# CLINICAL STUDY PROTOCOL

**Official Title**

## Furosemide Stress Test and Serum Biomarkers as Predictive Markers for Progression of Acute Kidney Injury in Patients with Hypoalbuminemia

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## Theoretical Framework

Acute kidney injury (AKI) is a potentially fatal disease in both the short and long term, with an increasingly higher incidence in hospitalized patients in both developed and developing countries. It is also a frequent complication in patients in the intensive care unit (ICU), presenting multiple etiologies and risk factors, causing adverse clinical outcomes, high costs, and may culminate in the development of chronic kidney disease (CKD) or patient death.

The definition of acute kidney injury has evolved from the "Risk, Injury, Failure, Loss, End-stage" (RIFLE) criteria and the AKI Network (AKIN) classification to the Kidney Disease: Improving Global Outcomes (KDIGO) classification [1,2,3].

According to KDIGO, acute kidney injury is defined by the presence of any of the following: an increase in serum creatinine by 0.3 mg/dL or more within 48 hours, or an increase in serum creatinine by 1.5 times or more from baseline within the last 7 days, or a urine output of less than 0.5 mL/kg/h for at least 6 hours (4, 5).

KDIGO classifies acute kidney injury as: KDIGO 1, defined as an increase in serum creatinine 1.5–1.9 times from baseline or ≥ 0.3 mg/dL or urine output < 0.5 mL/kg/hr for 6–12 hrs; KDIGO 2, an increase in serum creatinine 2–2.9 times from baseline or urine output < 0.5 ml/kg/hr for ≥ 12 hrs; KDIGO 3, an increase in serum creatinine 3 times from baseline or ≥ 4 mg/dl or initiation of renal replacement therapy or urine output < 0.3 ml/kg/hr for ≥ 24 hrs or anuria for ≥ 12 hrs (5).

AKI is a broad clinical syndrome encompassing diverse etiologies, including specific renal diseases (such as acute interstitial nephritis, acute glomerular and vasculitic renal diseases); non-specific conditions (for example, ischemia); as well as extrarenal pathology (e.g., prerenal azotemia and post-renal obstructive nephropathy) (6).

Due to the diverse causes and risk factors that generate acute kidney injury, it has been shown that the implementation of preventive strategies improves mortality in patients who develop it. For this reason, early diagnosis of acute kidney injury has become of great relevance in order to implement strategies that limit renal damage and therefore reduce disease progression and the need for renal replacement therapy (7,8).

One of the currently available tests to predict the progression of Acute Kidney Injury is the Furosemide Stress Test, as described by Chawla et al., which consists of the administration of Furosemide to assess renal function through urine output quantification (9). Furosemide, a loop diuretic, inhibits the sodium chloride cotransport system, causing inhibition of tubular sodium and chloride reabsorption in the proximal and distal tubules and the thick ascending limb of Henle, producing excessive excretion of water, sodium, chloride, magnesium, and calcium.

Patients undergoing the Furosemide Stress Test can be classified into two groups, "responders" and "non-responders," depending on the response to furosemide administration, measured by urine output. Patients are classified as responders when diuresis 2 hours after drug administration is greater than 200 ml, and as non-responders when diuresis is less than 200 ml at two hours after drug administration.

The cornerstone of AKI treatment is preventing additional damage and new nephrotoxic insults. Hypovolemia must be corrected and hemodynamic resuscitation performed. Renal replacement therapy is used in approximately 10–15% of critically ill patients with acute kidney injury, and in more than 75% it is initiated with this modality. Despite official guidelines, there is considerable variation in the correct timing for renal replacement therapy initiation, and there are also few high-quality indicators based on the prescription, delivery, and monitoring of renal replacement therapy quality of care. (10)

One of the most common abnormalities found in ICU patients is hypoalbuminemia, which is associated with a state of inflammation in the body and is defined as a serum albumin below 3.5–4.0 g/dL or less than or equal to 3.5 mmol/L (11, 12). A pro-inflammatory state increases capillary permeability and causes leakage of serum albumin, leading to expansion of the interstitial space and an increase in the volume of distribution of albumin. Increased vascular permeability is caused by trauma, critical and chronic illnesses, multiple/isolated organ failure, and cancer (11).

Hypoalbuminemia has been established as a risk factor for increased morbidity, mortality, and risk of developing acute kidney injury. According to the study *"Causal relationship between hypoalbuminemia and acute kidney injury"*, through observational studies in surgical and ICU patients, it was concluded that hypoalbuminemia is a significant predictor of AKI [combined odds ratio (OR) = 2.34, 95% CI: 1.74–3.14] and of death from AKI (combined OR = 2.47, 95% CI: 1.51–4.05) (12).

## Background

Several studies demonstrate the high incidence of AKI in Intensive Care Units. One such study is the AKI-EPI study, which showed that the incidence of acute kidney injury in ICU patients was 62.5%, with the most frequent comorbidities being cancer, systemic arterial hypertension, cardiac insufficiency, cirrhosis, Acquired Immunodeficiency Syndrome (AIDS), chronic obstructive pulmonary disease (COPD), or diabetes mellitus. The study demonstrated that the severity of acute kidney injury conferred a higher risk of mortality: KDIGO stage 1: OR 2.19 (1.44–3.35) [95% CI], KDIGO stage 2: OR 3.88 (2.42–6.21) [95% CI], and KDIGO stage 3: OR 7.18 (5.13–10.04) [95% CI]. 13.5% of patients required renal replacement therapy, with slow continuous renal replacement therapy representing the largest proportion at 75.2%, intermittent hemodialysis 24.1%, and peritoneal dialysis 0.7% (13).

In another more recent study called "Epidemiology of acute kidney injury in intensive care units in Beijing: the multicenter BAKIT study", the incidence of acute kidney injury in patients in intensive care was similar at 51%. The main etiologies were hypovolemia in 25.4%, followed by sepsis with 22%, and cardiac insufficiency with 20.5%. Regarding mortality, the severity of acute kidney injury was associated with higher mortality, consistent with the AKI-EPI study.

The requirement for renal replacement therapy in this study was lower, at 9%, compared to 13% in the AKI-EPI study. Finally, continuous renal replacement therapy was the most chosen modality at 97.9% (14).

These studies clearly demonstrate the high proportion of patients in the ICU who are admitted with a diagnosis of AKI, highlighting the importance of this condition due to the high mortality and morbidity it represents.

## Justification

Over the last 20 years, significant advances have been made in the identification of molecular biomarkers for the detection and evaluation of AKI. Among the biomarkers evaluated are Interleukin-18 (IL-18), Liver-type Fatty Acid Binding Protein (L-FABP), Kidney Injury Molecule-1 (KIM-1), Tissue Inhibitor of Metalloproteinase 2 (TIMP-2), and Insulin-like Growth Factor Binding Protein 7 (IGFBP7), among others. In September 2014, the United States Food and Drug Administration (FDA) approved the "Nephrocheck", which became the first authorized biomarker for assessing the risk of moderate to severe AKI in hospitalized patients in intensive care. "Nephrocheck" combines Tissue Metalloproteinase Inhibitor E2 in Urinary Tissue and IGFBP7, known as [TIMP-2] × [IGFBP7] (15,16).

Despite advances in biomarkers such as "Nephrocheck", the search for more sensitive and specific diagnostic tools continues. Neutrophil Gelatinase-Associated Lipocalin (NGAL) has emerged as a promising biomarker, demonstrating a sensitivity of 81% and a specificity of 91.3% in identifying patients at risk of AKI (17). This biomarker accumulates in plasma in response to a decrease in the glomerular filtration rate (GFR) during AKI, which allows its blood levels to rise within the first hours to days after renal injury, which is crucial for timely intervention and effective management.

Plasma NGAL measurement has been shown to be a better predictor of AKI progression compared to urinary NGAL. In one analysis, a plasma NGAL level greater than 323 ng/ml was associated with a more than seven-fold increased risk of AKI progression, while urinary NGAL levels did not show significant benefits after adjusting for clinical variables. Therefore, the inclusion of urinary NGAL biomarker detection in this study will not only allow evaluation of its efficacy and precision, but will also help validate its utility in clinical practice (18).

A limitation for the use of such markers in our setting is cost; however, in 2013 Chawla et al. described the "Furosemide Stress Test" (FST) to predict the progression of AKI severity, from AKIN stages I and II to AKIN III, concluding that this test is effective as a predictor for patients who would develop more severe and progressive AKI. Their research demonstrated that subjects with progressive AKI had significantly lower urine output after the FST in each of the first 6 hours ($p < 0.001$), and deduced that the ideal cut-off point for predicting AKI progression is 2 hours after drug administration, with progressors being those who produce a urine volume below 200 ml (sensitivity 87.1% and specificity 84.1%) (19).

However, according to findings from that study, it was noted that few studies took serum albumin into account. Only two studies reported serum albumin levels (mean serum albumin of Matsuura 2.8 g/dl and mean serum albumin of Sakhuja 2.9 g/dl) (20,21,22).

We therefore consider that hypoalbuminemia could be an important factor in the diuretic response after furosemide administration, given that 95% of furosemide binds to plasma proteins (primarily albumin) (23), causing resistance to this drug and therefore a decrease in its effectiveness, with a possible consequent alteration in the reliability of the Furosemide Stress Test.

For the above reasons, this study will seek to assess the effectiveness of the Furosemide Stress Test to predict AKI progression, mortality, and the need for renal replacement therapy in patients with hypoalbuminemia, as well as to utilize and determine the precision and efficacy of the "NGAL" diagnostic test as an equally predictive marker of AKI progression.

## Primary Objective:

- To determine the accuracy of the Furosemide Stress Test and NGAL as a predictor of Acute Kidney Injury progression to KDIGO III in patients with hypoalbuminemia and KDIGO I and II.

## Secondary Objectives:

- To determine the need for implementation of Renal Replacement Therapy.
- To evaluate mortality at 15 days from the diagnosis of Acute Kidney Injury.

## Alternative Hypothesis:

- In patients with Acute Kidney Injury at KDIGO stages 1 and 2 who present with hypoalbuminemia, the Furosemide Stress Test will not be useful in determining progression to KDIGO stage 3.

## Null Hypothesis:

- In patients with Acute Kidney Injury at KDIGO stages 1 and 2 who present with hypoalbuminemia, the Furosemide Stress Test will be useful in determining progression to KDIGO stage 3.

## Material and Methods:

Study type: Quasi-experimental clinical trial

Population:

Patients admitted to the Intensive Care Unit of the University Hospital "Dr. José Eleuterio González" with a diagnosis of Acute Kidney Injury at KDIGO stages 1 and 2 and who present serum albumin below 3 g/dL.

Period: June 2022 – June 2025

Inclusion criteria:

- Male and female patients older than 18 years.
- Patients with albumin below 3 g/dL.
- Patients with a diagnosis of AKI at KDIGO stages 1 and 2.
- Patients who have received adequate fluid resuscitation at the nephrologist's discretion.
- Patients with the presence of cellular casts in the urinary sediment, defined as a George Washington Urine Sediment Score greater than 2 or with Fractional Excretion of Sodium (FENa) greater than 1.
- Patients with a Foley catheter.
- Patients who consent to participate in the study through informed consent.

Exclusion criteria:

- Pregnant patients.
- Patients under 18 years of age.
- Patients with obstructive urinary pathology.
- Patients with evidence of active bleeding.
- Patients with allergy or sensitivity to loop diuretics.
- Patients with Acute Kidney Injury KDIGO 3.
- Patients with inadequate fluid resuscitation prior to the stress test.
- Patients with a Glomerular Filtration Rate below 30 ml/min.

Variable table:

| Variables | Types |
|---|---|
| **1. Age** | 1. Quantitative |
| **2. Sex** | 2. Qualitative |
| **3. Cause of Acute Kidney Injury** | 3. Qualitative |
| **4. Comorbidities** | 4. Qualitative |
| **5. Exposure to nephrotoxic drugs** | 5. Quantitative |
| **6. Diuresis** | 6. Quantitative |
| **7. Progression to KDIGO 3** | 7. Qualitative |
| **8. Death** | 8. Qualitative |
| **9. Need for Renal Replacement Therapy** | 9. Qualitative |
| **10. Responder or Non-Responder Patient** | 10. Qualitative |
| **11. NGAL** | 11. Quantitative |

Description of variables:

1. **Age:** Discrete quantitative variable indicating the number of years of life of the patient.
2. **Sex:** Dichotomous nominal quantitative variable that determines whether the patient is male or female.
3. **Cause of Acute Kidney Injury:** Polytomous nominal qualitative variable that indicates the etiology by which the patient developed Acute Kidney Injury, as follows: sepsis, hypovolemic shock, nephrotoxins, surgical pathology, and others.
4. **Comorbidities:** Polytomous nominal qualitative variable indicating the morbidities associated with the patient, classified as follows: arterial hypertension, Diabetes Mellitus, Chronic Kidney Disease, Cardiac Insufficiency, and others.
5. **Exposure to nephrotoxic drugs:** Discrete quantitative variable referring to the number of medications with nephrotoxic potential to which the patient was exposed.
6. **Diuresis:** Discrete quantitative variable that determines the amount of urine produced by the patient after furosemide administration, quantified from hours 1 to 6 after drug administration.
7. **Progression to KDIGO 3:** Dichotomous qualitative variable between "progressor" and "non-progressor" referring to those patients who transition from an AKI KDIGO stage 1 or 2 to stage 3, meeting their respective criteria.
8. **Death:** Dichotomous nominal qualitative variable between "yes" and "no" indicating whether the patient lost their life within the 15 days following the furosemide stress test.
9. **Need for Renal Replacement Therapy:** Dichotomous nominal qualitative variable between "yes" and "no" indicating whether the patient required a renal replacement procedure as treatment.
10. **Responder or Non-Responder Patient:** Dichotomous nominal qualitative variable between "responder" and "non-responder" patient, indicating the response to the furosemide stress test, classified as "responder" when 2 hours after furosemide administration the patient presented a diuresis equal to or greater than 200 ml, and as "non-responder" when they presented a diuresis below the indicated amount.
11. **NGAL:** Continuous quantitative variable referring to the result provided by the diagnostic test.

Procedures for information collection, instruments to be used, and methods for data quality control:

- Clinical record

Procedures to ensure ethical aspects in research involving human subjects:

- Assessment of the use of personal data from the patient's clinical record.
- Application of informed consent in research.
- Following the guidelines established by the Research Ethics Committee of the University Hospital "Dr. José Eleuterio González".

Sample size:

The sample size was obtained using the following formula for diagnostic tests, with the objective of determining the efficacy and utility of the Furosemide Stress Test. The sensitivity of this test is 87%, according to Chawla et al. (9), with a margin of error of 15%, along with a Z value of 1.64 given a significance of .05 and a power of 80%, requiring a total of 54 research subjects.

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| **za^2** | 1.64 | 2.6896 |
| **p** | 0.87 | 0.1131 |
| **q** | 0.13 | 1.21677504 |
| **CI** | 0.15 | **n = 54.0788907** |

Intervention:

Patients admitted to the Intensive Care Unit of the University Hospital "Dr. José Eleuterio González" who present a diagnosis of Acute Kidney Injury, meet the inclusion criteria, and consent to participate in the study through informed consent will have a urine sample collected for the "NGAL" test evaluation. They will subsequently undergo the "Furosemide Stress Test", which consists of administering an intravenous bolus of 1 mg/kg of the drug in patients who have not been exposed to loop diuretics in the last 7 days, and 1.5 mg/kg in those who have been exposed, with the purpose of evaluating renal function through quantification of urine output.

Methodology:

Diuresis will be quantified from the first to the sixth hour after the test is performed, along with the results of the "NGAL" test.

The purpose of evaluating the NGAL test in our study is to determine its utility as a predictor of AKI progression.

Patients will subsequently be classified into two groups: "responders" and "non-responders", depending on the amount of urine produced up to the second hour. The "responder" group will include those who have achieved a diuresis equal to or greater than 200 ml, and the "non-responder" group will include those who have produced less than 200 ml of urine at two hours after Furosemide administration.

Both groups will be followed up for 15 days in order to identify those patients who require renal replacement therapy or who die.

Additionally, the clinical record will be used to collect the remaining data corresponding to the variables already presented.

Both the results of the Furosemide Stress Test and the data collected from the clinical record will be stored in a database using the Microsoft Excel 2016 program until the required number of patients for our research has been reached.

The Kidney Disease: Improving Global Outcomes (KDIGO) classification will be used for AKI staging as it is the most widely used and globally accepted classification, and it also stratifies patients according to serum creatinine and urine output, assessments which are accessible to evaluate in our setting.

Additionally, prior to the furosemide stress test, patients will undergo screening by ultrasound and electrical bioimpedance in order to assess their volemic status, that is, how hydrated or dehydrated they are.

This intervention does not pose an additional risk to patients, nor will it modify the results of the furosemide stress test.

Ultrasound screenings are routinely performed in Intensive Care Unit patients, as are bioimpedance assessments.

Our intention in performing this assessment is to seek a relationship between the patient's hydration status (volemia) and their response to the test.

## Statistical Analysis:

The data and results obtained will be stored in a database in the Microsoft Excel 2016 program, with subsequent statistical analysis performed in the SPSS statistics program.

Qualitative variables will be represented as frequencies and percentages, and quantitative variables by their pertinent measures of central tendency; variables will be subjected to the Kolmogorov-Smirnov test to determine their type of distribution.

Categorical variables will be compared using Pearson's Chi-square test or Fisher's exact test. For quantitative variables, groups will be compared using the Student's t-test and/or the Mann Whitney U test for independent groups.

Diagnostic accuracy for Acute Kidney Injury progression for the Furosemide Stress Test and the "NGAL" biomarker will be determined using the Area Under the Curve (AUC) and ROC curves, as well as for mortality and the need for RRT.

## Confidentiality Mechanism:

Personal data of the subjects included in this research will be omitted from results, using only the clinical data of patients included in medical records. Only the principal investigator will have access to the personal data of patients, safeguarding the integrity of the research subjects.

## Informed Consent

If the patient decides to participate, in the company of two witnesses, they will be verbally and thoroughly informed about the nature of the study, the benefits that consenting to voluntary participation will offer, and all questions that may arise at the time will be

answered. A written informed consent form must then be signed, which will be attached to our file to document the consent provided by each participant.

In case patients are unable to provide consent due to their medical condition, special written informed consent will be provided to their caregiver.

## Ethical Considerations:

This study will adhere to the principles set forth in the Declaration of Helsinki, the official Mexican standard NOM-012-SSA3-2012, good clinical practice principles, and the provisions of the General Health Law regarding research. It will be submitted to the research ethics committee of the University Hospital "Dr. José Eleuterio González".

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