Steering Committee, before granting any application, will consider both the scientific validity and the possible impact on the anonymity of the participating centres. If required, the terms of collaboration will be established in advance by written agreement. The approval of the final version of all manuscripts, prior to submission, rests with the Scientific Committee. In case of disagreement within the Steering Committee, the Head of Research will make the final decision.

8. Data management and ownership

The study sponsor will act as the data custodian. In accordance with the principles of data preservation and data sharing, the Steering Committee, following publication of the overall database, will consider all reasonable requests for secondary analyses. The quality and validity of any proposed analysis shall be the main criteria to be taken into account when deciding on such requests. Only summary data will be publicly disclosed and it will be ensured that all data at international, national, institutional and patient level will be strictly anonymised. Patient data provided by participating hospitals are the sole property of their respective institutions. Once each local coordinator has confirmed the completeness and accuracy of the data provided by their hospital, the data will be transferred to a general database. The complete dataset of the participants will be coded for patients, hospitals and communities, and will be made freely available to the public for two years from the publication of the main scientific report. Prior

to this deadline, the Scientific Committee will not be obliged to release the data to any collaborator or third party if it considers that this does not align with the broader objectives of the project. All identifiable data collected, processed and stored for project purposes will be kept confidential at all times and will comply with Good Clinical Practice for Research (GCP) guidelines and the General Data Protection Regulation (GDPR) EU Regulation 2016/679.

9. Privacy and use of clinical information

The processing, communication and transfer of data will be carried out in a c c o r d a n c e with the provisions of Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of individuals with regard to data processing. and the free movement of data, and the Ley Org nica 3/2018, de 5 de diciembre, de Protecci n de Datos Personales y garant a de los derechos digitales.

10. Legal and organisational aspects.

10.1 Trial funding The study is not currently funded.

10.2 Compensation Neither trial sites, investigators nor patients w i l l receive financial compensation.

11. Bibliography

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